PREPARATION AND EVALUATION OF DIFFERENT LIQUISOLID COMPACTS CONTAINING MODEL HYDROPHOBIC DRUGS: NORFLOXACIN AND CINNARIZINE

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Abstract of Research

The project started with studying the unique characteristics of the zwitterionic drug (norfloxacin), considered as an example of very slightly water soluble drug. The study focused on the effects of its chemical structure on its interaction with surfactants (PEG200 and Synperonic ™ PE/L-61) in liquisolid systems and, consequently, on its release into water dissolution medium.

The next stage was an approach to solve the problems of the dissolution, compressibility and flowability of norfloxacin liquisolid formulations through adding water as a liquid binder to make wet granulated liquisolid formulations. The water in the liquisolid formulations works as a liquid binder to the carrier and coating particles, creating a wider space inside their structure, which allows the amount of the liquid vehicle (PEG200 and Synperonic ™ PE/L-61) to increase inside the formulations. This feature reflects positively on the flowability (decreasing the angle of the slide), compressibility (increasing the load factor) and the dissolution behaviour of norfloxacin (increasing drug release to more than 20%).

Another liquid binder (PVP) was used in the wet granulations and a comparison was made between PVP solutions, water and classical liquisolid formulations in terms of dissolutions, flowability, compressibility, DSC thermographs and FTIR spectra.

The successful application of wet granulation techniques with liquisolid formulations was tested with a very hydrophobic drug (cinnarizine). Due to its hydrophobicity, traditional mixing of surfactants and the drug particles did not improve its dissolution in water medium, although the solubility was relatively high.

The methodology was again applied to investigate how the dissolution of cinnarizine altered with several different types of surfactants. The results lead to a change from traditional mixing to a self-nano emulsifying drug delivery system (SNEDD). Optimization to select a suitable oil (Capmul® MCM EP), surfactant (Kolliphor® RH40) and co-surfactant (PEG400) was found to depend initially on the solubility of cinnarizine. Further optimisation identified the relative percentages (66.6:16.6:16.6 for oil, surfactant and co-surfactant, respectively) and the drug concentration required for the SNEDD (6.0% w/w) was found to depend on the mixture experimental design, using dissolution trends as an indicator.

Finally, the selected SNEDD system was converted to a liquisolid system using the water granulation technique to make tablets with acceptable compressibility and flowability. Due to the negative effect of coating material (Cab-O-Sil® M-5P) on the dissolution behaviour, a new method was developed to determine the compressibility load factor using a central composite design and response surface methodology. The predicted model was validated and the accuracy was over 95%, allowing it to be used for preparation of the SNEDDs. The new preparations were compared to tablets from the commercial sources. The new formulations show significant enhancement in the percentage of the drug releases in distilled water dissolution medium.

Research Activities

Research activities from the PhD research:

A. Said Suliman, R. J. Anderson and A. A. Elkordy "A novel approach of combining self-emulsifying drug delivery system (SEDDS), wet granulation and liquisolid techniques," in *UK-PharmSci 2016 conference*, Glasgow, UK, 5 - 7 Sep 2016

A.Said Suliman, R. Anderson and A. A. Elkordy, "Liquisolid technique in combination with wet granulation process for improving norfloxacin dissolution," in *Formulation and Drug Delivery Congress 2015*, London, UK, 18- 19 May 2015.

A.Said Sumliman, R. J. Anderson and A. A. Elkordy, "Norfloxacin as a model hydrophobic drug with unique release from liquisolid formulations prepared with PEG200 and Synperonic ™ PE/L-61 non-volatile liquid vehicles," *Powder Technology,* vol. 257, pp. 156-167, 2014.

A. Said Suliman, R. J. Anderson and A. A. Elkordy, "Liquisolid tablet preparation for norfloxacin dissolution enhancement," in *UK-PharmSci 2013 conference*, Edinburgh, UK, 2 -4 Sep 2013.

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List of Liquisolid Technology Related Abbreviations

LSC	Liquisolid compressibility test
LSF	Liquisolid flowability test
R	Excipient (solid) ratio
Q	Weight of carrier excipient
q	Weight of coating excipient
W	Weight of liquid vehicle
CW	Net liquid/ solid weight composition (w/w)
Φ value	Flowable liquid-retention potential value
Ψ number	Compressibility liquid-retention potential number
Ψ Lf	Compressible liquid load factor
Φ Lf	Flowable liquid load factor
Ω_o	Intrinsic pactisity
σ_i	Sponge index
Ω	Pactisity
Ψmix	Compressibility liquid retention potential of the powder system
Lo	Optimum load factor
qo	Optimum quantity of coating material
Qo	Optimum quantity of carrier material
Wo	Optimum weight of non-volatile liquid
Φ ca	Flowable number of carrier material
Φ co	Flowable number of coating material
Ψ ca	Compressible number of carrier material
Ψ co	Compressible number of coating material

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Chapter One: Introduction

1.1. General Introduction

The most appropriate and frequently employed route among drug delivery systems is oral delivery administration, due to its cost effectiveness, lowest sterility restrictions during manufacturing, ease of administration and flexibility of formulation design. Consequently, many pharmaceutical companies select bioequivalent oral drug production preferentially [1].

The common challenges with oral tablet formulations as a drug delivery system are related to solving the problem of poor bioavailability. The factors that affect oral bioavailability vary from dissolution rate to aqueous solubility and caused by a variety of reasons, such as to drug permeability, first-pass metabolism and the effect of efflux mechanisms.

Regarding dissolution, there is an established concept that the dissolution of active ingredients in oral dosage forms is an essential step before absorption can take place from the gastrointestinal tract to the blood circulation system. The two steps relate to each other in such a way that the rate of drug absorption is affected by the drug dissolution rate [2]. The classification of active ingredients generated by the Food Drug Administration (FDA) shows that most hydrophobic drugs have a tendency to provide erratic and poor dissolution profiles, which consequently leads to unpredictable bioavailability and highly dangerous probability of therapeutic in-equivalence [3].

Oral compacts containing poor water soluble drugs usually involve high doses in order to increase the plasma concentration to a therapeutic level after oral administration, as a low level of solubility does not help to attain therapeutic levels.

Thus, it is considered as a major problem facing any formulation design for both new chemical entities and generic development [3] .

According to the biopharmaceutics classification system (BCS) (see Table 1-1), more than 40% of drugs are poorly water soluble. These drugs have slow absorption into the plasma, leading to not only low and inadequate bioavailability, but also raised toxicity to the gastrointestinal mucosa due to its accumulation in the GI tract. As a result, the improvement of drug solubility and dissolution is a major goal to enhance oral bioavailability [4].

Table 1-1: The biopharmaceutical classifications system (BCS) and the relative drug needing in order to reach to the optimum level in the Class I [5] .

Classes	Solubility	Permeability	Needs
I	High	High	Optimum
II	Low	High	Formulation design
III	High	Low	Chemical structure optimization
IV	Low	Low	Chemical structure optimization

Several pharmaceutical techniques have been developed to solve the problem of poor dissolution profiles of hydrophobic drugs in oral dosage forms. A group of these techniques uses the advantages of incorporating liquid surfactants into oral solid formulations. They can interact with hydrophobic drugs on one side and with the polar molecules of the relative dissolution medium on the other side. As these surfactants have liquid physical properties, special excipients with carrier and coating properties are needed to convert them into a dry powder admixture. Using these excipients together creates a new realm of limits to achieve the best dissolution improvement with acceptable compressibility and flowability characteristics, putting the theory of liquisolid systems onto real ground. Therefore, the definition of liquisolid systems is "they are compacts with acceptable flowing

and compressible powdered forms of liquid medications, which represents oily liquid drugs and solutions or suspensions of water insoluble solid drugs carried in suitable non-volatile solvent systems termed the liquid vehicles" [6].

1.2. Liquisolid Mathematical principles:

The concept of the liquisolid technique determines liquid medications, which are a combination of the active ingredient/s and the selected non-volatile liquid vehicle/s, at a limit of acceptable flowing and compressible powdered forms. In other words, lipophilic drugs or water-insoluble solid active ingredients, dissolved in selected non-volatile liquid vehicles, have the possibility to convert to dry free flowing powders with acceptable compressibility, using suitable powder excipients as the carrier, such as various grades of microcrystalline or amorphous cellulose, and the coating materials, such as very fine particle size silica powders. The capacity of the carrier and coating materials in term of retaining a certain amount of liquid vehicle should be taken into consideration mathematically via specific methods and models to achieve optimization of the quantities of these materials in order to maintain acceptability of both the flowability and compressibility of the liquisolid powdered admixture.

Mathematically, the concept of a liquisolid system stands on two fundamental terms; the flowable Ø value and compressible ψ number liquid retention potentials.

The Ø value defines an acceptable level of powder flowability when adding the maximum amount of a given non-volatile liquid, whereas the ψ number specifies an acceptable level of powder compressibility when adding the maximum amount of the non-volatile liquid.

Spireas *et al.* determined two methods to predict the two terms [6]. The ψ number and Ø values are determined by applying liquisolid compressibility (LSC) and liquisolid flowability (LSF) tests, respectively.

For the LSF test, several powder systems are prepared, each containing different values of excipient ratio (R) where R=Q/q; Q represents the weight of a carrier excipient and q represents the weight of a coating excipient. Each mixture contains an increased amount of non-volatile liquid which will be used in the liquisolid preparation. The flowability of each prepared mixture is assessed by flow meter, angle of slide, angle of repose or any suitable flowability test to specify the flowable liquid load factor ØLf of each powder system. The ØLf can be given by the following equation:

$$ØLf = W/Q$$

where W is the weight of the liquid vehicle and Q is the weight of the carrier material.

Finally, the Ø value of a powder (carrier or coating excipient) is determined by plotting $ØL_f$ against the reciprocal excipient ratio (1/R), where the slope represents the Ø value of the carrier and the intercept indicates the Ø value of the coating.

In the liquisolid compressibility (LSC) test, the same liquid/ powder admixture prepared in the previous test is used to assess the maximum crushing strength of the compacts that can be obtained by applying a plateau compression force. The average of the crushing strength of each admixture will be divided by the average of the weight of the compacted tablets in order to determine the pactisity Ω value. Determination of the net liquid/solid weight composition (CW) of the crushed

tablets is used to indicate the intrinsic pactisity (Ω_o) and sponge index (σ_i)by plotting log Ω versus CW to give a log-linear equation:

$\log \Omega = \log \Omega_o - \sigma_i * CW$

The compressible liquid retention potential of the powder system (ψmix) can be given by the following equation:

$\psi mix = (\log \Omega_o - \log 20)/ \sigma i,$

where the fixed value of the logarithm of twenty comes from applying plateau force pressures to achieve the maximum crushing strength, which gives a pactisity Ω =20 kg/g.

Finally, the compressible liquid load factor (ψLf) of the powder system can be determined from the following equation:

$\psi Lf = \psi mix (1+1/R)$

Plotting the ψLf for each admixture against the reciprocal excipient ratio (1/R) will give a linear equation with a slope equals to compressible liquid-retention potential (ψ number) of the carrier and the intercept is the compressible liquid-retention potential (ψ number) of the coating.

The optimum load factor (Lo), which is used to determine the optimum quantities of the carrier and coating excipients, indicates an acceptable flowing and compressible liquisolid system. This term is given as follows:

Lo= ØLf if ØLf < ψLf

or

Lo= ψ Lf if ØLf > ψLf

where $ØL_f$ =Øca +Øco *(1/R) and

ψLf =ψca +ψco *(1/R).

The optimum quantity of the carrier Qo is given from this equation:

Qo = Wo/ Lo

where Wo = optimum weight of non-volatile liquid.

Finally, the optimum quantity of the coating material qo is given as follows:

qo= Qo/R.

All of these mathematical calculations are described in the literature [6].

1.3. Liquisolid formulation preparation:

The calculated amount of a drug and a non-volatile liquid are mixed together, either with or without heating to form a liquid medication solution or suspension. Then, the mixture is transferred to a mortar and the optimum amount of carrier and coating excipients, determined by the liquisolid flowability test or liquisolid compressibility test, are added to the mortar and mixed with the liquid medication for few minutes. The resulting admixture is spread on the mortar surface for approximately five minutes to allow the liquid medication particles to be absorbed completely into the interior powder particles and to allow coating particles to cover any excess liquid particles that are not absorbed into the internal framework of carrier particles.

The liquid/powder admixture formed represents a liquisolid system with suitable flowability and compressibility characteristics. Finally, a small amount of a

disintegrant (about 5% weight formulation) and a lubricant (about 1% of weight formulation) can be added to the liquisolid system to enhance the powder characteristics, such as decreasing the disintegrant time of the tablets and preventing the sticking of the powder to the compression machine.

A non-volatile solvent should be selected to be inert and with a high boiling point, preferably water miscible and not a highly viscous organic solvent, which could lead to fairly distribution to the drug inside the admixture and affect negatively on the drug content tests. The carrier excipient should be porous in nature and have sufficient absorption features. Finally, the coating excipient should be a substance with adsorptive properties and a small size (fine particles) [6]. Figure 1-1 summarizes the steps of liquisolid system formation.

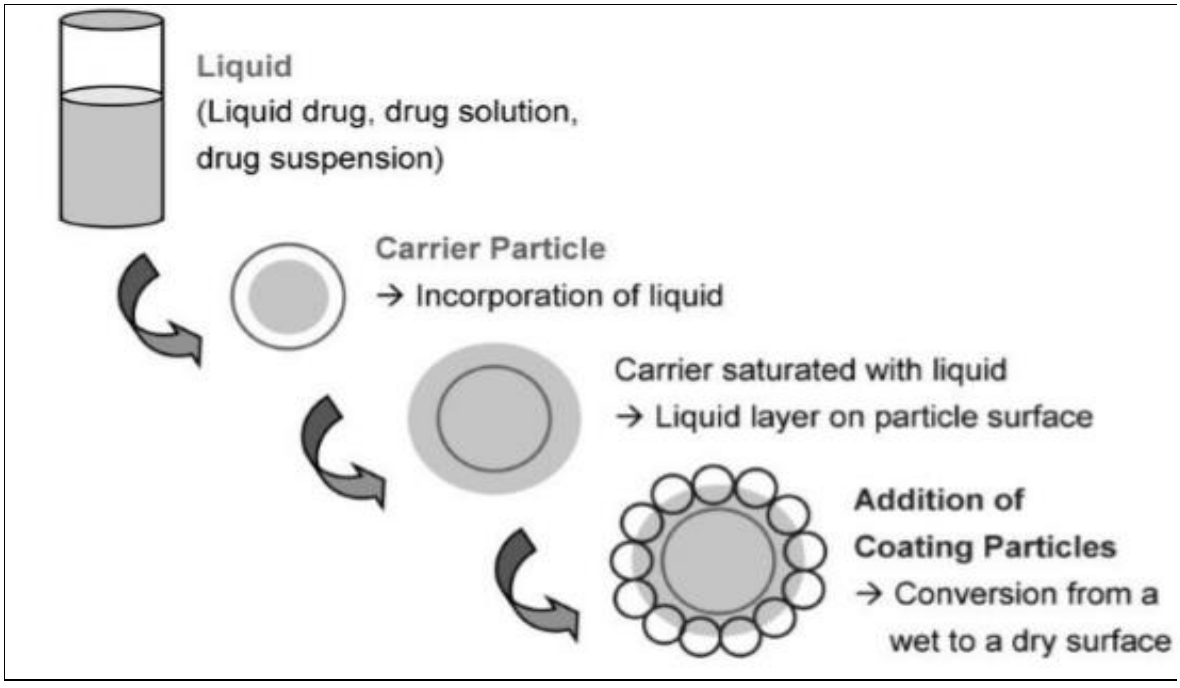

Figure 1-1: Schematic representation of liquisolid systems [7].

1.4. Mechanism of liquisolid action inside the dissolution medium:

Several mechanisms have been suggested that try to describe the action of the liquisolid system inside the dissolution medium leading to enhanced hydrophobic drug release. They can be summarized in three points;

1. Increase of the surface area of the drug available for release into the dissolution medium

2. Increase of the solubility of the drug in the liquid vehicle

3. Improvement of the wettability of the drug, or the formation of a complex between the drug and excipients (suspension or solution), which can be detected by DSC instrument.

Regarding the first point, the location of a drug inside a powder excipient system in the form of a molecular dispersion, makes the surface area of the drug for release greater than the drug particles in directly compressed compacts [8] & [9].

The theory behind increasing drug solubility in a liquisolid formulation assumes that, although the quantity of liquid vehicle in the liquisolid compacts is not sufficient by itself to increase the overall solubility of the drug in the dissolution medium, the microenvironment of the solid-liquid interface between a single liquisolid particle and the dissolution medium helps the diffusion of drug particles out of the liquisolid compacts into the release medium. This phenomenon can only be explained if the liquid vehicle works as a co-solvent [8] & [9].

The presence of surface active agents in liquisolid formulations improves the wettability of liquisolid particles, compared to conventional tablets, due to low

surface tension. Such a phenomenon is demonstrated by the determination of lower contact angles and shorter water rising time tests [9] & [10].

1.5. Optimization of liquisolid formulations with enhanced drug release:

It is known that the main limitation of liquisolid formulation is the small amount of active ingredient included in such compacts, because increasing the weight of pure drug leads to an increase in the weight of liquid vehicle, which consequently leads to an increase in the amount of carrier and coating substances. Thus, a large tablet would be formed which is difficult to swallow.

Several attempts aimed to solve this problem, focusing on making different formulations. The principle aim was to select a suitable liquid vehicle. The criterion of such a selection was the drug solubilisation. However, other factors such as viscosity, polarity, chemical structure and lipophilicity, could also participate in selecting good vehicles for the formulations [8] & [11] .

To increase the loading factor with decreasing tablet weight can also be achieved using high specific surface area carrier and coating, or adding poly vinyl pyrrolidone (PVP) to liquisolid formulations. An example of a high specific surface area excipient is microcrystalline cellulose (MCC), compared to other excipients, such as lactose, starch and sorbitol. MCC has a specific surface of1.18 m^2/g, whereas lactose, starch and sorbitol have specific surface areas less than 1 m^2/g. As a consequence, MCC enhances drug release into the dissolution medium through its higher liquid adsorption capacity, raising the amount of the liquid load factor [12].

On the other hand, PVP has an ability to prevent drug retention in the cavities of porous excipients, which enhances the release of drug into dissolution medium [13].

The optimization of liquisolid formulations does not stop at the type of carrier and coating materials, even though the percentage of each has an important role in improving drug release. Increasing the excipient ratio (R) also increases the wicking and decreases the disintegration time of compacts. This phenomenon is frequently demonstrated when using MCC as the carrier and silica as the coating excipient [14]. On the other hand, decreasing the R value, i.e. increasing the amount of silica in the formulation, affects negatively on drug release, due to the hydrophobicity of silica, which can retard drug release if it is added in a high amount [15].

The possibility of re-crystallization and precipitation of the drug increases when the amount of silica increases. This problem could be solved by the possibility of adding more amount of liquid vehicle in order to overcome the probability of drug precipitation. However, increasing the amount of silica would lead to a higher loading factor, so that the ability of the drug to diffuse out into the dissolution medium becomes more effective as a consequence of adding more liquid vehicle [16] & [17].

Finally, adding carmellose sodium or sodium starch glycolate, which act as super-disintegrants, improves drug dissolution, because such excipients can assure the drug release and it would not be affected by a slow disintegration from the dosage form [18].

1.6. Poly vinyl pyrrolidone (PVP) as a liquid binder:

The structure of poly vinyl pyrrolidone (PVP) or poly-[1-(2-oxo-1-pyrrolidinyl) ethylene] at a specific molecular weight can be synthesized by polymerization of vinyl pyrrolidone with a mass range from 2500 to 3000000 Da. The classification of PVP depends on the K-value that can be calculated form Fickentscher's equation, where the logarithm of the relative viscosity between the solution and the solvent is directly proportional to the concentration of the solute in the solution (%w/v) [12]. PVPs with longer chain length and higher molecular weight have higher K-values.

The two features that distinguish PVP are its good water solubility and its enhancement of wettability. These two characteristics lead to improvement of the rate of dissolution from a tablet dosage form if PVP is used as a solvent for hydrophobic drugs in solid dispersion. On the other hand, the length of the chain of PVP affects the dissolution rate; an increase in the length of such a chain causes increased viscosity at the adjacent diffusion boundary layer of the dispersed system, decreasing the rate of drug particle transport from the solid dispersive matrix into the dissolution medium, although the feature of water solubility and wettability of PVP still exists. An example of this was reported in a study of the dissolution of indomethacin (a hydrophobic drug) in different solid dispersion tablet formulations. A slightly slower dissolution was noticed in the tablets containing PVP K-90 compared to the formulation containing PVP K-17, reaching a general conclusion that the longer the PVP chain length, the poorer the dissolution rate [19].

In addition to the length of the PVP chain, wettability and water solubility, another aspect that should be considered is the ratio of PVP to the drug. The quantity of

the PVP inside the solid dispersion affects the drug release in the dissolution medium, so that the higher proportional PVP formulations show better water solubility and drug release. For example, in-vivo studies of the release of furosemide from PVP solid dispersion formulations were carried out, where the relationship between the degree of drug crystallinity, detected by X-ray diffraction, and the ratio of PVP/ drug were investigated. The dispersion of the drug was amorphous at a higher percentage of PVP and showed a significant increase in the bioavailability of the drug, whereas there was some degree of crystallinity at lower percentages of the carrier, affecting negatively on the human bioavailability of furosemide [20].

1.7. Pharmaceutical wet granulation process:

Granulation can be defined as the process of particles agglomeration to form larger semi-permanent granules, keeping the ability to distinguish the original particles. In wet granulation processes, the design of particles can be achieved by connecting particles together via a liquid binder that creates viscous and capillary forces, forming permanent forces after drying or sintering [21].

In the wet granulation process, three sets of process can be recognized (see Figure 1-2); first, wetting and nucleation, where the bed of dry powder contacts with the liquid binder, leading to distribution of the liquid inside the bed and the formation of nuclei granules. The second process is named consolidation and granule growth, where collision among granules themselves, granules with the equipment and granules with feeding powder, which leads in total to granule growth. Thirdly, there is breakage to wet granules or attrition to dry granules due to

impact or compact in the granulator or subsequent processes, such as sieving [21] & [22].

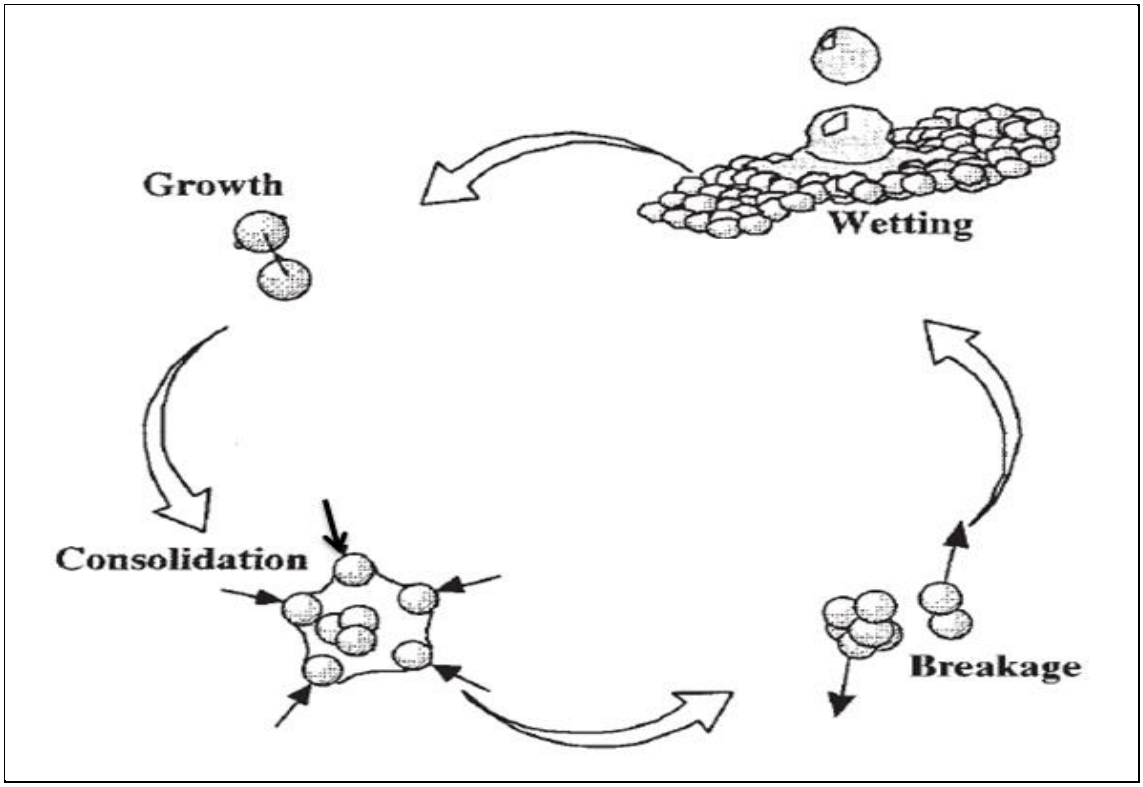

Figure 1-2: A summary of granulation process, which includes wetting and nucleation, granule growth and consolidation, breakage [21].

Regarding nucleation process, it can be recognized from a term called wetting zone. It is the area that the liquid binder initially contacts the surface of the powder and forms the nuclei. The important processes in this zone are nuclei formation, which happens where the contact angle between the liquid binder and the solid powder, the spreading coefficient where the liquid and solid phases spread over each other and the powder-binder dispersion where the quality of the mixing has a strong effect on the binder delivery method. These three processes are considered as the main mechanical terms that used to describe the wetting zone [23].

Considering the wetting zone thermodynamically, there is a relationship between the contact angle and the particle size; when the former increases (i.e. the

wettability of the powder mixture decreased), the latter decreases. This relationship can be specifically identified when formulations contain a hydrophobic drug [24]. In the same field, the nucleation and wetting can be described in terms of surface free energy via the spreading coefficient, explained by the solid and liquid spreading over each other, related to the work differences between the cohesion and adhesion processes. If the coefficient is positive, spontaneous spreading occurs and there is two possibilities: the binder forms a film over the surface of the powder and liquid bridges between powder particles, leading to form a strong granule, or binders form bonds only where liquid and solid contact initially, leading to no film formation and giving a weaker granule [25].

On the other hand, granule dispersion is strongly affected by binder delivery methods, of which there are mainly three ways; pouring, spraying and melting. Focusing only on the pouring method, as it is the only way used in the prepared formulations of the current work, the initial stage shows poor liquid distribution and the probability of forming coarse granules is high, compared with other methods. This is probably due to the creation of local patches of high moisture content [26] & [27].

In the stage of granular growth and consolidation, the granules colloid to each other, reducing the porosity and squeezing out the entrapped air, as well as squeezing out the liquid binder to the surface of the solid powder. This could enhance and accelerate the consolidation process [25].

Two main factors affect the stages of granules development and formation: binder content and binder viscosity. It was found that increasing the amount of a low viscosity binder, such as water, may help to increase particle mobility, leading to

greater rearrangement into more compact configurations [28]. On the other hand, an increase in the amount of a high viscosity binder could increase or decrease the rate of the consolidation. For example, PEG6000 increases the rate of the granular growth; with a viscosity of approximately 1100 mPa s, it increases consolidation in a high shear mixer [29]. In contrast, increasing the amount of a high viscosity binder (e.g. glycerol) led to a decrease in the rate of granule growth. This was attributed to the dominancy of the liquid viscous forces over the inter-particular friction forces [30].

1.8. Wet granulation and liquisolid tablets:

The inclusion of an extra additive to liquisolid systems, in order to enhance and control the hydrophobic release in dissolution media, started when using PVP to increase the capacity of the carrier/coating bed powder in order to load the liquid vehicle (i.e. increase the value of the flowability load factor ($ØL_f$). The results showed an increase of the flowability load factor to reach 0.42 when 10% PVP-K25 was used as additive in different ratios of MCC to silica powder mixture in the presence of PEG200 as liquid vehicle in a 50% w/w mixture with carbamazepine, a hydrophobic drug. The percentage of drug release was the best with the PVP additive, compared with other additives, such as HPMC and PEG3500 [16]. However, there was no consideration of the compressibility of the load factor (ψ Lf), keeping the hardness of the tablet between 5.7and 7.1 KgF for all tablets. This degree of hardness is less than the acceptable level of compressibility determined by Spireas *et al.* [6], which should have been, in this case, 14.7 KgF. This means that, although the direct addition of solubilizing agents to the liquisolid systems enhances drug release and flowability, it does not overcome the problem of the compressibility. After that, there was an attempt to use the benefits of PVP

characteristics in liquisolid systems using the wet granulation technique. In this work, glibenclamide was the hydrophobic drug, prepared with PEG400, Synperonic ™ PE/L-44 or Cremophor® ELP at 10 %w/w, using a flowable load factor. This study showed a significant enhancement in the dissolution profile compared with traditional liquisolids, yet it depended on the calculated flowable load factor of each liquid vehicle [31]. In other words, there is an assumption that the value of the calculated liquid factor does not change when adding a liquid binder, although there is an enhancement in flowability and compressibility of the designed formulations. As a result, the crushing forces for PEG400, Synperonic ™ PE/L-44 and Cremophor® ELP were still less than an acceptable level of compressibility, which in this case were 6.16 KgF, 4.20 KgF and 2.56 KgF, respectively.

1.9. The Self-Emulsifying Drug Delivery System (SEDDS) and its relative components:

Self-emulsifying drug delivery systems (SEDDS) are defined as an isotropic mixture of oils, surfactants and hydrophilic co-solvents or co-surfactants that, when mixed together gently, form a homogenous mixture, and can emulsify or micro-emulsify in aqueous media [32] & [33]. The oil can be considered the most important part of the SEDDS, as it has the ability to dissolve a marked amount of hydrophobic drug, cause self-emulsification, and enhance the transportation of lipophilic drug through the intestinal lymphatic system, so that it increases absorption via the GI tract [34]. Several long and medium chain triglycerides are used for making self-emulsifying drug delivery systems. In particular, modified and hydrolysed vegetable oils have been used extensively in SEDDS due to their ability to form good emulsification systems in corporation with a large number of

surfactants used for oral administration. Furthermore, they have several advantages in terms of their physiological degradation that have similarity to the end products of the GI tract [35].

Examples of vegetable oils used in SEDDS include olive and peanut oils. While the first one was used with cyclosporin A (10%) in the presence of polyglycolyzed glycerides (HLB between 3 and 4) as surfactants and ethanol as co-solvent, the second was used with medium chain mono- and diglycerides, Tween 80, PEG25 glyceryl trioleate, and polyglycolyzed glycerides (HLB = 6-14) as a group of surfactants in order to enhance the absorption of a naphthalene derivative with no need for co-solvents [36] & [37].

In relation to the role of surfactants, those most commonly recommended are the so-called non-ionic surfactants with relatively high HLB values for easier dispersion inside the aqueous media. The most famous examples are Tween 80 and Cremophor® EL or RH40. The recommendation comes from their higher safety compared with ionic surfactants, although they have in some cases a reversible permeability at intestinal lumen level [38]. The high HLB value of surfactants helps immediate release formulations to spread rapidly as oil/water emulsion droplets in an aqueous medium. They also inhibit the precipitation of the drug in the GI tract and they help the drug particles to be solubilized for a long time at the site of absorption [39].

The relationship between the droplet sizes and the concentration of the surfactants used can vary depending on the type of hydrophobic drugs and the dissolution medium. In some cases, an increase of the surfactant concentration could result in a decrease in the droplet size of the emulsion. An example of this is Labrafac CM-

10, which consists of a mixture of polyglycolized glycerides at a saturated level that works at the interfacial layer between oil and water [40].

On the contrary, an increase of the surfactant concentration could lead in some cases to an increase in the droplet size of the emulsion. This could happen when the water droplets penetrate the emulsion system, so that they disrupt the interfacial layer between the oil and aqueous medium. An example of this phenomenon is seen when using Cremophor® EL with paclitaxel in either I.V. or oral administration forms [41].

Finally, the permeability of hydrophobic drug through the lipid bilayer of the epithelial cell membrane could increase in the presence of surfactants, as they work to enhance the absorption via the passive transcellular route [42]. Furthermore, surfactants work to disrupt the arrangement of the lipid bilayer on the cell membrane, leading to increased permeability of the drug, in addition to their role in dissolution rate improvements [43].

The role of co-solvent is to produce an optimum SEDDS through enhancing the dissolution of a large amount of hydrophilic surfactant or drug in an oil phase. These materials could act as co-solvents, such as ethanol and other alcoholic solvents, or as co-surfactants at the micro-emulsion level, such as polyethylene glycol (PEG) or propylene glycol (PG). However, the limitation of such co-solvents is their probability to evaporate from the wall of the capsule when SEDDS is filled into hard, soft or sealed gelatine capsules, which results in drug precipitation [44].

1.10. SEDDS mechanism of action:

The action of the self-emulsification has been suggested to take place when the required energy for changing the surface area of the dispersion is less than the change in the entropy of the dispersion. The relationship between the free energy of emulsion formation and the energy required to form a new surface between the oil and water phases is a direct function. The free energy will reduce with time as a result of the oil and water phases' separation, so that they create a new interfacial surface. At this level, the emulsifying agents play an important role in reducing the interfacial energy via creating a monolayer surrounding the emulsion droplets, which helps to stabilize the system and decrease the incidence of coalescence between droplets [44] & [45]. However, spontaneous emulsification can occur at low interfacial tension so that the interfacial structure does not have resistance against surface shearing and the free energy of the dispersion is at low level. This change in the entropy energy should be distinguished from the micellar formation and its relative energy considerations [44] & [45].

When seeing the mechanism of action of SEDDS from the formation of a lyotropic liquid crystal perspective, the ease of self-emulsification can be identified as the water droplets penetrate into the lyotropic liquid crystal phase. The addition of oil/surfactant mixtures to aqueous phase increases the interface between the oil and water phases. The continuous penetration of water droplets inside the oil phase will move the solubilisation to the interface limit and form the lyotropic liquid crystal dispersed phase. At this level, the concentration of the surfactant will determine the ease of penetration of water droplets into the lyotropic liquid crystal phase; with gentle agitation, the interface disrupt, and SEDDS becomes resistant to coalescence [32].

1.11. SEDDS classification and the relative pharmaceutical challenges:

The classification can be considered to depend upon the percentage of the SEDDS components and it can be divided into 4 groups; the first (Type I) consists of 100% oil or a mixture of oils, which are usually triglycerides or mixed glycerides. The next group (Type II) consists of 40-80% oils and 20- 60% surfactants. These surfactants usually have an HLB value less than 12. The third group (Type III) is divided into two subgroups; Type IIIA consists of 40- 80 % oils, 20-40% surfactants (HLB > 11) and 0-40% hydrophilic co-solvents, and Type IIIB, which usually consists of less than 20% oils, from 20 to 50% surfactants (HLB > 11) and from 20 to 50% co-solvent [46]. The fourth group (Type IV) consists of 0-20% water-insoluble surfactant (HLB < 12) instead of including oils, 30- 80% water-soluble surfactant (HLB > 12) and 0-50% hydrophilic co-solvents [5].

The best SEDDS formulations take the importance of the unit dose of a drug into consideration. The required dose depends on the presence of solvent capacity in the formulation, so that it allows good administration of the drug in the gut. However, the type of drug is still the most important factor in forming the SEDDS, because some drugs are classified as difficult drugs due to their limited solubility in both water and lipids (when the value of log *P* is approximately 2.0) [46].

Regarding the classification of SEDDS, the drug should be selected among any type, provided that it is sufficiently soluble in the selected type, it does not cause any precipitation, and it provides a rapid absorption. Types II and III have superiority over Type I system, as they have rapid gastric emptying, thus their colloidal formation will be faster than Type I [46].

The effect of the SEDDS droplet size has been investigated on the rate of cyclosporin A absorption, where it increases with two finer emulsion compared with the relative coarse ones [47]. However, the case of droplet size effect is still difficult to assign, especially when a small amount of lipid is dissolved in the upper part of the small intestine form the capsule shell. Here, other factors could have more important effects than the droplet size. Nevertheless, the susceptibility to digest as mixed micelles of bile salts remains denoting the importance of droplet size of SEDDS in the GI tract [47].

On the other hand, changing the percentages of the SEDDS components have an effect on the rule of droplet size. For example, when decreasing the percentage of oil and increasing the percentage of surfactant and co-solvent, the droplet size becomes less sensitive to digestion mixtures. Thus, the approach used to make SEDDS at the beginning affects the production of colloidal dispersion and, consequently, the self- emulsification of the system [48].

Regarding the SEDDS classification, Type IIIB, and to some extent Type II, produce systems with droplet sizes at the nano level (ranging between 100 nm and 250 nm), which could be due to the role of the water-soluble surfactants and co-solvents in the SEDDS [44] & [46].

The risk of drug precipitation comes from the fact that the solvent capacity of hydrophilic co-solvents, such as poly ethylene glycol (PEG) or propylene glycol (PG), falls logarithmically when the SEDDS is dispersed in water, leading to separation of such co-solvents from the oil formulations and forming micelles in the continuous phase [49]. However, there are some questions about lowering the

solvent capacity of the drug if this phenomenon happens. In other words, what other factors could control drug precipitation?

In fact, two factors should be considered here; the first one is the log *P* of the drug and the second one is the contribution of the selected surfactant in the role of solubilisation. Furthermore, several attempts were made to anticipate the risk of drug precipitation from SEDDS. A recent one used the determination of equilibrium saturated solubility and mole fraction solubility for SEDDS and its relative individual components with a range of temperatures (22 ^{o} C to 47 ^{o} C).

Also, it tried benefit from Apelblat's model to predict and evaluate the thermodynamic behaviours of the hydrophobic drug (indomethacin) in the form of SEDDS [50].

1.12. Solid SEDDDS and the selection of the relative powder excipients:

The term of "solid SEDDS" is used for the engineered treatment of self-emulsifying mixtures in order to form different types of solid powder, such as tablets, granules, pellets and microspheres. It is one of the treatment methods, including dry emulsion and silica-lipid hybrid (SLH), that is aimed to convert the lipid-based formulations to oral solid states [51].

The corner stone in the solid SEDDS is the use of a suitable porous powder in order to adsorb the relative large quantity of the liquid SEDDS mixture. Several studies depended on materials having a large specific surface area or a high porosity. The commonly used porous powder was silica, which was either introduced to the liquid SEDDS mixture via a simple blending process or incorporated into a dispersion of lipid droplets after a drying process. A screening

study aimed to investigate the effect of different types of silica on the tabletability, using six different types of silica, namely; Aerosil 200, Spirnat 22, Sylysia 350, Zeopham 600, Neusilin US2 and Neusilin CFL2 in combination with 20% microcrystalline cellulose [52]. The study showed that, without the addition of any liquid, the tensile strength of the Aerosil 200, Spirnat 22, Sylysia 350 formulations did not reach 1 MPa, whereas there was no possibility to make tablets when incorporating a SEDDS mixture at a ratio 1:1 w/w with the silica. In comparison, Zeopham 600, Neusilin US2 and Neusilin CFL2 formulations showed tensile strength above 1 MPa without the addition of liquid. Nevertheless, only Neusilin US2 showed acceptable tensile strength when adding the liquid at 1:1 w/w ratio. The expected reason for this was explained from the images captured by a scanning electron microscopy (SEM). In the case of the failed coating materials, it is the liquid that is adsorbed at the surface of the silica particles, whereas, in the case of Neusilin US2, the liquid adsorbed inside the pores of the coating structure [52]. The good physicochemical properties of aluminium magnesium metasilicate (Neusilin US2) make it the first choice when making solid SEDDS tablets (Figure 1-3). Its high specific surface area (approximately 300 m^2/g) allows the adsorption of oils approximately three times its weight [51]. It was used alone as a carrier material with the HIV protease inhibitor darunavir [53] in its SEDDS mixture and with microcrystalline cellulose as a carrier material in order to adsorb cyclosporin A [54] and Probucol [55] dissolved in their SEDDS mixtures. The adsorption capacity or the flowable load factor that is used in the case of darunavir SEDDS liquid medication reaches 0.82% w/w for 55.5% MCM C8, Tween 80 and Transcutol® P SEDDS mixture. The Carr's compressibility index and Hausner's ratio in this case indicated good flowability behaviour with approximately 18.6% and 1.18%,

respectively. However, there was no mention about the crushing force in this study [53].

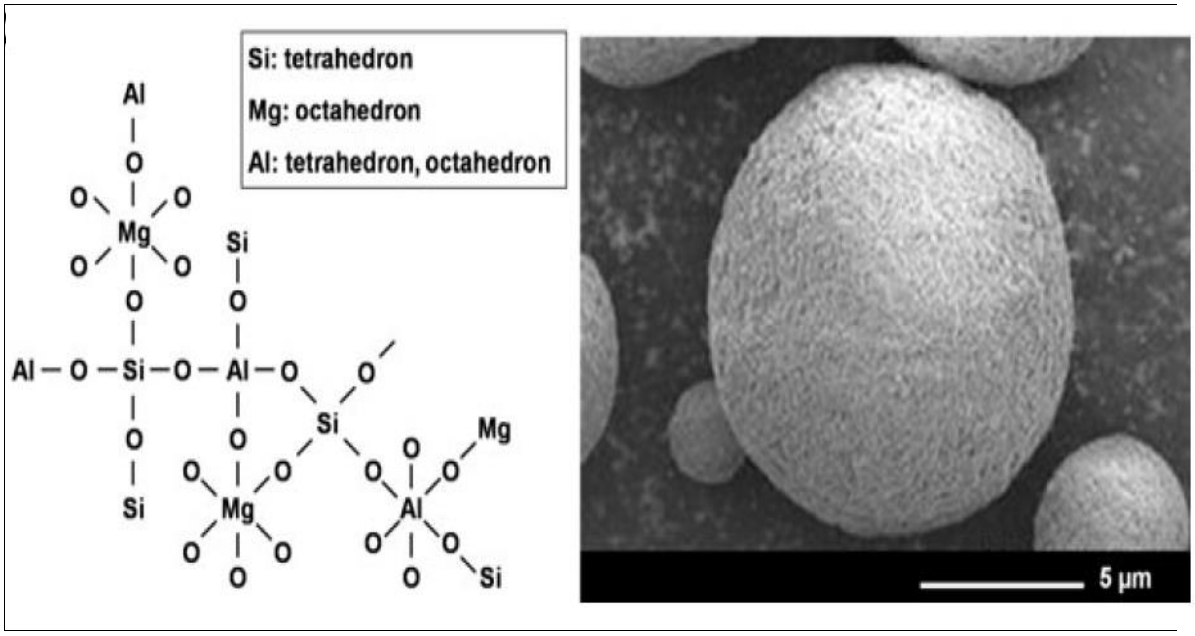

Figure 1-3: Molecular structure and scanning electron microscopic image of Neusilin® magnesium aluminium metasilicate [51] .

Moreover, the adsorbing ratio that was used in the case of Probucol SEDDS mixture, which includes Capmul® MCM, Captex 355 and Cremophor® EL, was 1:1 w/w in the presence of microcrystalline cellulose at 20%. The flowability was evaluated by the same techniques and the compressibility index ranged between 11 and 17, indicating good powder characteristics. The tabletability of these mixtures was studied via determination of the tensile strength of the prepared formulations at a range of compression pressures from 45 MPa to 135 MPa. The results showed similarity in the behaviours of the tensile strengths. The plateau level for the selected solid SEDDS mixture was between 1 MPa to 2 MPa approximately. However, the tensile strength starts decreasing over 135 MPa and the explanation for this referred to squeezing the liquid outside the admixture [55]. A second example of the addition of microcrystalline cellulose as a carrier with

Neusilin US2 succeeded in keeping the flowable liquid load factor at a high level, but the crushing force was still under the Spireas' criteria [6]. In the case of cyclosporin A SEDDS mixture, the oil was a combination between Maisine 35-1 and Lauroglycol FCC in 1:1 w/w ratio, and the surfactant and co-solvents were PEG-35 castor oil and PEG400, respectively. Where Hausner's Ratio=1.243 and Carr's Index=19.565%, indicating a good flowability behaviour, the hardness was 5.18 KgF and the tensile strength 0.47 MPa for a tablet weight of 651 mg [54].

Apart from using aluminium magnesium metasilicate, granulated silica is also used as a solid mixture with diluents. A study used Labrafil®, Tween 80 and Transcutol® HP at a ratio (10:60:30) and granulated silicon dioxide (Aeroperl® 300) in a mixture with Avicel® or Starch 1500 in order to enhance the oral bioavailability of simvastatin. The compressibility index ranged between 12% and 25%, depending on the content of each formulation and the solid ratio used, which was either 5 or 10. The friability test, however, was between 0.32% and 0.98%, which is considered near to the acceptable BP limits [56], although the flowability load factor was only 0.2 and the concentration of liquid medication was 12.5% w/w at 10 mg drug for all formulations. As a consequence, the crushing forces did not exceed a range between 4.26 KgF and 6.67 KgF for approximate tablet weights equal to 500 mg [57].

The effect of carrier type on the solid SEDDS was studied by screening several types of microcrystalline cellulose. A study used Vitamin A (15 mg) in order to carry out *in vivo* and *in vitro* evaluations via using SEDDS mixture consisting of soybean oil, Cremophor® EL and Capmul® MCM-C8. The liquid medication concentration was approximately 20% w/w, the weight of different grades of

Avicel® (PH 101, PH 102, PH 105, PH 112, PH 113 and PH 200) was 750 mg and 4% of talc powder was added to enhance the flowability. Avicel® PH 200 recorded the lowest compressibility index value (22%), whereas the highest one (39%) was when using Avicel® PH 103 or Avicel® PH 105. The flowability results were directly proportional to the crushing force values, where the formulae containing Avicel® PH 200 was recorded the highest value with 15.22 KgF and the one containing Avicel® PH 105 was 8.8 KgF [58].

The method of determining the critical responses and the main factors that help to find the optimum percentages for the SEDDS mixtures and, consequently, the best SEDDS tablets was investigated via a quality by design approach in order to enhance the oral bioavailability of irbesartan [59]. This approach included a full factorial design, consisting of three levels and two factors: the concentration of oil (X1) and the surfactant to co-surfactant ratio (X2). These two factors met many responses, indicating globule size, emulsification time, polydispersibility index, zeta potential, refractive index, the percentage of transmittance, and the percentage of drug content. Applying principle component analysis (PCA), a second quality-by-design approach managed to reduce these selected responses to only two; globule size and emulsification time. Using ANOVA helped to reduce the coefficient regressions of the fitted polynomial models so that it increased the accuracy of them. Although these approaches helped to optimize the percentage of the SEDDS components, the screening of carrier and coating materials still depended on the traditional method for selecting the type of materials. The flowable liquid retention potential was used to select Neusilin US2 as a carrier material and Aerosil 200 as a coating material. As a consequence, the

compressibility index was 18.45%, indicating a good flowability, but the hardness was approximately 4.0 KgF for a tablet weight of 767 mg [59].

1.13. Aims and Objectives

The first aim of this project is to study the unique characteristics of the zwitterionic drug (norfloxacin) and how its chemical structure affects its interaction with surfactants in liquisolid systems and consequently in its release in aqueous dissolution medium. The second aim is to study the effect of adding wet granulation process to liquisolid tablet production in order to enhance the compactibility, flowability and the drug release in aqueous dissolution medium. The last aim is to optimize and predict a statistical model, combining Self Emulsifying Drug Delivery System (SEDDS), wet granulation and liquisolid techniques in order to enhance the dissolution behaviour of cinnarizine in distilled water using statistical mixture designs, central composite design and surface response methodologies. SEDDS was replaced with the classical liquid medication preparation due to the very hydrophobicity nature of cinnarizine in the aqueous dissolution media.

The objectives of this research are as follows:

- Preparation of classical liquisolid tablets of norfloxacin as a model of hydrophobic drug tablets.
- Determination of Synperonic ™ PE/ L-61 compressibility liquid load factor and then use as an optimum load factor in order to prepare liquisolid tablets.
- Exploring the unique behavior of norfloxacin with non-volatile liquid vehicles (PEG200 and Synperonic ™ PE/L-61) in distilled water as a dissolution

medium, via studying the aqueous dissolution behaviors of the liquid medication of norfloxacin and analyzing the products via FTIR.

- Apply *in vitro* dissolution studies to examine the differences in the percentage of norfloxacin release inside different dissolution media (acetate buffer (pH=4.0 and distilled water (pH=6.1).
- Studying the solubility of norfloxacin in several surfactants with different HLB values.
- Investigating the combination of liquisolid and wet granulation pharmaceutical processes in terms of compressibility and flowability.
- Applying the findings of the combination of wet granulation and liquisolid on two liquid vehicles (PEG200 and Synperonic ^{TM} PE/L61) in term of *in vitro* dissolution of norfloxacin, a drug with sparing water solubility.
- Comparing two liquid binders (water and 10% w/w PVP-K17 solution), in terms of compressibility, flowability and *in vitro* dissolution test, when combining wet granulation and liquisolid pharmaceutical processes.
- Enhancing the solubility and aqueous dissolution profiles of cinnarizine as a water-insoluble drug model, using self-emulsifying drug delivery systems (SEDDS).
- Combining SEDDS, wet granulation and liquisolid pharmaceutical processes in order to enhance the drug release of cinnarizine from tablets in aqueous medium, using different statistical approaches.

Chapter Two: Materials and Methods

2.1. Materials:

Pure norfloxacin and pure cinnarizine were obtained from Sigma–Aldrich, UK, whereas the 15 mg commercial tablets of cinnarizine (Stugeron®) were obtained from the local market. Other powder excipients used to prepare the formulations include microcrystalline cellulose (Avicel® PH 101), (FMC Biopolymer Corp., Philadelphia, USA); colloidal silicon dioxide (Cab-O-Sil ® M-5P and Cab-O-Sil® M-5DP), (Cabot GmbH, Werk Rheinfelden, Germany); Croscarmellose sodium USP/NF/EP (Vivasol®), (CHP Carbohydrate Pirna GmbH & Co. KG, Pirna, Germany); magnesium stearate (MEDEX, Morthants).

The oils, surfactants and co-solvents/ co-surfactants that were used in solubility or dissolution tests are Propylene Glycol (Sigma- Aldrich, Germany); Sorbitan Monooleate (Span 80)(Sigma-Aldrich, Germany); Polyethylene Glycol 200 (Sigma-Aldrich, USA); Sorbitan Monolaurate (Span 20) (Sigma-Aldrich, South Korea); Synperonic ™ PE/L61 (ICI surfactants, Everberg, Belgium); Polyethylene Glycol 400 (Sigma-Aldrich, Belgium); Cremophor® EL (poly-oxy-35-castor oil), Solutol® HS 15 and Cremophor® RH40 form BASF, Germany; Pluronic® L-35 (Sigma-Aldrich, USA); Polyethylene Glycol 300 (Sigma-Aldrich, Germany); Tween 80 viscous liquid (Sigma-Aldrich, UK); Tween 20 viscous liquid (sigma-Aldrich, France),Kolliphor® RH40 (Sigma-Aldrich, UK), Poly vinyl pyrrolidone (PVP K-17) (Sigma-Aldrich, UK)(It is also used for wet granulation), Birji® S100 (Sigma-Aldrich, UK), Capryol™ 90 (Gattefossé, France),Capmul® MCM EP(Abitec, USA), Diethylene glycol mono ethyl ether (Transcutol® P)(Sigma-Aldrich, UK), Isopropyl myristate (IPM) (Sigma-Aldrich, UK) and Pharmaceutical Lactose Standard (Lactochem®) from BoRculo Whey Products U.K. Ltd., UK. Acetic acid (Sigma-Aldrich, UK) with Sodium Hydroxide pellets (Sigma-Aldrich, UK) were used for

acetate buffer solution (pH=4.0) preparation. Orthophosphoric acid HPLC electrochemical grade (Fisher Scientific, UK) with Acetonitrile HPLC grade (Fisher Scientific, UK) were used together in the norfloxacin content uniformity test, whereas the same Acetonitrile HPLC grade and 0.1 M Hydrochloric acid (0.1 M HCl) from Fisher Scientific, UK were used in cinnarizine calibration curve, stock solution preparation and solubility tests.

Finally, buffer tablets pH= 4.0(BDH Chemical Ltd., England) and Buffer tablets pH=7.0 (Asons Laboratory reagent, UK) are used for calibrating Jenway 3505 pH meter that used to measure the dissolution media. All materials were of pharmacological or analytical grade.

2.2. Pre-formulation studies:

2.2.1. Calibration curve and solubility studies (Norfloxacin):

2.2.1.1. Solvent preparation (500 ml of acetate buffer solution at pH=4.0):

Pure sodium hydroxide was weighed (5.0 g) in a small beaker and then dissolved in 10 ml distilled water to make 50% w/v sodium hydroxide solution. According to British Pharmacopoeia [56], approximately 450 ml of distilled water was poured in a 500ml beaker. Then, acetic acid (1.43 ml) was added to the beaker with mixing. Slowly adding about 0.25 ml of the sodium hydroxide solution made a mixture with continues stirring. Finally, distilled water was added until 500 ml with adjusting the pH of the solution to reach to pH= 4.0. The pH meter was calibrated using two different solvents at pH= 7.0 and pH=4.0 before each measurement.

2.2.1.2. Preparation of stock solutions:

Norfloxacin was weighed (20.0 mg) and dissolved in 100 ml of either the acetate buffer solution pH=4.0, distilled water or acetonitrile in 100 ml volumetric flask to make a concentration equals to 200 mg/l. The stock solution was mixed until the drug completely dissolved (i.e. after 30 min for the acetate buffer solution, 1 hour for acetonitrile, or 6 hours for distilled water). By applying a suitable dilution, the three different solutions were scanned between 250 nm and 400 nm wavelengths with a bandwidth equals to 1.5 nm by a double beam UV/Vis spectrophotometer (Nicolet Evolution 300, Thermo electron corporation with Vision pro version 2.03 software) to indicate the suitable drug wavelength peaks for each stock solution. The norfloxacin peak wavelength was 318 nm for acetonitrile solution, 321 nm for distilled water and 315 nm for acetate buffer solution (pH=4). The reason of the drug wavelength shifting is the difference in the polarity of each solvent [60].

2.2.1.3. Serial dilution preparation:

Serial dilution was prepared by taking 7.5 ml, 5 ml, 2.5 ml, 1.25 ml, 0.5 ml and 0.05 ml from the stock solution and added them to 42.5 ml, 45 ml, 47.5 ml, 48.75 ml, 49.5 ml and 49.95 ml of the solvent used to prepare the stock solution in 50 ml volumetric flask to give solutions with concentrations 30 mg/l, 20 mg/l, 10 mg/l, 5 mg/l, 2 mg/l and 0.2 mg/l, respectively. The calibration curve construction was repeated three times.

2.2.1.4. Solubility studies:

The solubility of norfloxacin in several surfactants, which are PEG200, PEG300, PEG400, Span 20, Span 80, Tween 20, Tween 80, Synperonic ^{TM} PE/L61,

Pluronic L-35, Propylene Glycol and Cremophor® EL as well as distilled water, was performed to evaluate the solubility of the non-volatile liquid vehicles as solvent and suspending agents for norfloxacin. Saturated solutions were prepared by adding excess amount of norfloxacin into 1 mL of each liquid vehicle. The resulting solutions were sealed and kept at room temperature (21 ^{o}C) and body temperature (37 ^{o} C) for 72 h. After this period, the solutions were centrifuged using a centrifuge rotor (Mikro 12-24, Hettich, Germany) for 10 min, at 4000 rpm. The supernatants were transferred to 1 ml Eppendorf tubes and re-centrifuged until no drug particles precipitate. The drug concentration in each supernatant was determined using a single beam UV/Vis spectrophotometer (Model M501, Camspec LTD, Cambridge, UK) at 318 nm after dilution in acetonitrile as appropriate. The concentration of norfloxacin in each liquid vehicle was calculated based on the calibration curve of norfloxacin that constructed according to the procedures mentioned in section 2.2.1.3, by substituting y values in the following equation with the obtained absorbance in order to calculate the concentration in mg/L.

$$y = 0.0398\,x - 0.0032$$

2.2.2. Calibration curve and solubility studies (Cinnarizine):

2.2.2.1. Preparation of stock solutions:

Cinnarizine pure powder (15.0 mg) was weighed and dissolved in 100 ml of 0.1 M Hydrochloric acid or acetonitrile solutions. The stock solution was sonicated for 15 minutes (0.1M HCl) or 30 minutes (acetonitrile) until the drug completely dissolved. By applying a suitable dilution, the solution was scanned between 200 nm and 400 nm wavelengths with a bandwidth equals 1.0 nm by a UV/Vis spectrophotometer

(Model M501, Camspec Ltd., Cambridge, UK) to determine the maximum wavelength peaks for the stock solution. The peak wavelength was 253 nm for HCl stock solution and 249 nm for acetonitrile stock solution. The solubility of the drug in the solvent was checked by measuring the absorbance at the relevant wavelengths.

2.2.2.2. Serial dilution preparation:

Serial dilution was prepared by taking 6 ml, 5 ml, 2.5 ml, 1 ml, 0.25 ml and 0.05 ml from the stock solutions and add them to 44 ml, 45 ml, 47.5 ml, 49 ml, 49.75 ml and 49.95 ml of the relevant solvent in 50 ml volumetric flask to give solutions with concentration 18 mg/l, 15 mg/l, 7.5 mg/l, 3 mg/l, 0.75 mg/l and 0.15 mg/l, respectively. The calibration curve construction was repeated three times.

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2.2.2.3. Solubility studies:

Cinnarizine as pure powder were dissolved in several surfactants, co-solvents and fatty acids, which are PEG200, PEG300, PEG400, Span 20, Span 80, Tween 20, Tween 80, Synperonic™ PE/L61, Pluronic® L-35, Propylene Glycol (PG), Cremophor® EL, Kolliphor® RH40, Isopropyl myristate (IPM), Transcutol® P, Capmul® MCM EP and Capryol™ 90, in order to study the drug solubility. Saturated solutions were prepared by adding excess amount of cinnarizine into 1 ml of either surfactant or fatty acid. The resulting liquids were sealed and kept at room temperature (21 °C) and at 37 °C for 72 h. After this period, the solutions were centrifuged using a centrifuge rotor (Mikro 12–24, Hettich, Germany) for 10 min, at 4000 rpm. The supernatants were transferred to 1 ml Eppendorf tubes and

re-centrifuged until no drug particles precipitate. The drug concentration in each supernatant was determined using a single beam UV/Vis spectrophotometer (Model M501, Camspec LTD, Cambridge, UK) at 249 nm after dilution in acetonitrile as appropriate. The concentration of cinnarizine in each liquid vehicle was calculated based on the calibration curve of cinnarizine dissolved in acetonitrile.

2.2.3. Flowability studies and determination of optimal flowable liquid-retention potential (ϕ-value):

2.2.3.1. Classical liquisolid formulations (Chapter 3):

The angle of slide measurement was used to determine the optimal flowable liquid-retention potential (ϕ-value) of each powder excipient (Avicel® PH 101 and Cab-O-Sil® M-5DP) with Synperonic ™ PE/L61 and PEG200. Each powder excipient (2.5 g) was mixed with increasing amount of the two non-volatile liquid vehicles, and the resulting admixture was placed on an edge of a polished metal plate, tilted gradually until the admixture starts to slide. The angle of the plate with the horizontal surface is defined the angle of slide. The ϕ-value of Avicel® PH 101 and Cab-O-Sil® M-5DP in different concentrations of liquid vehicles is calculated based on the following equation:

ϕ-value = weight of the liquid vehicle/weight of solid

The calculated ϕ-values against the resulting angle of slides were plotted to select the optimum ϕ-value of the powder excipient in the corresponding liquid vehicle at 33º. However, all corresponding angles were less than 33º, so the nearly highest

angle was selected to represent the optimum flowability number [14]. The results are summarized in Table 2-2, Figure 2-1 and Figure 2-2.

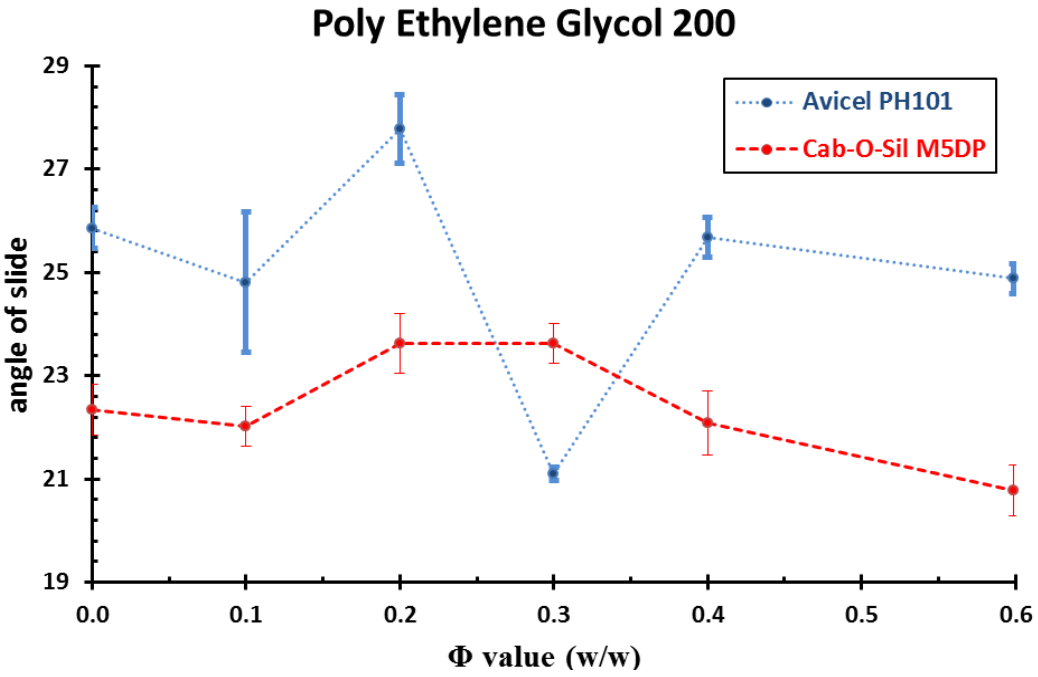


Figure 2-1: The optimum flowability value for PEG200 and Avicel® PH 101 admixture (0.2) and PEG200 with Cab-O-Sil® M-5DP admixture (0.2).

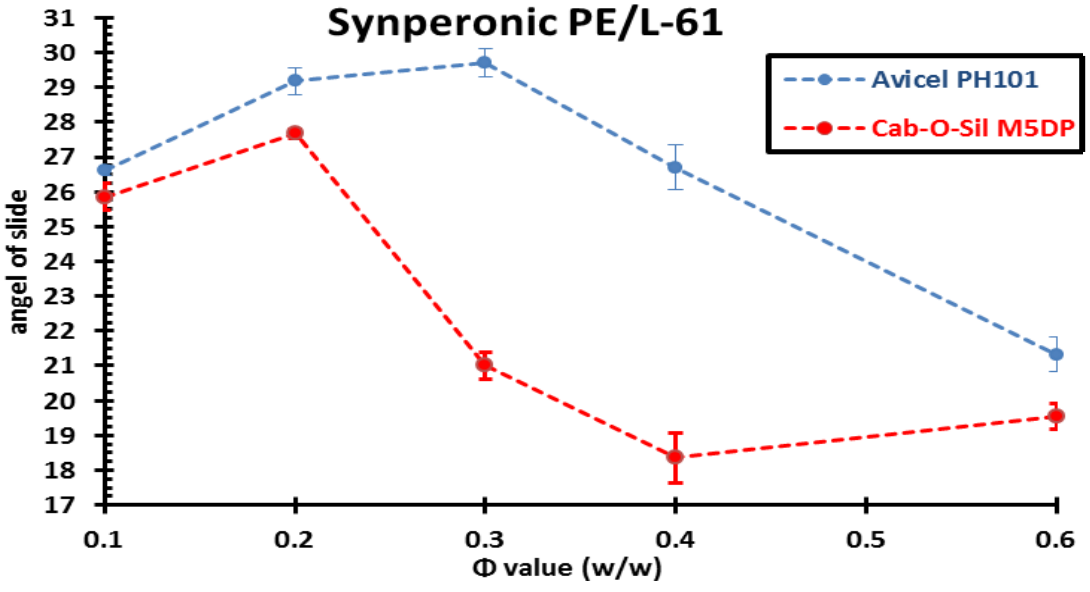


Figure 2-2: The optimum flowability value for Synperonic™ PE/L-61 and Avicel® PH 101 admixture (0.3) and Synperonic™ PE/L-61 with Cab-O-Sil® M-5DP admixture (0.2)

2.2.3.2. Wet granulated liquisolid formulations (Chapter 4 &Chapter 5):

Specific amount of distilled water or 10% w/w PVP solution (i.e. 1 g of the PVP powder to 9 g of water and keep the solution in the water bath at 60 ^{o}C until the powder completely dissolved, the evaporated water was calculated and add to the mixture in order to obtain an accurate concentration) were added to powder systems consisting of Avicel® PH 101and Cab-O-Sil® M-5P at specific R-values, which is equal to weight of carrier on weight of coating, so that the weight of water or the PVP solution is equal to the half weight of the powder system. Then, liquid vehicle (PEG200 or Synperonic™ PE/L-61) was added to the wet mass system, depending on the CW (w/w) values, which is the amount of liquid vehicle divided by the amount of the solid materials(in the case of PVP granulation, the amount of PVP powder was added to the total amount of the solid materials) . After weighing the ingredients, they are mixed in a mortar and pestle for 3 minutes and then sieved with a mesh size sieve of 1000 micrometres. After that, the wet granulated powder is put inside the oven at 80 ^{o}C (+/- 5 ^{o}C) for 120 minutes. The dried granules are passed through a sieve with mesh size of 710 micrometres. Finally, angle of slide was used to evaluate the flowability of the prepared mixtures in term of the increasing the amount of CW (w/w). The level of acceptable flowability was determined at 33^{0}. The powdered systems after preparation are placed on a polished metal plate. The plate was tilted gradually until the powder was about to slide. Then, the angle that was formed between the plate and the horizontal surface was known to be the “angle of slide (θ)”. Each powder system measurement was repeated three times in order to record the averages and standard deviations [61].

2.2.4. Compressibility studies and determination of optimal compressibility liquid-retention potential (ΨLf):

2.2.4.1. Classical liquisolid formulations (Chapter 3):

Powder systems consisting of Avicel® PH 101 and Cab-O-Sil® M-5DP at different excipient ratios; R= 10 and R=20; where R equals to the weight of Avicel® PH 101divided by weight of Cab-O-Sil® M-5DP were prepared with increasing amount of Synperonic™ PE/L-61 . Firstly, the mixtures without the liquid vehicle were compressed by Manesty Type F3 single punch compactor at a fixed die volume and a compression force to give the maximum tablet hardness, which are measured by Schleuniger-2E hardness tester. Then, the liquid vehicle was added gradually to give different liquid/solid weight compositions (CW). The pactisity (Ω) of each admixture is calculated by dividing the average hardness of tablets (KgF) on the average weight of the crushed tablets (g). By determining the average liquid content of the crushed compacts and calculating the net liquid/solid weight composition (CW) of the crushed liquid/powder admixture, a plot of CW against log-pactisity to determine the characteristic intrinsic pactisity (Ω_o) as an intercept and sponge index (σ_0) of the powder system, where

$$\log \Omega = \log \Omega o - \sigma_0 * CW$$

The compressible liquid retention potential (Ψ-number) of the powder system (Ψmix) was calculated according to the following equation:

$$\Psi mix = \frac{\log \Omega o - \log 20}{\sigma_0}$$

Finally, by calculating the $\Psi\mathrm{mix}$ value for each powder system, the compressible liquid-load factor (ΨLf) of the mixture of Synperonic ™ PE/L-61 with powder excipient (Avicel® PH 101 and Cab-O-Sil® M-5DP) at specific excipient ratios (R) was determined according to the following equation:

$$\Psi Lf = \Psi\mathrm{mix}\,(1 + \frac{1}{\mathrm{R}})$$

This method was applied simulating Liquisolid Compressibility (LSC) Test [6].

2.2.4.2. Water granulated liquisolid formulations (chapter 4):

The water granulation formulations were prepared by the same method mentioned in the section of flowability studies. The methodology that is used for calculating the average pactisity is used here as well so that it is possible to compare the changes in the Log pactisity values with the change of CW for both liquid vehicles (PEG200 and Synperonic ™ PE/L-61) in the case of water granulation. The plot of the reciprocal R values with compressible liquid-load factor (ΨLf) is applied in order to obtain a liner equation so that it is possible to calculate the amount of carrier and coating at any R value in the range of the equation.

2.2.4.3. PVP-K17 granulated liquisolid formulations (chapter 5):

The effect of PVP concentration on the pactisity values was studied by preparing wet granulation formulations at a specific R and CW values with changing in the PVP solution concentrations for the both liquid vehicles (PEG200 and Synperonic ™ PE/L-61). The method that is used for preparing wet granulation formulation and the one is used for calculating the average pactisity do not change. Then, a comparison between the effect of water and PVP-K17 at 10% w/w on the pactisity

when changing the CW between the amount of PEG200 and the amount of solid materials at R = 6.59 and R =15. Finally, the plot of the reciprocal R values with compressible liquid-load factor (ΨLf) is applied in order to obtain a liner equation so that it is possible to calculate the amount of carrier and coating at any R value in the range of the equation when using PEG200 as a liquid vehicle and 10 % w/w PVP-K17 solution as a liquid binder.

2.2.5. Construction of ternary phase diagram to screening SEDDS systems:

The purpose of this study is to find out the best self-emulsifying drug delivery system (SEDDS) that provides the highest percentage of the drug release in an aqueous dissolution medium. The existences of SEDDS were identified by using a simplex ternary phase mixture design for formulae containing oil, surfactant and co-solvent; each one of them represents an apex of the triangle. Three ternary phase diagrams were constructed with different types of the compositions; Capryol™ 90, Kolliphor® RH40 and Transcutol® P for the first one, IPM, Kolliphor® RH40 and Transcutol® P for the second one and Capmul® MCM EP, Kolliphor® RH40 and PEG400 for the third one. For each diagram, ten ternary systems, represented in Table 2-5 (from formulation F35 to F41 and from F48 to F51 plus F27, F30 and F31), and in Table 2-6 (from formulations F1 to F10) with a fixed liquid medication concentration (3.0% w/w for 15 mg active ingredient of cinnarizine) of oil, surfactant and co-solvent were prepared so that any formulae were always added to 100% for its components (Figure 2-3). Each formula was prepared by weighing the relative amount of the components and then was mixed with a gentle heating at 40 ^{o} C to make a homogeneous mixture. After that, the weighed amount of the drug powder dissolved with the mixture system by mixing and heating at 60 ^{o} C until it is completely dissolved.

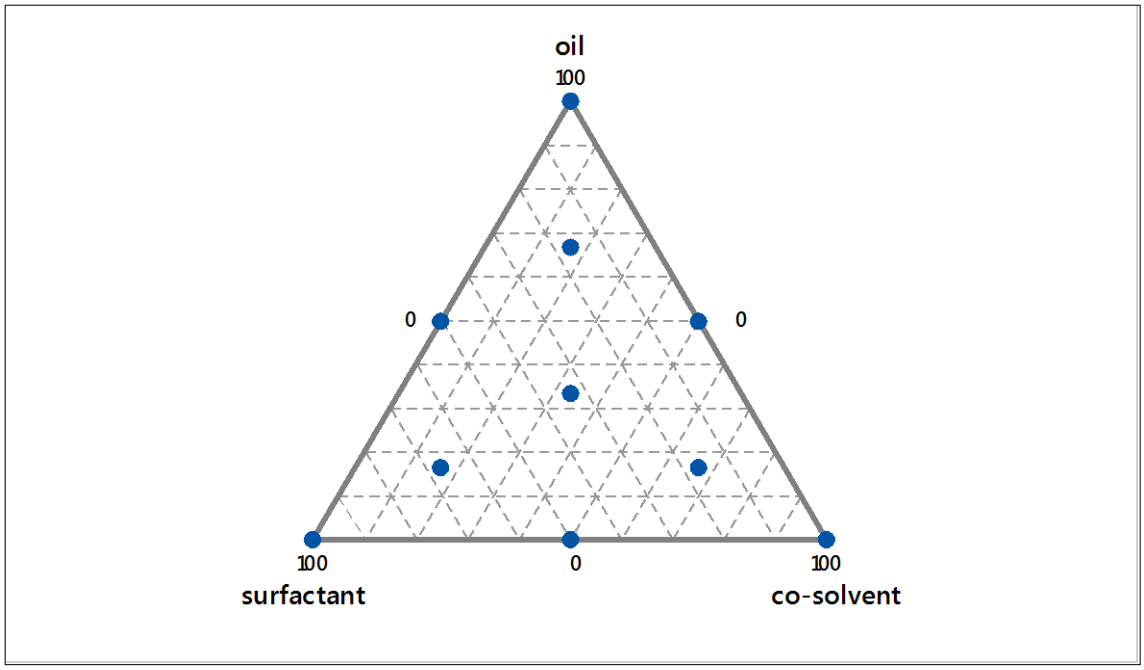


Figure 2-3: Ternary phase diagram plot shows the position of the prepared formulae according to simplex mixture design with ten points.

2.2.6. Experimental Design:

In order to find the best set of values, statistical central composite design was selected so that it is possible to build a mathematical approach in order to find the optimum response according to a set of factors and levels. Multiple linear regression analysis was used to develop the polynomial model, depending on the statistical significance of the variables (X) and their interactions on the response (Y). This allows predicting the response of log pactisity (KgF/g) (Y) in terms of the factor CW (w/w) (X1) and the percentage of water as a liquid binder (Water (w/w)) (X2) for SEDDS wet granulated liquisolid tablets. As there are two factors, the design is built to make thirteen runs as follows;

The cube points (2^k points, where k is the number of factors), which are located at the corner of the cube. These points evaluate the estimation of linearity and interaction effects. However, they are not used for estimation of curvature.

The centre point, which is located in the middle of the cube and it is repeated 4 times. These points are to check the presence of the curvature. However, they do not for quadratic estimation.

The axial points, which are the points that lay outside the surface of the cube coming from the centre point with a distance ($\alpha = \sqrt{2}$). They are usually used to determine the quadratic terms.

All points and their distributions are represented in Figure 2-4.

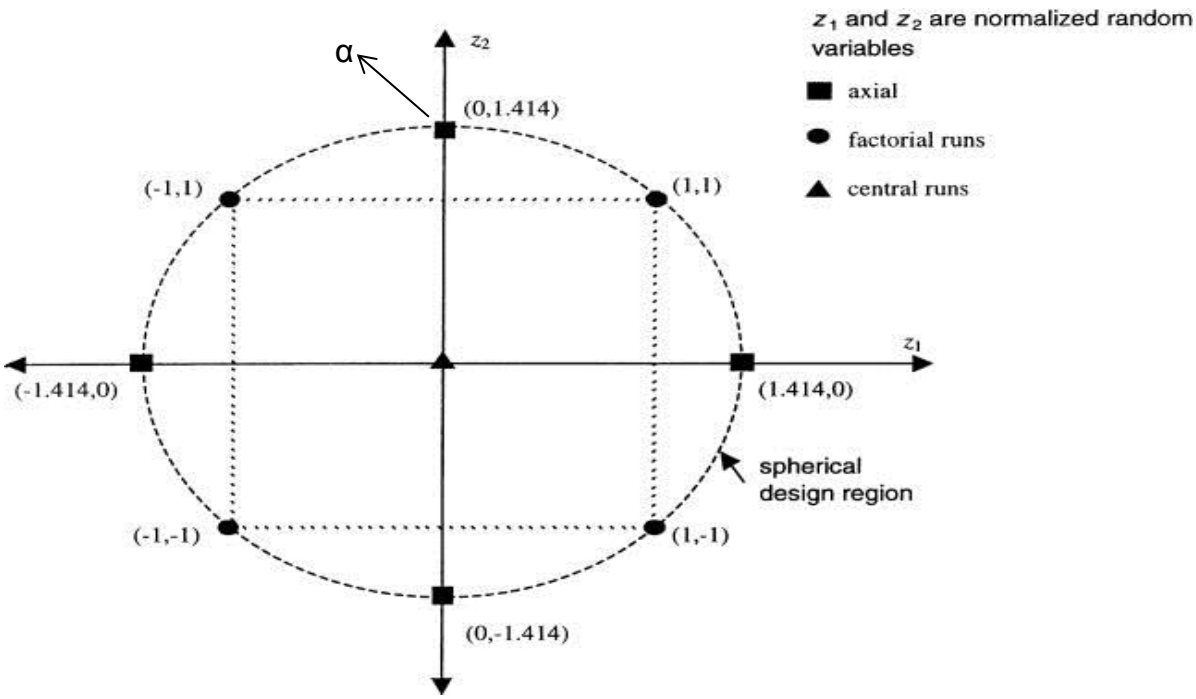


Figure 2-4: Central composite design for two factors and the distribution of its runs (Z1 and Z2 are normalized random variables of X1 and X2, respectively).

The independent factors, their levels and the analysed dependent response are shown in Table 2-1. The selected levels are within practical use and were chosen to have a measurable effect on the response. The statistical experimental design was generated, evaluated for the quality of fit of the model and the constant and

regression coefficients were calculated using the Minitab software (Version 17.2.1).

Table 2-1: Variables in central composite design and the true values of the levels.

Variables name	Used levels				
Independent variables	$-\sqrt{2}$	-1	0	+1	$+\sqrt{2}$
X1 : CW (w/w)	0.209	0.250	0.350	0.450	0.491
X2: Water (w/w)	0.217	0.300	0.500	0.700	0.783
Dependent variable					
Y: Log pactisity (KgF/g)					

Finally, the details about the components of the formulations is mentioned in Table 2-6 from formula F17 to F29, and the details about the formulations were used for model validation in Table 2-6 from formula F30 to F33.

2.3. Liquisolid formulations and compacts preparations:

2.3.1. Classical liquisolid formulations (chapter 3):

The calculated amounts of both carrier and coating materials in each liquisolid formula were determined according to the flowability numbers for the formulations containing PEG200 and compressibility liquid load factor for the Synperonic ™ PE/L-61 formulations. The reason for choosing the compressibility liquid load factor in these formulations is the lower value obtained comparing with flowability liquid load factor for the same formulations. However, this is not applied for PEG200 formulations due to the ability to compress the powder at flowability liquid load factor and obtain acceptable compressibility compacts, which means it is less

than the corresponding compressibility liquid load factor for the same formulations [6].

The equation used to calculate the flowability liquid load factor is:

$\Phi Lf = \phi_{car} + \phi_{co}\,(\frac{1}{R})$, where $\phi_{car}\ and\ \phi_{co}$ are the flowability number of the carrier and coating, respectively, which are determined from the highest angle of slide under 33^0.

The excipient ratio (R) was chosen to be either 10 or 20 for all liquisolid formulations. Moreover, 20 mg of norfloxacin active ingredient was selected to be in each tablet. As a result, the required amount of liquid medication (W) is calculated depending on drug concentration in the liquid medication (i.e. 20% w/w or 40% w/w). After determining the liquid load factor, the desired amount of carrier can be calculated by applying the following equation: $Lf = \frac{W}{Q}$ and the specific amount of coating is from R= Q/q. Liquisolid and conventional formulations are summarised in Table 2-2.

The detailed procedure for liquisolid formulation preparation is as follows; firstly, pure norfloxacin was dispersed in the liquid vehicle (PEG200 or Synperonic ™ PE/L61) to form a liquid medication. Then, the carrier (Avicel® PH 101) and the coating (Cab-O-Sil® M-5DP) excipients were added to the liquid medication with continuous mixing by mortar and pestle until obtaining a dry powder mixture. Carmellose sodium disintegrant (5% w/w of the unit dose) and magnesium stearate lubricant (1% w/w of the unit dose) were added to the liquisolid mixture with continuous mixing until reach to homogeneous mixture.

Finally, all formulae were compacted into tablets using the single punch tablet press with acceptable level of hardness. For high unit dose weight, each sample unit was divided into 2 or 4 tablets so that they contain 20 mg of norfloxacin. The reason for this is to ensure that each tablet is within a reasonable size and hardness.

By using mortar and pestle, the conventional norfloxacin tablets were prepared by mixing carrier and coating (R=20) with 20 mg of the drug and with the same percentages of lubricant and disintegrant. The resulting powder mixture was directly compressed into tablets through the single punch compactor.

Table 2-2: Components of the liquisolid formulations that used in chapter 3.

Formula	non-volatile liquid vehicle	Liquid medication (%w/w)	R value	liquid vehicle (mg)	Drug (mg)	Carrier(mg)	coating (mg)	liquid load factor	Disintegrant mg (~ %5)	lubricant (mg) (~%1)	unit dose (mg)
F1	PEG 200	20	10	80	20	454.6	45.45	0.22	31.91	6.38	638.3
F2	PEG 200	20	20	80	20	476.2	23.81	0.21	31.91	6.38	638.3
F3	PEG 200	40	10	30	20	227.3	22.73	0.22	15.96	3.19	319.2
F4	PEG 200	40	20	30	20	238.1	11.90	0.21	15.96	3.19	319.2
F5	S-L-61*	20	10	80	20	716.9	71.69	0.14	47.27	9.45	945.4
F6	S-L-61*	20	20	80	20	962.6	48.13	0.10	59.08	11.82	1181.7
F7	S-L-61*	40	10	30	20	358.5	35.85	0.14	23.63	4.73	472.7
F8	S-L-61*	40	20	30	20	481.3	24.07	0.10	29.54	5.91	590.8
conventional	-	-	-	-	20	254.5	25.50	-	16.00	3.20	319.2

*Synperonic ^{TM} PE/L-61

2.3.2. Wet granulated liquisolid formulations (chapter 4 and 5):

Norfloxacin wet granulated liquisolid formulations were prepared using PEG200 or Synperonic ™ PE/L61 as liquid vehicles, with 40% or 20 % w/w liquid medication concentrations. To prepare one tablet, the first step was to weigh 20mg of norfloxacin and dispersed in the liquid vehicle (PEG 200 or Synperonic ™ PE/L61) with continuous mixing using pestle and mortar. The mixing process was performed until drug particles dispersed completely. After that, the calculated amount of liquid binder (water or 10%w/w PVP-K17 solution) is added to the liquid medication with continuous mixing. This is then followed by the gradual addition of the appropriate amount of carrier which was Avicel® PH 101.Following this, the Silica, which acts as a coating material, is added to convert the wet mixture into dry powder under continuous mixing. The carrier and coating materials can be calculated from the equation of excipient ratios (R) and the equation of the load factor, which is in the case of water granulation, the following equations were used:

$\Psi Lf = 0.5343 \times \frac{1}{R} + 0.3737$ for PEG200 water granulated formulations, and

$\Psi Lf = 0.4139 \times \frac{1}{R} + 0.2868$ for Synperonic ™ PE/L-61 water granulated formulations.

When 10 % w/w PVP-K17 solution was used as a liquid binder, the following equation was used:

$\Psi Lf = 0.8904 \times \frac{1}{R} + 0.3247$ For PEG200 PVP-K17 granulated formulations.

The amount of the binder solution is equal to the sum of the weight of the carrier and coating divided by two. Then, 5% w/w carmellose sodium and 1% w/w of magnesium stearate are added into the admixture. The mixing will continue for 3 minutes before the powder system is sieved on a 1000 µm mesh size sieve. After that, the wet granulated liquisolid formulations are put inside the oven at 80 ^{o}C (+/- 5 ^{o}C) for 120 minutes. Then, the dried granules are passed through another sieve (710 µm). Finally, all formulations were compacted into tablets using the single punch tablet press with acceptable level of hardness. For high unit dose weight, each sample unit was divided into smaller tablet weight so that they contain 20 mg of norfloxacin. The reason for this is to ensure that each tablet is within a reasonable size and hardness.

Table 2-3 and Table 2-4 represent all the formulations that are used in chapter 4 and chapter 5, respectively. When the liquid binder solution weight is equal to 0, this means that the formulation is prepared in a classical methodology (Table 2-2), whereas when the PVP- K17 powder weight is equal to 0, this means that water was used as a liquid binder (Table 2-3). Some formulations were used the load factor of the classical formulations to prepare wet granulated ones. The aim of this is to see the effect of the changing the amount of carrier and coating on the dissolution rate.

Table 2-3: Components of the liquisolid formulations that used in chapter 4.

Formula	non-volatile liquid vehicle	Liquid medication (%w/w)	R value	liquid vehicle (mg)	Drug (mg)	carrier (mg)	coating (mg)	liquid load factor	Disintegrant (mg) (~ %5)	Lubricant (mg) (~%1)	Liquid binder solution weight (mg)	unit dose (mg)
F1	PEG200	20	10	80	20	454.6	45.45	0.2200	31.91	6.38	0.00	638.30
F2	PEG200	20	20	80	20	476.2	23.81	0.2100	31.91	6.38	0.00	638.30
F3	PEG 200	40	10	30	20	227.3	22.73	0.2200	15.96	3.19	0.00	319.15
F4	PEG 200	40	20	30	20	238.1	11.90	0.2100	15.96	3.19	0.00	319.15
F5	PEG200	20	10	80	20	454.6	45.45	0.2200	31.91	6.38	250	638.30
F6	PEG200	20	20	80	20	476.2	23.81	0.2100	31.91	6.38	250	638.30
F7	PEG 200	40	10	30	20	227.3	22.73	0.2200	15.96	3.19	125	319.15
F8	PEG 200	40	20	30	20	238.1	11.90	0.2100	15.96	3.19	125	319.15
F9	PEG 200	20	10	80	20	234.0	23.40	0.4271	19.00	3.8	129	380.20
F10	PEG 200	20	20	80	20	250.0	12.50	0.4000	19.28	3.85	131	385.63
F11	PEG 200	40	10	30	20	117.0	11.70	0.4271	9.50	1.9	64.4	190.10
F12	PEG 200	40	20	30	20	125.0	6.250	0.4000	9.64	1.93	65.6	192.82
F13	S-L-61	20	10	80	20	716.9	71.69	0.1394	47.27	9.45	0.00	945.35
F14	S-L-61	20	20	80	20	962.6	48.13	0.1038	59.08	11.82	0.00	1181.7
F15	S-L-61	40	10	30	20	358.5	35.85	0.1394	23.63	4.73	0.00	472.67
F16	S-L-61	40	20	30	20	481.3	24.07	0.1038	29.54	5.91	0.00	590.84
F17	S-L-61	20	10	80	20	716.9	71.69	0.1394	47.27	9.45	394	945.35
F18	S-L-61	20	20	80	20	962.6	48.13	0.1038	59.08	11.82	505	1181.7
F19	S-L-61	40	10	30	20	358.5	35.85	0.1394	23.63	4.73	376	472.67
F20	S-L-61	40	20	30	20	481.3	24.07	0.1038	29.54	5.91	253	590.84
F21	S-L-61	20	10	80	20	335.2	33.50	0.2984*	24.93	4.99	184	498.59
F22	S-L-61	20	20	80	20	341.5	17.00	0.2929*	24.39	4.88	179	487.77
F23	S-L-61	40	10	30	20	167.6	16.76	0.2984*	12.46	2.49	92.2	249.30
F24	S-L-61	40	20	30	20	170.7	8.535	0.2929*	12.20	2.44	89.6	243.80

*The load factor in these formulations is substituted with the value of the compressibility mixture due to the sensitivity of Synperonic ^{TM} PE/L61 to the reciprocal excipient ratio factor as a decreasing variable of the value of the dry powder.

Table 2-4: Components of the liquisolid formulations that used in chapter 5.

Formula	liquid vehicle	Liquid Medication (%w/w)	R value	liquid vehicle (mg)	Drug (mg)	carrier (mg)	coating (mg)	liquid load factor	Disintegrant mg (~ %5)	Lubricant (mg) (~%1)	PVP K17 Powder weight (mg)	Liquid Binder solution weight (mg)	unit dose (mg)
F1	PEG 200	20	10	80	20	241.7	24.17	0.414	20.16	4.03	13.29	132.9	403.34
F2	PEG 200	20	20	80	20	270.8	13.5	0.369	21.20	4.24	14.2	142.2	423.98
F3	PEG 200	40	10	30	20	120.9	12.085	0.414	10.08	2.01	6.65	66.47	201.68
F4	PEG 200	40	20	30	20	135.4	6.771	0.369	10.60	2.12	7.10	71.01	212.01
F5	PEG 200	20	10	80	20	454.6	45.45	0.220	33.20	6.65	25.0	250.0	664.85
F6	PEG 200	20	20	80	20	476.2	23.81	0.210	33.20	6.65	25.0	250.0	664.85
F7	PEG 200	40	10	30	20	227.3	22.73	0.220	16.60	3.40	12.5	125.0	332.50
F8	PEG 200	40	20	30	20	238.1	11.90	0.210	16.60	3.40	12.5	125.0	332.50
F9	PEG 200	20	10	80	20	234.0	23.4	0.427	19.00	3.80	0.00	128.7	380.20
F10	PEG 200	20	20	80	20	250.0	12.5	0.400	19.28	3.85	0.00	131.3	385.63
F11	PEG 200	40	10	30	20	117.0	11.7	0.427	9.50	1.90	0.00	64.35	190.10
F12	PEG 200	40	20	30	20	125.0	6.25	0.400	9.64	1.93	0.00	65.63	192.82
F13	PEG 200	20	10	80	20	454.6	45.45	0.220	31.91	6.38	0.00	250.0	638.30
F14	PEG 200	20	20	80	20	476.2	23.81	0.210	31.91	6.38	0.00	250.0	638.30
F15	PEG 200	40	10	30	20	227.3	22.73	0.220	15.96	3.19	0.00	125.0	319.15
F16	PEG 200	40	20	30	20	238.1	11.90	0.210	15.96	3.19	0.00	125.0	319.15

2.4. Pre-compression studies:

2.4.1. Determination of flow property:

Assessing the flowability of prepared powders depends on Carr's Compressibility Index (CI%) and Hausner's ratio (H ratio). They are calculated from determination of the relative poured bulk density (P_b) and the tapped density (P_t) of each powder formulation. The weight of each powder formulation was recorded and then the powder was poured into a 250 mL cylinder on a tap volumeter (JV1000, Copley Scientific, UK). Both poured bulk volume (V_b) and tapped volume (V_t), which is the constant volume obtained after application of a sufficient number of taps (usually after 500 taps x 3 times), are recorded. The densities are determined from dividing each weight of the powder on the relative volumes. Finally, CI% and H-ratio are calculated and evaluated depending on the criteria in the British Pharmacopoeia [56]. The equations that are used to calculate the values of CI% and H-ratio are:

$$Cl\% = 100 \times (P_t - P_b)/P_t$$

$$H - ratio = \frac{P_t}{P_b}$$

2.4.2. Differential Scanning Calorimetry (DSC):

Pure drugs and the prepared formulation powders were exposed to DSC scan via DSC Refrigerated Cooling System (Model Q1000, TA Instruments, UK). Each sample contained about 2.5-12 mg. Then, it was hermitically sealed in an aluminium pan before analysis. Two samples of Indium at the beginning and at the end of each run were used to validate the accuracy of the instrument. The

investigation of the thermal behaviour of each sample was at a scanning rate 10 ^{o} C/min, from 0 ^{o} C to 300 ^{o} C.

2.4.3. Fourier Transform Infrared Spectroscopy (FTIR):

Infrared spectra were acquired for all relative materials and prepared formulations using Spectrum BX FTIR Spectrophotometer (Perkin–Elmer, Cambridge, UK). Small amount of each sample was directly loaded into the instrument without any treatments. The frequency ranged from 4000 cm^{-1} to 650 cm^{-1} at 1.0 cm^{-1} resolution. The data was obtained by Spectrum BX series software version 5.3.1.

For further investigation of the unique behaviour of norfloxacin, IR spectra were collected for wet powder of norfloxacin, which prepared by adding one drop of distilled water (pH= 6.1) to norfloxacin powder and then compared with the dry powder, PEG200, Synperonic ^{TM} PE/L-61, the interfacial layer consisting from liquid medication of norfloxacin with either PEG200 or Synperonic ^{TM} PE/L-61 at 20 % w/w concentration for 20 mg active ingredient. The interfacial layer was collected after running the dissolution tester for 30 minutes in 750 ml of distilled water (pH=6.1) with a paddle speed 50 rpm in apparatus II at 37 ^{o} C. The samples directly uploaded to the FTIR spectrophotometer without any pre-treatment. The spectra were presented in chapter 3.

Moreover, infrared spectra were acquired for pure cinnarizine, the blank and the sample of formula F45 (Table 2-5), and the crystals that formed after one hour dissolution test, which were collected by pouring the content of the vessel on a 125 µm sieve and dried for one hour in an oven at 65 ^{o} C, and then collected to a filter paper by a brush. The data presented in chapter 6.

2.4.4. Emulsion droplet size analysis:

Formulations from F25 to F41 (Table 2-5) and formulations from F1 to F10 in Table 2-6 were prepared and then diluted to a concentration equals 15 mg/L, using distilled water (pH=6.1) in 100 ml flask. The droplet size analysis of the resulting emulsions was performed using dynamic light scattering analyser (Brookhaven Instrument Corporation, USA) at 21 ^{o} C and a 90° angle. The data are expressed as effective mean diameter and plotted using MATLAB.

2.5. Evaluation of liquisolid tablets:

2.5.1. Drug content uniformity, tablet dimensions, hardness, friability, disintegration and tensile strength tests:

2.5.1.1. Content uniformity test:

Tablets containing 20 mg of norfloxacin were weighed and crushed by mortar and pestle in order to determine the drug content in classical liquisolid, wet granulated liquisolid (water or PVP) and conventional tablets. Then, the crushed powder was dissolved in 1 L acetate buffer solution at pH=4. The solution were mixed for 1 hour and filtered. Finally, the samples were analysed for determining the drug concentration using UV spectrophotometer at 315 nm. The percentage of drug content with respect the theoretical amount was determined.

Regarding cinnarizine tablets, the same procedure of norfloxacin was applied except that the solvent is 1 L of 0.1 M hydrochloric acid, mixing for 20 minutes, and the used UV spectroscopy wavelength is 253 nm. The tablet that contains the MCM EP SEEDS mixture as a liquid vehicle was diluted by acetonitrile with a dilution factor equals 2.0.

2.5.1.2. Friability test:

Tablets friability was measured using a Comply FRV 1000 friability device. Ten tablets for every formula were weighed accurately and then rotated in the tester for 100 rounds at a speed 25 rpm. Then the tablets were de-dusted and the weight after applying the test was measured. The percentage of the friability was calculated according to the following equation:

$$\%\text{Friability} = \left(\frac{\text{weight before the test} - \text{weight after the test}}{\text{weight before the test}}\right) \times 100\%$$

2.5.1.3. Disintegration test:

Using Comply DTG200 disintegration tester, the disintegration test was performed where six tablets were placed individually in the baskets then the time for each tablet to disintegrate completely was recorded. The test was performed at 37°C in the dissolution media (distilled water).

2.5.1.4. Tensile strength, Hardness and tablet dimensions:

Ten tablet thickness and diameter were determined by micrometre (Moor and Wright, England).Tensile strengths of tablets were calculated by applying the following equation:

$$S = \frac{2P}{\Pi\ x\ dx\ t}$$

Where S (MPa) is the tensile strength, P (N) is the crushing force which determined by Schleniger-2E hardness tester, d (m) is the diameter of the tablet and t (m) is the tablet thickness.

2.5.2. *In vitro* dissolution studies:

In vitro dissolution studies were executed for pure norfloxacin, conventional and all liquisolid tablet formulations presented in Table 2-2, Table 2-3 and Table 2-4 by using USP dissolution apparatus II (Caleva 8ST Ltd., Dorset, UK). Two different dissolution media were used for all liquisolid and conventional tablets; distilled water (pH= 6.1) and the acetate buffer solution (pH=4.0). Both dissolution media volumes were 750 ml with a paddle speed 50 rpm maintained at 37 ^{o}C according to BP specifications [56]. 10 ml sample was withdrawn at time intervals of 5, 10, 15, 20, 25, 30, 45, 60 and 90 min, and the withdrawn samples were replaced with equal volumes of the dissolution medium. The drug content in each withdrawn sample was determined using UV/Vis spectrophotometer (Model M501, Camspec Ltd., Cambridge, UK) at 315 nm for acetate buffer solution and 321 nm for distilled water dissolution medium. The reported data are an average of three samples with the relevant standard deviation and the calibration curve was used to calculate the relative drug concentrations. Each sample included a number of tablets so that it contains 20 mg of the active ingredient. This idea was taken from a similar study [62].

Regarding *in vitro* dissolution studies of cinnarizine, the screening tests mentioned in chapter 6 and Table 2-5 were executed for the first 24 formulations. According to the relevant formulations, three different dissolution media were used; distilled water (pH= 6.1), 0.1 M hydrochloric acid (pH= 1.0) and phosphate buffer solution at pH = 7.2. The phosphate buffer solution was made by mixing 17.7954 g of KH_2PO4 and 47.6968 g Na_2HPO4 with distilled water in order to make 7000 ml buffer solution. Both dissolution media volumes were 1000 ml with a paddle speed 50 rpm maintained at 37 ^{o}C. The withdrawn sample system is similar to the

one applied in the case of norfloxacin. The drug content in each withdrawn sample was determined using UV/Vis spectrophotometer (Model M501, Camspec Ltd., Cambridge, UK) at 253 nm for the both dissolution media. The calibration curve was used to calculate the relative drug concentration. When the drug shows an interference with formulations, such as formulations from F35 to F41 and from F47 to F51 in Table 2-5 and all formulations mentioned in Table 2-6, two millilitres of the withdrawn samples were diluted with 2 ml of acetonitrile. The blank for the relevant formulations show no absorbance at 253 nm wavelength. Also, a standard solution consisting of 15 mg cinnarizine powder dissolved in 100 ml acetonitrile: distilled water (pH=6.1) in a percentage of (50:50), sonicated for 30 minutes and then 5 ml was taken to 50 ml of the same solvent, the maximum wavelength records at 253 nm and the average of the absorbance was 0.855, which is the same absorbance value that can be obtained from the calibration equation of the cinnarizine dissolved in 0.1 M HCl solution.

The similarity factor (f2) was used as a statistical technique to compare between the dissolution profiles.

$f_2 = 50 \times log\left\{\left[1 + (\frac{1}{n})\sum_{t=1}^{n}(R_t - T_t)^2\right]^{-0.5} \times 100\right\}$, where R_t is the reference data, T_t is the test data, n is the number of samples. If the percentage is over 50%, this means the two groups of data are similar; otherwise it is not significantly similar [63].

Table 2-5: The components of cinarizine formulations, presented in chapter 6.

Formula	surfactants	surfactant weight (mg)	Components and preparations
F1	PEG200	60	PEG200 alone =59.8 mg ; PEG200 + drug =(60.7 + 15.0) mg
F2	Synperonic TM PE/L61	60	Synperonic TM PE/L-61 alone =59.7 mg / Synperonic TM PE/L-61 + drug =(60.4 + 15.0) mg
F3	Tween 20	60	Tween 20 alone =60.0 mg / Tween 20 + drug =(60.1 + 15.0) mg
F4	PG	60	PG alone =60.2 mg / PG+ drug =(60.6 + 15.1) mg
F5	PEG400	60	PEG400 alone =60.2 mg / PEG400+ drug =(60.6 + 15.0) mg
F6	Cremophor® RH40	60	Cremophor® RH40 alone =60.1 mg / Cremophor® RH40+ drug =(60.9 + 15.1) mg
F7	Solutol® HS 15	60	Solutol® HS15 alone =60.9 mg / Solutol® HS15+drug =(60.9 + 15.2) mg with heating (60 ° C) until the drug particles disappear completely
F8	Cremophor® RH40	60	Cremophor® RH40 alone=60.5 mg/ Cremophor® RH40 + drug = (60.9+15.4) mg with heating (60 ° C)
F9	Cremophor® RH40/ Cremophor EL	30 + 30	Cremophor® RH40 + Cremophor® EL alone=30.2 + 29.4 mg/ Cremophor® RH40 + Cremophor® EL + drug = (29.3+30+14.9) mg with heating (60 ° C)
F10	Cremophor® EL/ Solutol® HS 15	30 + 30	Cremophor® EL+ Solutol® HS15 alone =30.2+30.3=60.5 mg / Cremophor® EL+ Solutol® HS15+ drug =(30.3 + 29.6+15.0) mg with heating (60 ° C)
F11	Cremophor® RH40/ Solutol® HS 15	30 +30	Cremophor® RH40+ Solutol® HS15 alone =29.6+29.7=59.3 mg / Cremophor® RH40+ Solutol® HS15+ drug =(29.6 + 29.9+15.1) mg with heating (60 ° C)
F12	Cremophor® RH40/ Solutol® HS 15/ Cremophor EL	20 + 20 + 20	Cremophor®RH40+ Solutol® HS15 + Cremophor® EL alone =20.7+20.8+19.8=60.8 mg / Cremophor® RH40+ Solutol® HS15+ Cremophor® EL+ drug =(20.8 + 19.1+20.8+14.8) mg with heating (60 ° C)

F13	Solutol® HS 15	60	Preparation of Solutol and cinnarizine at 20% w/w : Lf= 0.21/// drug: 15.0 mg, Solutol: 60 mg, lactose : 357 mg, Cab-O-Sil® M-5P: 18 mg, Croscarmellose sodium: 24 mg and Mg stearate: 4.7 mg/// practically: drug; 14.9 mg , Solutol 59.5 mg , lactose: 357.2 mg , Cab-O-Sil® M-5P 17.8 mg, Croscarmellose sodium = 24.3 mg and Mg stearate: 3.7 mg/// Blank preparation; drug : 0 mg, Solutol : 59.4 mg , lactose: 358.2 mg, Cab-O-Sil® M-5P : 18 mg, Croscarmellose sodium : 23.6 mg, Mg stearate 4.0 (practically) with heating at (60 º C). The dissolution test conditions: phosphate buffer at pH=7.2 (1 L) at 50 rpm speed and (37 º C).
F14	Cremophor® RH40	60	Preparation of Cremophor® RH40 and cinnarizine at 20% w/w : Lf= 0.21/// drug: 15.0 mg, Cremophor® RH40: 60 mg, lactose 357: mg Cab-O-Sil: 18 mg, Croscarmellose sodium: 24 mg and Mg stearate :4.7// practically: Drug: 15.0 mg , Solutol® HS 15: 60.4 mg , lactose: 358.8 mg , Cab-O-Sil: 18.6 mg, Croscarmellose sodium : 24.2 mg and Mg stearate: 4.1 mg /// Blank : Drug ; 0 mg, Cremophor® RH40 : 60.8 mg , lactose: 359.2 mg, Cab-O-Sil® M-5P : 17.8 mg, Croscarmellose sodium : 24.7mg, Mg stearate: 5.7(practically) with heating at (60 º C) and in phosphate buffer dissolution media at pH =7.2 (1 L) with 50 rpm and (37 º C).
F15	PEG 200	60	Preparation of PEG200 and cinnarizine at 20% w/w : Lf= 0.21 with heating at (60 º C) /// drug: 15.0 mg, PEG200: 60 mg, lactose: 357 mg, Cab-O-Sil: 18 mg, dis 24 mg and lubricant 4.7 practically: AI ; 14.9 mg , Solutol® HS 15: 61.5 mg , lactose: 359.8mg , Cab-O-Sil® M-5P: 17.6 mg, Croscarmellose sodium: 25 mg and Mg stearate: 4.4 mg /// Blank : no need as the PEG200 does not have absorbance at 253 nm wavelength/// dissolution test: phosphate buffer dissolution media at pH = 7.2, 50 rpm and (37 º C).
F16	Cremophor® RH 40	120	Cremophor® RH40+ drug=120.6+15.0 mg / Cremophor® RH40 alone = 119.8 mg in phosphate buffer solution at pH = 7.2 with heating at (60 º C)
F17	Cremophor® RH 40	200	Cremophor® RH40+ drug=200.4+15.0 mg / Cremophor® RH40 alone = 200.0 mg with heating at 60 º C and in phosphate buffer solution (pH= 7.2)
F18	Cremophor® RH 40	400	Cremophor® RH40+ drug=400.3+15.0 mg / Cremophor® RH40 alone = 400.6 mg with heating at 60 º C and in phosphate buffer solution (pH= 7.2)
F19	Cremophor® RH 40	120	Cremophor® RH40+ drug=120.2+15.1 mg / Cremophor® RH40 alone = 120.2 mg with heating at 60 º C and in distilled water (pH= 6.1)
F20	Cremophor® RH 40	200	Cremophor® RH40+ drug=199.8 +15.1 mg / Cremophor® RH40 alone = 199.9 mg with heating at 60 º C and in distilled water (pH= 6.1)
F21	Cremophor® RH 40	400	Cremophor® RH40+ drug=400.1 +15.1 mg / Cremophor® RH40 alone = 400.1 mg with heating at 60 º C and in distilled water (pH= 6.1)
F22	Brji® S 100	200	Brji® S 100+ drug=201.2 +15.0 mg / Brji® S 100 alone = 202.3 mg with heating at (60 º C) and in distilled water (pH= 6.1)

F23	PVP/ Cremophor® RH40	10 + 200	PVP-K17 + Cremophor® RH40 + drug=10.3 + 200.8+ 15.0 mg / PVP-K17 + Cremophor® RH40 = 10.7 + 200 mg with heating at (60 ° C) and in distilled water (pH =6.1)
F24	Cremophor RH 40	200	Blank: drug:0 mg ,Cremophor® RH40:200.6 mg, Avicel® PH 101: 997.2 mg, Cab-O-Sil® M-5P :48.3 mg , Croscarmellose sodium: 65.6 mg , Mg stearate: 13.3 mg/// practically: drug:15.0 mg ,Cremophor® RH40: 200.1 mg, Avicel® PH 101: 966.5 mg, Cab-O-Sil: 49.7 mg , Croscarmellose sodium: 65.2 mg, Mg stearate: 13 mg with heating at (60 o C) and in distilled water at pH =6.1 dissolution medium
F25	Capryol™ 90	500	Drug/ liquid medication = 15.1 mg / 499.5 mg ; blank =484.5 mg
F26	Capryol™ 90/ Transcutol® P	500	Drug/liquid medication (50:50) = 14.9 mg / 500.2 mg; blank = 486.8 mg
F27	Kolliphor® RH40	500	Drug / liquid medication = 15.1 mg /501.5 mg ; blank = 483.8 mg
F28	Capryol™ 90/ Kolliphor® RH40/ Transcutol® P	500	Drug/ liquid medication(16.66:16.66:66.67) = 15.0 mg /499.5 mg; blank = 483.5 mg
F29	Capryol™ 90/ Kolliphor® RH40	500	Drug / liquid medication (50:50) = 14.9 mg/ 499.3 mg ; blank = 485.6 mg
F30	Kolliphor® RH40/ Transcutol® P	500	Drug / liquid medication (50: 50) = 15.0 mg / 503.3 mg; blank = 486.0 mg
F31	Transcutol® P	500	Drug/ liquid medication = 15.1 mg / 500.0 mg ; blank = 484.4 mg
F32	Capryol™ 90/ Kolliphor® RH40/ Transcutol® P	500	Drug/ liquid medication(16.66:66.67:16.66) = 14.9 mg /501.2 mg; blank = 485.6 mg
F33	Capryol™ 90/ Kolliphor® RH40/ Transcutol® P	500	Drug/ liquid medication(66.67:16.66:16.66) = 15.0 mg /500.4 mg; blank = 485.3 mg
F34	Capryol™ 90/ Kolliphor® RH40/ Transcutol® P	500	Drug/ liquid medication(33.33:33.33:33.33) = 14.8 mg /501.2 mg; blank = 487.0 mg

F35	IPM	500	Drug/ liquid medication = 14.8 mg / 499.8 mg ; blank=484.1 mg
F36	IPM/ Transcutol® P	500	Drug / liquid medication (50:50) = 15.0 mg/ 500.4 mg ; blank = 484.7 mg
F37	IPM/ Kolliphor® RH40/ Transcutol® P	500	Drug/ liquid medication(66.67:16.66:16.66) = 14.8 mg /500.2 mg; blank = 485.4 mg
F38	IPM/ Kolliphor® RH40	500	Drug / liquid medication (50:50) = 15.0 mg/ 498.7 mg ; blank = 484.7 mg
F39	IPM/ Cremophor® RH40/ Transcutol® P	500	Drug/ liquid medication(16.66:66.67:16.66) = 15.3 mg /503.2 mg; blank = 485.1 mg
F40	IPM/ Kolliphor® RH40/ Transcutol® P	500	Drug/ liquid medication(16.66:16.66:66.67) = 14.9 mg /501.2 mg; blank = 485.5 mg
F41	IPM/ Kolliphor® RH40/ Transcutol® P	500	Drug/ liquid medication(33.33:33.33:33.33) = 15.0 mg /500.4 mg; blank = 484.7 mg
F42	Capryol™ 90/ Kolliphor® RH40/ Transcutol® P	100	Drug/ liquid medication(70:15:15) = 15.0 mg /100.1 mg; blank = 85.0 mg
F43	Capryol™ 90/ Kolliphor® RH40/ Transcutol® P	200	Drug/ liquid medication(70:15:15) = 15.1 mg /200.5 mg; blank = 185.9 mg
F44	Capryol™ 90/ Kolliphor® RH40/ Transcutol® P	300	Drug/ liquid medication(70:15:15) = 15.1 mg /300.0 mg; blank = 285.5 mg
F45	Capryol™ 90/ Kolliphor® RH40/ Transcutol® P	400	Drug/ liquid medication(70:15:15) = 15.0 mg /398.8 mg; blank = 385.6 mg
F46	Capryol™ 90/ Kolliphor® RH40/ Transcutol® P	500	Drug/ liquid medication(70:15:15) = 15.2 mg /501.7 mg; blank = 486.4 mg

F47	IPM/ Kolliphor® RH40/ Transcutol® P	100	Drug/ liquid medication(35:35:30) = 15.2 mg /100.1 mg; blank = 85.0 mg
F48	IPM/ Kolliphor® RH40/ Transcutol® P	200	Drug/ liquid medication(35:35:30) = 15.0 mg /200.5 mg; blank = 184.5 mg
F49	IPM/ Kolliphor® RH40/ Transcutol® P	300	Drug/ liquid medication(35:35:30) = 15.1 mg /300.6 mg; blank = 284.9 mg
F50	IPM/ Kolliphor® RH40/ Transcutol® P	400	Drug/ liquid medication(35:35:30) = 15.1 mg /400.3 mg; blank = 385.3 mg
F51	IPM/ Kolliphor® RH40/ Transcutol® P	500	Drug/ liquid medication(35:35:30) = 14.8 mg /500.4 mg; blank = 485.0 mg

Table 2-6: the components of cinnarizine formulations, presented in chapter 7

Formula	Surfactants	surfactant weight (mg)	Components and preparations
F1	Capmul® MCM EP	500	Drug / liquid medication = 14.9 mg/ 500.0 mg ; blank = 485.0 mg
F2	Capmul® MCM EP/ PEG400	500	Drug/ liquid medication(50:50) = 15.0 mg /500.3 mg; blank = 486.4 mg
F3	Kolliphor® RH40	500	Drug / liquid medication = 15.1 mg /501.5 mg ; blank = 483.8 mg
F4	Capmul® MCM EP/ Kolliphor® RH40/ PEG400	500	Drug/ liquid medication(16.7:16.7:66.6) = 15.0 mg /499.9 mg; blank = 485.5 mg
F5	Capmul® MCM EP/ Kolliphor® RH40	500	Drug/ liquid medication(50:50) = 15.2 mg /500.4 mg; blank = 485.3 mg
F6	Kolliphor® RH40/ PEG400	500	Drug/ liquid medication(50:50) = 15.1 mg /500.1 mg; blank = 484.1 mg
F7	PEG400	500	Drug/ liquid medication= 14.9 mg /500.2 mg; blank = 485.0 mg
F8	Capmul® MCM EP/ Kolliphor® RH40/ PEG400	500	Drug/ liquid medication(16.7:66.6:16.7) = 14.9 mg /499.8 mg; blank = 484.1 mg
F9	Capmul® MCM EP/ Kolliphor® RH40/ PEG400	500	Drug/ liquid medication(66.6:16.7:16.7) = 15.0 mg /499.8 mg; blank = 485.1 mg
F10	Capmul® MCM EP/ Kolliphor® RH40/ PEG400	500	Drug/ liquid medication(33.3:33.3:33.3) = 15.0 mg /485.7 mg; blank = 484.9 mg
F11	Capmul® MCM EP/ Kolliphor® RH40/ PEG400	200	Drug/ liquid medication(66.6:16.7:16.7) = 15.0 mg /200.8 mg

F12	Capmul® MCM EP/ Kolliphor® RH40/ PEG400	250	Drug/ liquid medication(66.6:16.7:16.7) = 15.0 mg /250.5 mg
F13	Capmul® MCM EP/ Kolliphor® RH40/ PEG400	300	Drug/ liquid medication(66.6:16.7:16.7) = 15.0 mg /299.4 mg
F14	Capmul® MCM EP/ Kolliphor® RH40/ PEG400	350	Drug/ liquid medication(66.6:16.7:16.7) = 15.0 mg /350.8 mg
F15	Capmul® MCM EP/ Kolliphor® RH40/ PEG400	400	Drug/ liquid medication(66.6:16.7:16.7) = 15.0 mg /400.4 mg
F16	Capmul® MCM EP/ Kolliphor® RH40/ PEG400	450	Drug/ liquid medication(66.6:16.7:16.7) = 15.0 mg /450.0 mg
F17	Capmul® MCM EP/ Kolliphor® RH40/ PEG400	749.6	Liquid medication = 0.7496 g, Avicel® PH 101 = 3.0006 g , water = 0.9004 g ;(CW/Water%= 0.25/0.3)
F18	Capmul® MCM EP/ Kolliphor® RH40/ PEG400	1350.0	Liquid medication = 1.3500 g, Avicel® PH 101 = 3.0008 g , water = 0.8994 g;(CW/Water%= 0.45/0.3)
F19	Capmul® MCM EP/ Kolliphor® RH40/ PEG400	750.4	Liquid medication = 0.7504 g, Avicel® PH 101 = 2.9995 g , water = 2.1015 g;(CW/Water%= 0.25/0.7)
F20	Capmul® MCM EP/ Kolliphor® RH40/ PEG400	1350.0	Liquid medication = 1.3500 g, Avicel® PH 101 = 3.0003 g , water = 2.0992 g;(CW/Water%= 0.45/0.7)
F21	Capmul® MCM EP/ Kolliphor® RH40/ PEG400	628.0	Liquid medication = 0.6280 g, Avicel® PH 101 = 3.0018 g , water = 1.5000 g;(CW/Water%= 0.209/0.5)
F22	Capmul® MCM EP/ Kolliphor® RH40/ PEG400	1475.3	Liquid medication = 1.4753 g, Avicel® PH 101 = 3.0007 g , water = 1.5030 g;(CW/Water%= 0.491/0.5)
F23	Capmul® MCM EP/ Kolliphor® RH40/ PEG400	1049.9	Liquid medication = 1.0499 g, Avicel® PH 101 = 2.9990 g , water = 1.5008 g;(CW/Water%= 0.35/0.217)
F24	Capmul® MCM EP/ Kolliphor® RH40/ PEG400	1049.6	Liquid medication = 1.0496 g, Avicel® PH 101 = 2.9995 g , water = 2.3507 g;(CW/Water%= 0.35/0.783)
F25	Capmul® MCM EP/ Kolliphor® RH40/ PEG400	1050.4	Liquid medication = 1.0504 g, Avicel® PH 101 = 3.0014 g , water = 1.5005 g;(CW/Water%= 0.35/0.5)

F26	Capmul® MCM EP/ Kolliphor® RH40/ PEG400	1049.8	Liquid medication = 1.0498 g, Avicel® PH 101 = 3.0012 g , water = 1.5024 g;(CW/Water%= 0.35/0.5)
F27	Capmul® MCM EP/ Kolliphor® RH40/ PEG400	1049.8	Liquid medication = 1.04980 g, Avicel® PH 101 = 3.0021 g , water =1.5007 g;(CW/Water%= 0.35/0.5)
F28	Capmul® MCM EP/ Kolliphor® RH40/ PEG400	1049.7	Liquid medication = 1.0497 g, Avicel® PH 101 = 3.0002 g , water = 1.5004 g;(CW/Water%= 0.35/0.5)
F29	Capmul® MCM EP/ Kolliphor® RH40/ PEG400	1050.1	Liquid medication = 1.0501 g, Avicel® PH 101 = 3.0005 g , water = 1.5001 g;(CW/Water%= 0.35/0.5)
F30	Capmul® MCM EP/ Kolliphor® RH40/ PEG400	749.6	Liquid medication = 0.7496 g, Avicel® PH 101 = 2.9998 g , water = 1.2024 g;(CW/Water%= 0.25/0.4)
F31	Capmul® MCM EP/ Kolliphor® RH40/ PEG400	750.4	Liquid medication = 0.7504 g, Avicel® PH 101 = 3.0005 g , water = 1.8001 g;(CW/Water%= 0.25/0.6)
F32	Capmul® MCM EP/ Kolliphor® RH40/ PEG400	1350.3	Liquid medication = 1.3503 g, Avicel® PH 101 = 3.0005 g , water = 1.1995 g;(CW/Water%= 0.45/0.4)
F33	Capmul® MCM EP/ Kolliphor® RH40/ PEG400	900.0	Liquid medication = 0.9000 g, Avicel® PH 101 = 3.0015 g , water = 1.8002 g;(CW/Water%= 0.30/0.6)
F34	Capmul® MCM EP/ Kolliphor® RH40/ PEG400	235	Drug = 15 mg, liquid vehicle= 235 mg; Avicel® PH 101(carrier)= 744 mg; croscaremellose sodium (disintegrant) = 52 mg ; water (for granulation) = 447 mg (total= 1046 mg / 5 tablets)
F35	Capmul® MCM EP/ Kolliphor® RH40/ PEG400	168.67	Drug = 10 mg, liquid vehicle= 156.67 mg; Avicel® PH 101(carrier)= 496 mg; croscaremellose sodium (disintegrant) = 34.67 mg ; water (for granulation) = 298 mg (total= 697.3 mg / 4 tablets)
F36	Capmul® MCM EP/ Kolliphor® RH40/ PEG400	78.3	Drug = 5 mg, liquid vehicle= 78.33 mg; Avicel® PH 101(carrier)= 248 mg; croscaremellose sodium (disintegrant) = 17.3 mg ; water (for granulation) = 149 mg (total= 348.6 mg / 2 tablets)
F37	Capmul® MCM EP/ Kolliphor® RH40/ PEG400	185	Drug = 15 mg, liquid vehicle= 185 mg; Avicel® PH 101(carrier)= 595.24 mg; Croscaremellose sodium (disintegrant) = 41.85 mg ; water (for granulation) = 357.144 mg (total= 837.09 mg / 3 tablets)

2.5.3. Kinetic model analysis of drug release:

In order to inspect the mechanism of norfloxacin release from the classical liquisolid, wet granulated liquisolid and conventional tablets, several kinetic release models were applied on data obtained from dissolution tests. These models are; zero order, first order, Higuchi and Hixson-Crowell kinetic models. Regarding zero order model, it can be described as a system that all drug particles transfer process to dissolution medium is confided to the surface area of the system. The data of the cumulative percentage of the drug release can be plotted against the time [64]. In terms of first order, the drug release is related to the drug concentration and it can be applied by plotting logarithm of the cumulative percentage release of the remaining drug versus the time [64]. Moreover, in Higuchi model, plotting the cumulative percentage of the drug release against the square root of time should be linear if the drug release from the tablet a controlled diffusion [65]. Furthermore, Hixson-Crowell model depends on the theory that particle area is proportional to the cubic root of its volume. As a result, the plotting data is the cubic root of the drug remaining in the tablet versus the time [66]. The highest square of correlation coefficient (R^2 value) was selected to indicate the most appropriate model to represent the norfloxacin release from liquisolid formulation [64]. Statistically, Paired t-tests were used to determine whether there is a significant difference between the models, regardless the differences in the type of formulations. Due to dealing with model predictions, the significant probability was selected to be more robust at 0.1 levels.

2.6. Stability studies:

The stability of the prepared tablets containing norfloxacin was performed in a stability room chamber with an accelerated condition at dark, 21 ^{0}C and 75 % humidity for either three months period time for conventional, classical liquisolid and wet granulated liquisolid (PVP) tablet formulations, and for 6 months for the water granulated liquisolid tablet formulations.

For the tablet formulations containing cinnarizine (i.e. formulations form F34 to F37 in Table 2-6), the same conditions were applied for 3 months.

Content uniformity tests, *in vitro* dissolution tests in distilled water condition (pH=6.1), DSC and FTIR analysis were applied at time zero and the after the storage periods and the result were compared and evaluated using paired t-test.

2.7. Statistical analysis:

In the tests of evaluation norfloxacin tablet test (flowability, friability, hardness, tensile strength, content uniformity and disintegration tests), Paired t-test was used to compare between the PEG200 classical liquisolid tablets and Synperonic™ PE/L-61 classical liquisolid tablets, classical liquisolid and water granulated liquisolid for each liquid vehicle and wet granulated (water and PVP) liquisolid tablets. One sample t-test was used to compare between liquisolid tablets in general, PEG200 liquisolid tablets and Synperonic™ PE/L-61 liquisolid tablets in one side and conventional tablet from the another side. All the data results were quoted as significant where $P < 0.05$. Finally, F-test is used to compare the variations of the tensile strength values among classical liquid formulations (i.e. PEG200 *vs*. Synperonic™ PE/L-61).

Chapter Three: Classical liquisolid preparations with norfloxacin

3.1. Introduction:

Recent synthesized drugs show an increase in the number of hydrophobic groups, which have difficulties in oral delivery due to their poor solubility and bioavailability. An example of these drugs is norfloxacin. It is used to treat urinary tract infections because it works as a chemotherapeutic antibacterial agent. Only 30-40 % of norfloxacin can be absorbed through passive diffusion [67]. Moreover, *in vitro* tests, using either non-everted intestinal sacs or caco-2 cells, recorded low percentage permeability, confirming norfloxacin classification as a poorly permeable compound [68].

In addition to this, norfloxacin can be classified as a zwitterionic molecule. It represents a U-shaped profile in term of pH-solubility studies - a high solubility when pH is less than 5, low solubility in neutral region, and a high again when pH is over 10. As a result, it is classified as a low water soluble drug [69].

One method used to enhance both solubility and dissolution of hydrophobic drugs is liquisolid pharmaceutical technique. The definition of liquisolid systems is "they are compacts with acceptable flowing and compressible powdered forms of liquid medications, which represents oily liquid drugs and solutions or suspensions of water insoluble solid drugs carried in suitable non-volatile solvent systems termed the liquid vehicles" [6]. According to this definition, liquisolid method can be selected to improve the water solubility of norfloxacin.

A range of surfactants have been selected, in this study, for liquisolid preparations. The selection stands on covering a wide range of Hydrophobic Lipophilic Balance (HLB) values. For example, poly ethylene glycol 200 (PEG 200), which has HLB value= 18.1 and poloxamer 181 copolymer (Synperonic ^{TM} PE/L-61) with HLB =3.

Regarding PEG200, it is a stable –hydrophilic water-miscible surfactant. It can be used as a suspending agent to form liquid medication with a hydrophobic drug that allows miscibility in water. A wider view to polyethylene glycol determines an advantage for the low molecular weight group, which increase the rate of the drug release from liquid medication. On the other hand, the higher molecular weight, more enhancement of the effectiveness of compact binder, even though when the concentration is over 5%, it could prolong the disintegration. In general, PEGs are stable in both air and solution. However, the low molecular weight of PEG demonstrate a level of hygroscopicity. In conclusion, PEGs can be considered as a good solvent to prepare immediate release liquisolid formulations [70].

Another example is Poloxamer 181, which represents the group of low HBL value liquid vehicles. The chemical structure consists of three synthetic blocks, representing hydrophilic and lipophilic parts. The first and the third blocks are two poly (oxyethylene) groups from each side, while the middle block is thirty poly (oxypropylene) groups. This structure allows the surfactant to be more hydrophobic with HLB value = 3. The general use of poloxamers is as binders or coaters in tablet production. However, the physical properties and viscosity of these surfactants change depending on the length chain of hydrophobic and hydrophilic blocks. Also, poloxamers are stable if they present in acids, alkaline or metal ions. They are classified as non-toxic and non-irritant substances. As a result, the physicochemical properties make them good candidates to be used in liquisolid formulations [70].

Therefore, the aim of this study is to explore the behaviour of norfloxacin with non-volatile liquid vehicle (PEG200 and Synperonic ^{TM} PE/L-61) in aqueous dissolution

medium, via preparing liquisolid formulations after determining their relative optimum liquid load factors.

3.2. Pre-compression studies and characterization of powder admixtures:

3.2.1. Calibration Curve and solubility studies:

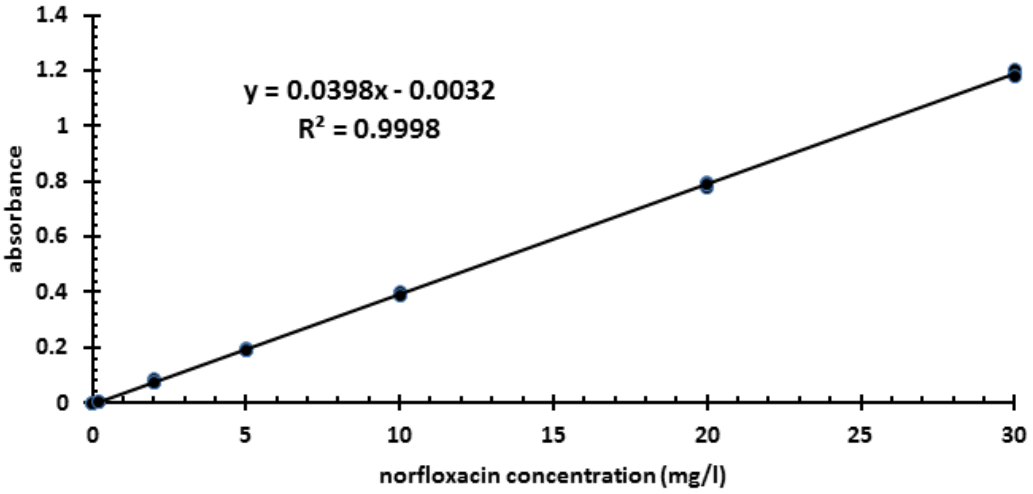


Figure 3-1: Norfloxacin calibration curve, the repeatability n =3.

Table 3-1 : The solubility of norfloxacin in a range of surfactants and distilled water at room temperature (24 ° C).

Surfactants	Average of solubility (mg/ml)	Standard deviation
PEG200	2.507	0.066
Span 80	1.997	0.266
PG	1.734	0.239
PEG300	1.547	0.132
Tween 20	1.085	0.056
Tween 80	0.954	0.251
Span 20	0.6374	0.033
PEG400	0.428	0.131
Cremophor® EL	0.366	0.113
Pluronic L-35	0.35	0.194
Distilled water	0.34	0.03
Synperonic ™ PE/L-61	0.167	0.006

All solubility calculation depends on the calibration equation in Figure 3-1. From Table 3-1, norfloxacin has the highest solubility value in PEG200, whereas the lowest one is in Synperonic TM PE/L-61. It can be noticed that with the increase in the molecular weight of the PEGs, the solubility of norfloxacin decreases. Moreover, the drug has low solubilises with the both types of poloxamers (Synperonic TM PE/L-61 and Pluronic L-35), although they have different HLB values, i.e. Pluronic L-35 is > 20 and Synperonic TM PE/L-61 is 3. The solubility of the drug in distilled water is 0.34 mg/ml, allowing the drug to be classified as a very slightly water soluble one. The highest and the lowest solubility values were chosen to be used in the liquisolid formulation to investigate the effect of the solubility on the percentage of the drug release in the dissolution tests.

3.2.2. Determination of flow property:

The importance of powder flowability in tablet production comes from its effect on the consistency of tablet weight and drug content. One of the methods to determine the powder flowability is Carr's compressibility index (CI%), where the percentage of the differences between bulk powder density before and after tapping divides by the tapped density. This law was used to determine the flowability of the all liquisolid and conventional formulations. The results are summarized in Table 3-2, and the criteria depends on British Pharmacopoeia, indicating that any formulation has CI% below 25 represent better flow properties [56]. The statistical analysis shows that there is a significant differences between liquisolid formulations and conventional powder ($P= 0.002 < 0.05$). This differences comes mainly from the difference between the Synperonic TM PE/L-61 formulations and conventional powder ($P= 0.047 < 0.05$). In general, all liquisolid formulations recorded CI% over 20% and no significant differences between

PEG200 liquisolid formulations and Synperonic ™ PE/L-61 liquisolid formulations ($P=0.406 > 0.05$).

According to Spireas *et al.*, the amount of carrier and coating materials in the liquisolid formulations determines its flowability as they play an important role in adsorbing the liquid vehicle on the surface of the carrier materials, allowing coating particles specifying a certain amount of retained liquid vehicle with an acceptable level of flowability [61]. Consequently, the increasing amount of the liquid in the formulation leads to increase the carrier and coating particles which enhances the powder flowability and reduces the CI%. This clearly appears in both PEG200 and Synperonic ™ PE/L-61 liquisolid formulations, wherever there is a high percentage of the liquid, there is an increase in the amount of carrier and coating. However, the low percentage of the liquid vehicle leads to less amount of carrier and coating materials and produces either poorly or very poorly flowable formulations.

Table 3-2: Flow properties of conventional and classical liquisolid powder mixtures.

Formulations*	CI%	position
F1	22.22	Passable
F2	23.64	Passable
F3	29.03	Poor
F4	39.29	Very poor
conventional	17.39	Good
F5	24.11	Passable
F6	21.21	Passable
F7	31.03	Poor
F8	35.38	poor

*For more information about the Formulation composition, see Table 2-2.

3.2.3. Differential scanning calorimetry (DSC):

Figure 3-2 and Figure 3-3 represent a comparison between all thermograms of the liquisolid and conventional formulations with and without the thermogram of pure norfloxacin.

It is clear that norfloxacin pure drug has a sharp endothermic peak at melting temperature (222.36 ^{o}C) with relatively high enthalpy value (107.7 J/g). This sharp peak indicates the crystallinity of the drug and the melting of the sample, referring the end of the thermogram to the decomposition of norfloxacin [71]. Moreover, the sharp endothermic peak disappears in all liquisolid formulations (PEG200 and Synperonic ^{TM} PE/L-61), indicating a change in the amorphous state of the drug.

Furthermore, the percentage of R value seems to have effects on the liquisolid thermograms. This integrates with the type and the percentage of the liquid vehicles. In the case of PEG200 liquisolid formulations, a boarder peak appears when the percentage of the weight of norfloxacin to the weight of PEG200 is 40% w/w at 139.04 ^{o}C with a small amount of enthalpy capacity equals to 27.92 J/g (F3) and when the liquid medication is 20% w/w (F1). Although this indicates that the drug is not completely dissolved or dispersed in PEG200, the reduction in melting temperature point improves that there is a certain of reaction happened (H-bond formation) between the vehicle and the drug. Complementarily with this, the broad small peak disappeared completely when increasing the amount of PEG200 vehicle in the liquisolid formulations (F2 and F4). In conclusion, at R =10, a small peak appears, whereas at R=20, the peak disappears. Thus, the incorporation of PRG200 as a liquid vehicle leads to reduce or disappear the

endothermic peak of norfloxacin depending on the amount of the carrier in the formulations.

Guyot *et al.* reached to a similar conclusion in terms of disappearance of the endothermic norfloxacin peak at 222 ^{o}C when incorporating co-surfactant, such as PEG. However, due to using co-surfactant (PEG6000) with higher molecular weight and changing the pharmaceutical preparation to solid dispersion technique, another peak appeared at 62 ^{o}C when the percentage of the surfactant exceeds 50% with the drug [71].

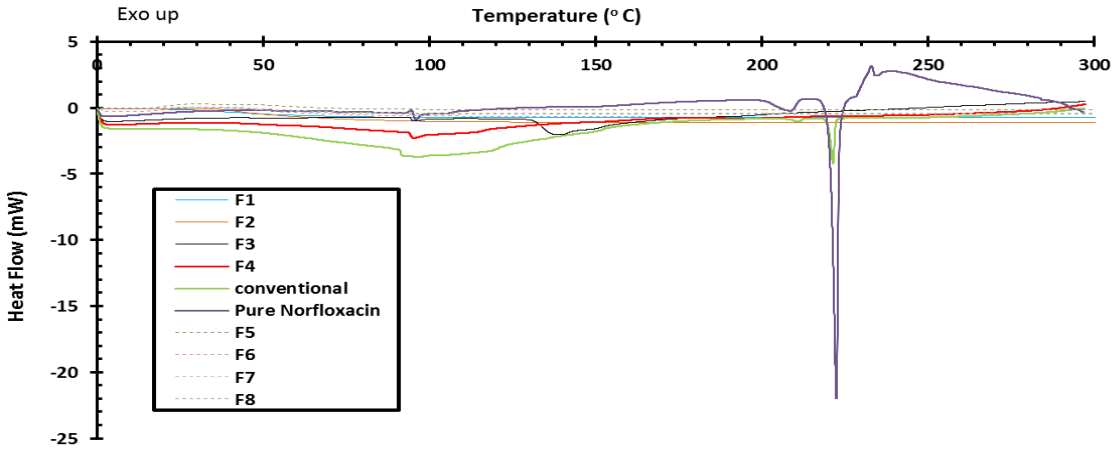


Figure 3-2: Differential scanning calorimetery for norfloxacin pure powder, conventional and all liquisolid formulations (for more information about the formulation components, see Table 2-2).

On the other hand, very tiny peaks were indicated at the same melting temperature of norfloxacin with very small enthalpy capacities, which ranges from 0.045 J/g to 0.24 J/g. This is accompanied with one or two degrees of temperature decrease (220 -221 ^{o}C). The probable reason for this is that less degree of solubility of norfloxacin in the vehicle (0.167 mg/ml). However, this does not give a negative effect on the dissolution profile. On contrary, it enhances the percentage of the drug release comparing with PEG200 liquisolid formulations as whole.

Finally, the sharp endothermic peak appears clearly in the case of the conventional powder, where there is no added liquid vehicle to the formulations. It appears at 221.37 ºC with enthalpy equals to 0.9524 J/g, indicating a slightly change in drug crystallinity comparing with the liquisolid formulations.

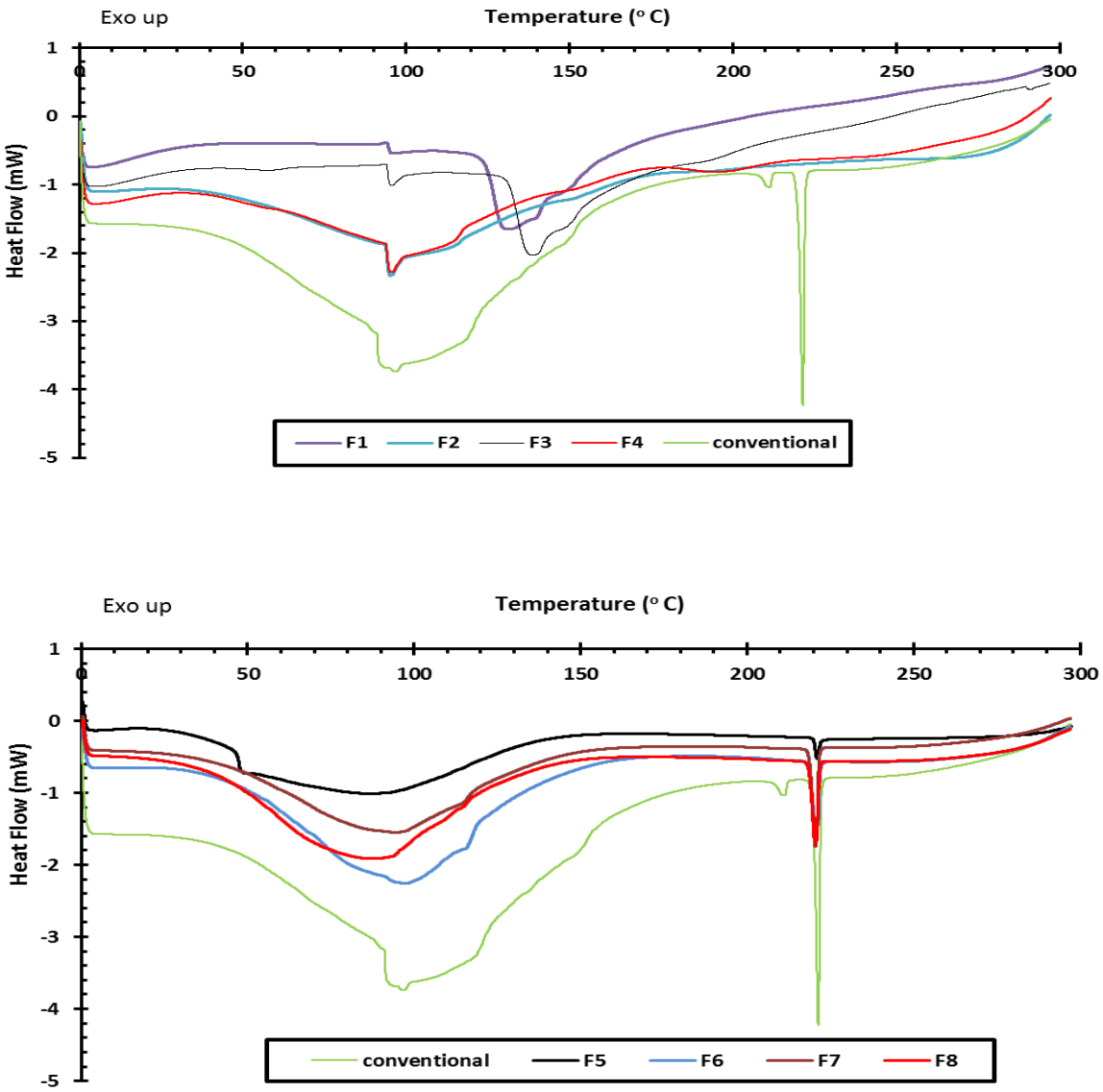


Figure 3-3: Differential Scanning Calorimetry for conventional and all PEG200 liquisolid formulations (upper part) and all Synperonic ™ PE/L-61 liquisolid formulations (lower part) (for more information about the formulation components, see Table 2-2).

3.2.4. Fourier Transform infra-red spectroscopy (FTIR):

From Figure 3-4 to Figure 3-9, the FTIR spectra provide information about of pure norfloxacin (Figure 3-4), the carrier and the coating (Figure 3-5), lubricant and disintegrant (Figure 3-6), the liquid vehicles (Figure 3-7), the PEG200 liquisolid formulations (Figure 3-8) and the Synperonic ^{TM} PE/L-61 liquisolid formulations (Figure 3-9). The last two figures provide a comparison between the classical liquisolid formulations (see Table 2-2), conventional powder and pure norfloxacin powder.

From Figure 3-8 and Figure 3-9, it is obvious that characteristic fingerprint FTIR peaks of norfloxacin between 1700 cm^{-1} to1250 cm^{-1} faced massive changes in the IR spectra related to liquisolid formulations. These changes are expressed in several ways, such as reduced in the intensity of signal, shift or disappearance of the whole peaks, suggesting that there is interaction between the drug and the excipients.

Supporting the presence of hydrogen bonds is the disappearance of sharp vibrations between 1650 cm^{-1} and 1550 cm^{-1} in all mentioned liquisolid formulations (PEG200 and Synperonic ^{TM} PE/L-61) compared with pure norfloxacin. This region denotes the bending vibration of the secondary amine functional group (R_2NH). This indicates that there is hydrogen bond between N-H functional group in norfloxacin and the hydrogen molecule in hydroxyl group in the vehicle. Consequently, the formation of hydrogen bonds between the drug and the vehicle contributes in increasing the solubility of the drug in the vehicle, which reflects mainly on the dissolution profiles [60].

As a result, FTIR spectra analysis complies with DSC results, indicating a solubilisation of norfloxacin crystals in the liquid vehicles, decreasing the crystallinity of norfloxacin.

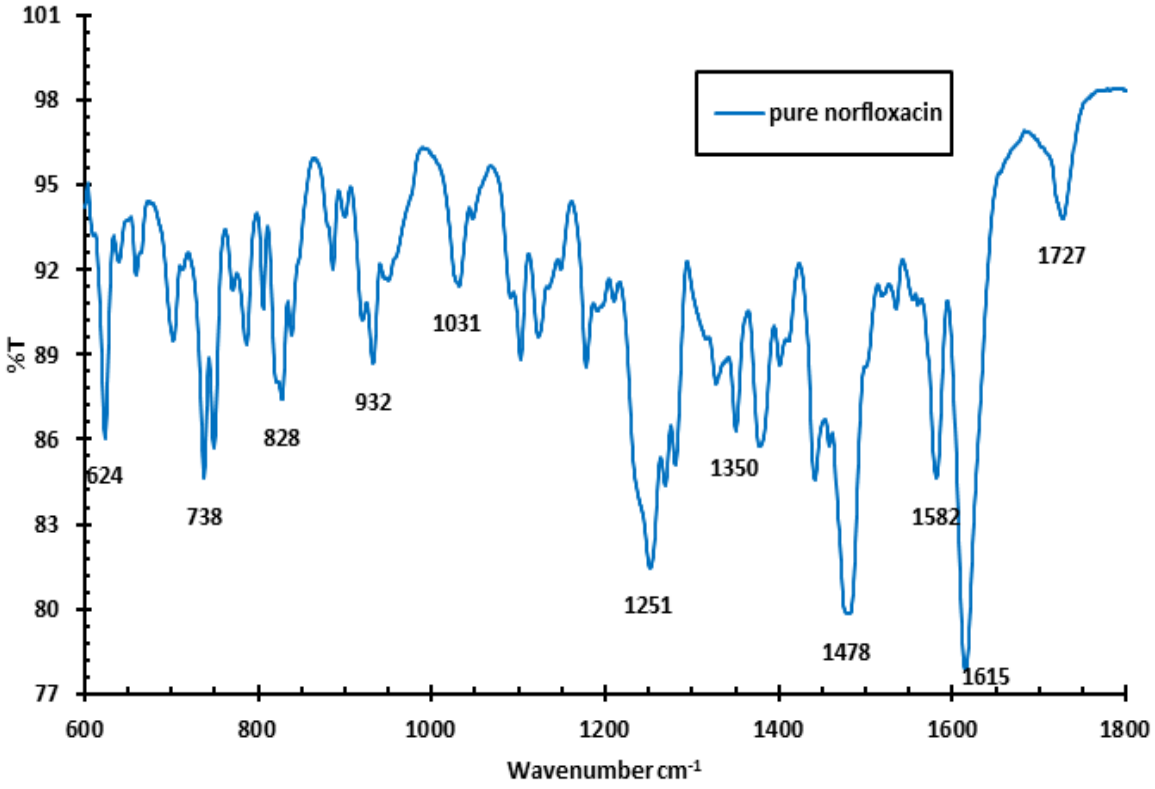


Figure 3-4: FTIR spectrum of pure norfloxacin powder (%T is % transmittance).

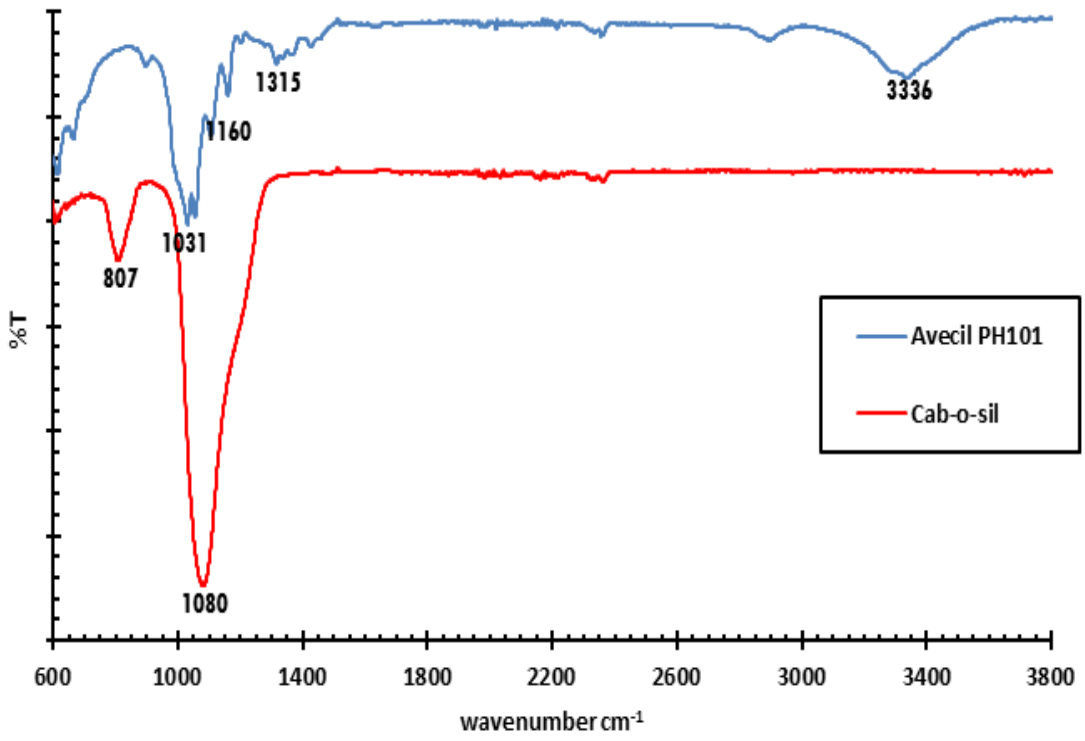


Figure 3-5: FTIR spectra for pure excipients (Avicel® PH 101 and Cab-O-Sil® M-5DP).

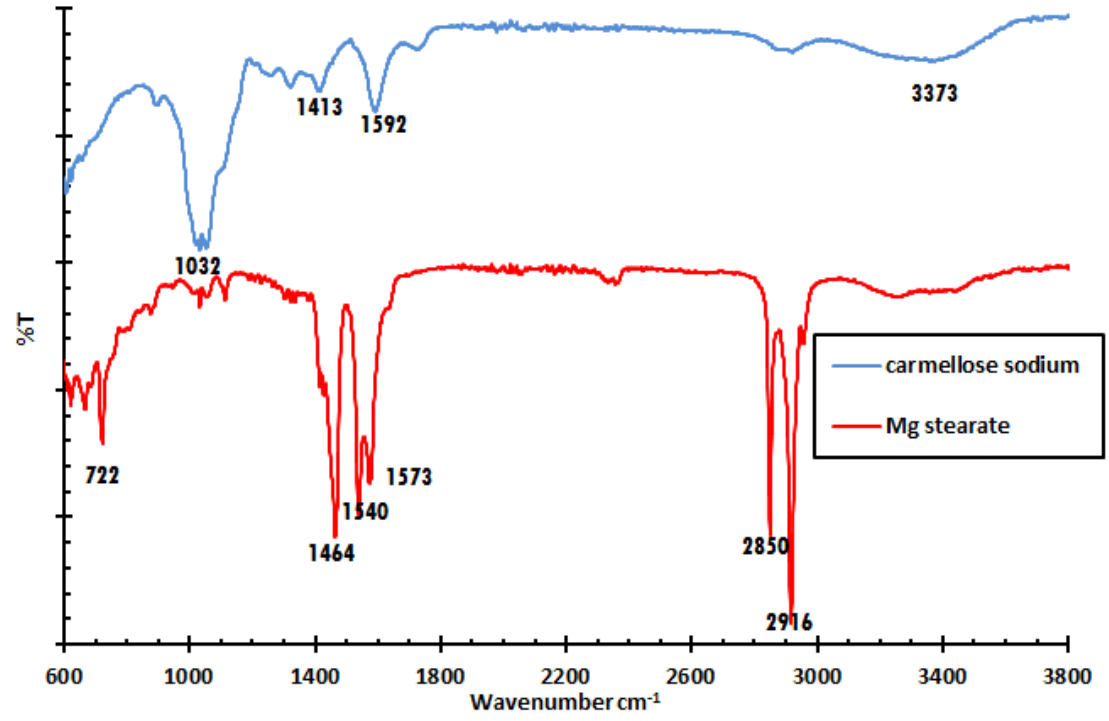


Figure 3-6: FTIR spectra for pure excipients (carmellose sodium and magnesium stearate).

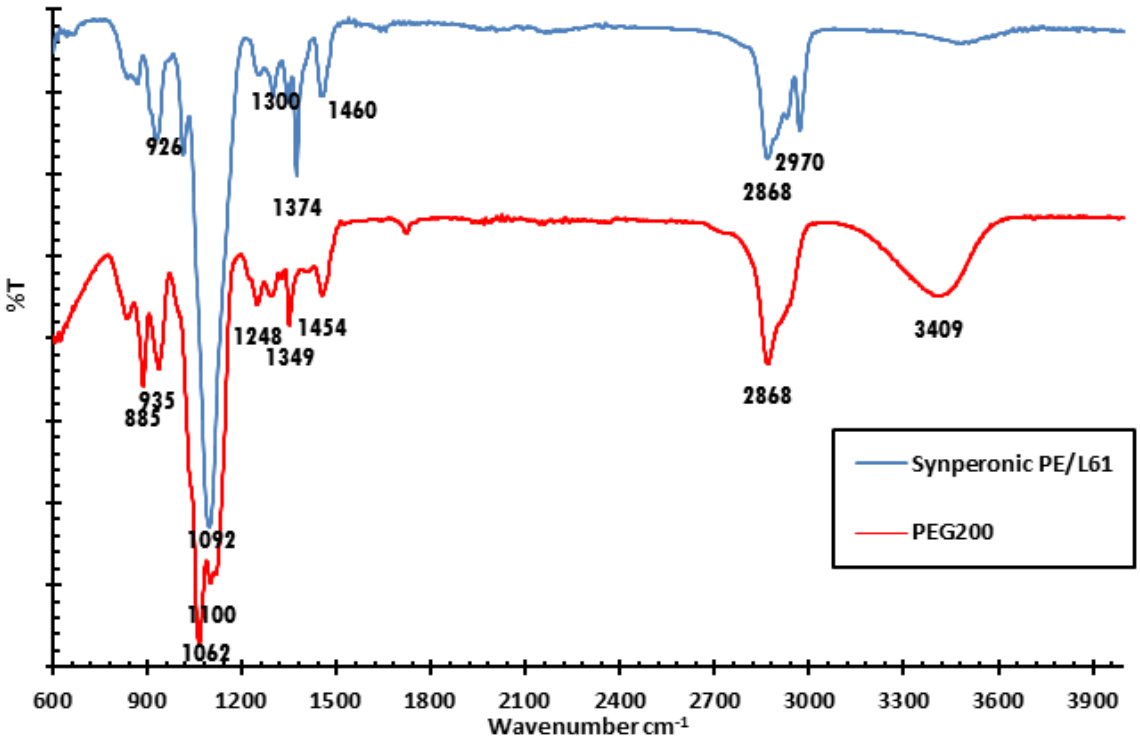


Figure 3-7: FTIR spectra for liquid vehicles (PEG200 and Synperonic™ PE/L-61).

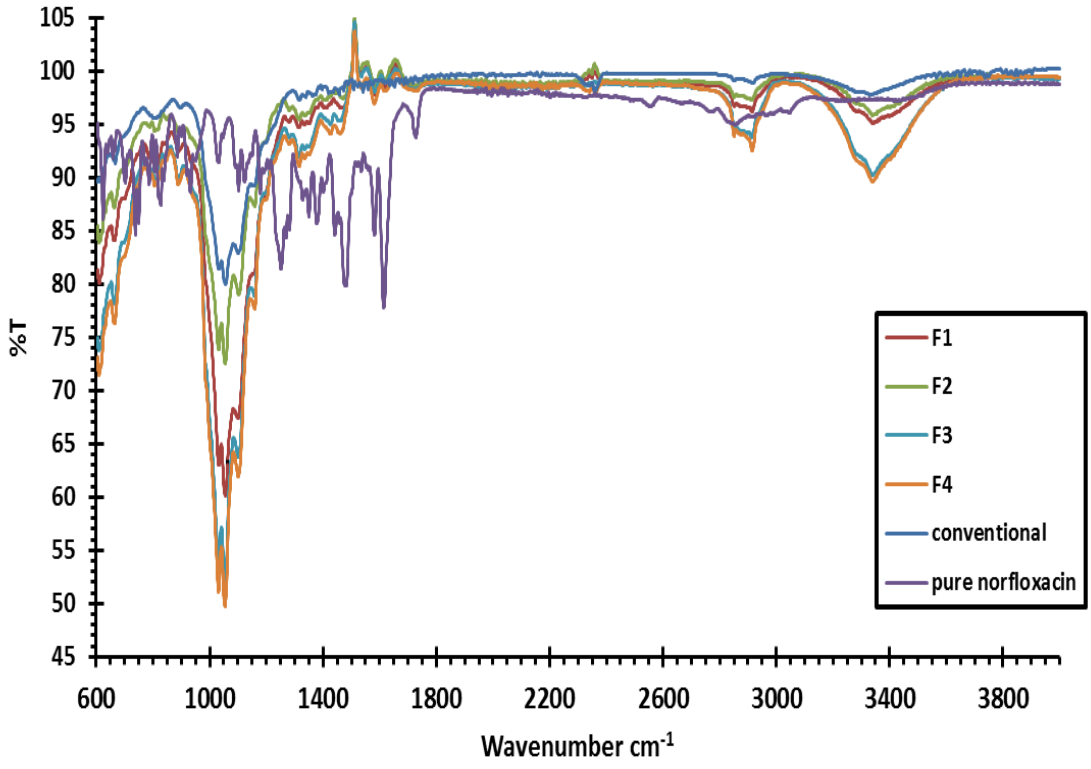


Figure 3-8: FTIR spectra for pure norfloxacin, conventional powder, and the all classical PEG200 liquisolid formulations (for more information about the formulation components, see Table 2-2).

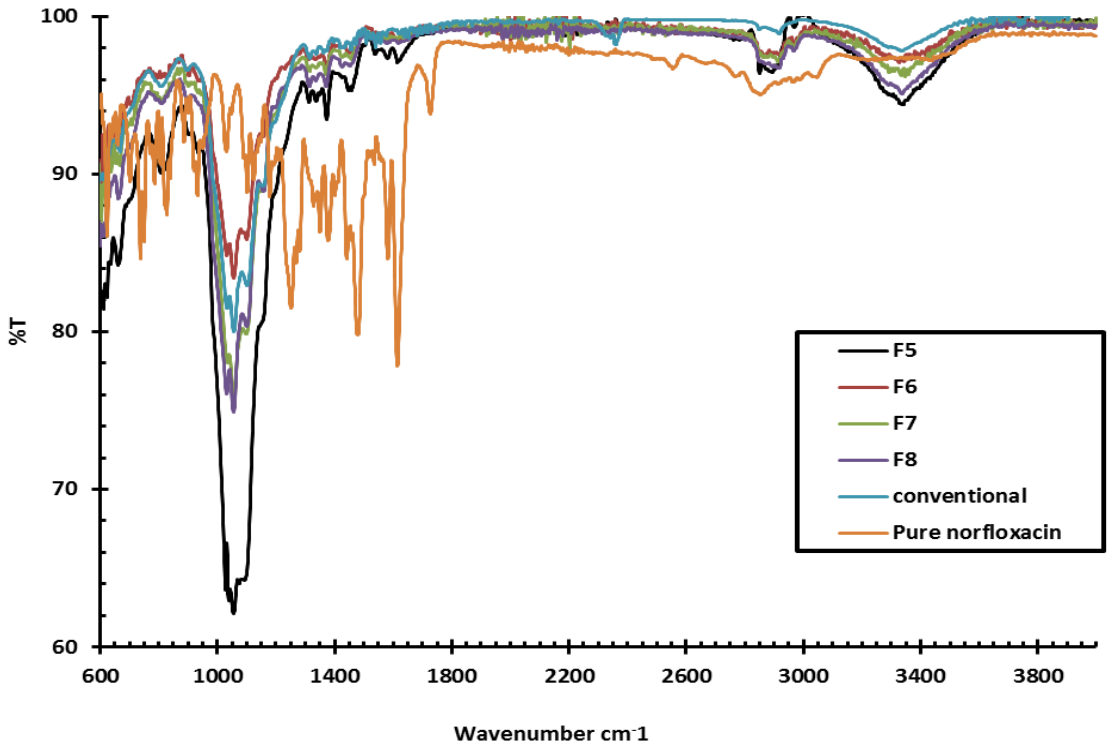


Figure 3-9: FTIR spectra for pure norfloxacin, conventional powder, and the all classical Synperonic™ PE/L-61 liquisolid formulations (for more information about the formulation components, see Table 2-2).

3.3. Evaluation of classical liquisolid tablets:

3.3.1. Drug content uniformity, tablet dimensions, hardness, tensile strength, friability and disintegration tests:

A summary of results expressed by the average and the standard deviations of tablet hardness, tensile strengths, friability, disintegration and drug content for all liquisolid (PEG200 and Synperonic™ PE/L-61) and conventional tablets is presented in the Table 3-3.

British Pharmacopoeia specifies the accepted limits of the percentage of the active ingredient in tablets between 85% and 115% [56]. According to this, all liquisolid (PEG200 and Synperonic™ PE/L-61) and conventional formulations are in this

range. Moreover, the statistical analysis for the drug contents indicated that there is no significant differences between either conventional and PEG200 formulations (P=0.430), conventional and Synperonic ™ PE/L-61 formulations (P=0.437) or PEG200 and Synperonic ™ PE/L-61 formulations (P=0.293).The reason of this could be referred to the high percentage of the carrier excipient in the unit dose of the PEG200 tablets (ranged between 71.2 % and 74.6%), the Synperonic ™ PE/L-61 tablets (from 75.83% to 78.41%) and the conventional tablet(79.73%). This leads to increase in the surface area that absorbs the liquid medication into the internal part of the carrier framework, allowing a homogeneous distribution throughout the bed powder of the batches [61]. As a result of this, all drug percentages are ranged between over 90% and less 105%.

The reason for variations in the tablet thickness can be explained in terms of the variation in the weights of the tablets, which are determined to allow sufficient tablet hardness with an appropriate disintegration time (usually less than 5 minutes).

Table 3-3: Tablet hardness, tensile strengths, disintegration time, friability and content uniformity for conventional and the all liquisolid tablets (average +/- standard deviation) (for more information about the formulation components, see Table 2-2).

Formulations	Hardness (N)	Tensile strength (MPa)	Disintegration time (sec.)	Friability (%)	Content uniformity (%)
F1	51.97 +/- 3.75	0.880 +/-0.189	275.6 +/- 61.5	0.474	94.83 +/-1.6
F2	91.93 +/- 21.5	1.508 +/-0.368	192.8 +/- 70.0	0.405	104.7 +/- 5.1
F3	46.75 +/- 4.50	0.789 +/-0.093	148.2 +/- 72.8	0.842	94.90 +/- 3.1
F4	45.60 +/- 7.18	0.707 +/- 0.085	91.70 +/- 11.4	0.724	96.74 +/- 7.5
conventional	47.56 +/- 5.63	0.754 +/- 0.119	62.50 +/- 9.50	0.864	99.94 +/- 0.5
F5	46.85 +/- 3.01	1.172 +/- 0.083	49.20 +/- 6.90	0.304	98.62 +/- 5.6
F6	57.75 +/- 3.58	1.097 +/- 0.067	39.80 +/- 11.3	0.275	100.9 +/- 5.1
F7	48.27 +/- 2.90	1.206 +/- 0.064	40.30 +/- 4.40	0.167	100.5 +/- 1.7
F8	58.25 +/- 2.40	1.059 +/- 0.043	30.30 +/- 1.50	0.338	102.9 +/- 2.3

The tensile strength of the Synperonic ™ PE/L-61 formulations show more consistency (i.e. less variations) compared with the PEG200 formulations. This is expressed by F-test which determines a significant difference between the Symphonic PE/L-61 and PEG200 formulations when taking the range of all recorded data in the test (P-value < 0.001). This is probably due to the fact that Synperonic ™ PE/L-61 formulations were prepared using compactible liquisolid test which allow preparing the formulations at a plateau compression forces with an optimum pactisity value (20 Kg/g). As a result of this, it determines lesser tensile strengths compared with the PEG200 formulations, which were prepared depending on the acceptable flowability value for both carrier and coating materials by angle of slide test, not allowing a sufficient control in the compression forces.

From the industrial perspective, it is important to balance between disintegration time and tablet hardness. Moreover, there is a relationship between tablet hardness and its porosity. Decreasing the porosity among the particles in the tablets is due to increasing the compression forces and the hardness of the tablets. Consequently, there is a decrease in the intermolecular distance, promoting more formation of solid bridges among the tablet particles [14].

In this study, the range of hardness is between 45.60 N and 91.94 N (Table 3-3). Using microcrystalline cellulose (Avicel® PH 101) as a carrier with high percentages leads to cover the surface and increase solid bridges among particles. This is due to the ability of the carrier to exhibit plasticity which explains the deformation of particles undergoing non-reversible changes of shape as a response to applied compression forces [18].

The investigation of the percentages of weight loss in friability tests demonstrates that the all formulations passed the BP specifications [56]. In other words, no formulations lost more than 1% from tablet weights, with no markedly cracked or broken tablets during the test. Consequently, liquisolid tablets have the ability to resist the expected abrasions when applying further manufacturing processes.

For disintegration data, the averages of the time of the PEG200 formulations is over 90 seconds, whereas the average of the Synperonic ™ PE/L-61 formulations records a time less than 50 seconds. Table 3-3 presents the range of the time of the PEG200 formulations between 91.6 and 275.6 seconds, while the time of the Synperonic ™ PE/L-61 formulations is between 30.3 and 49.2 seconds. There are fewer variations in the case of the Synperonic ™ PE/L-61 liquisolid formulations compared with the PEG200 liquisolid formulations. Also, the statistical analysis showed no significant differences between the PEG200 and the conventional formulations ($P=0.06 > 0.05$), whereas there is a significant difference ($P=0.01< 0.05$) in the case of the comparison between the time of disintegration of the Synperonic ™ PE/L-61 and the conventional tablets. To sum up, all liquisolid formulations recorded disintegration times less than 5 minutes, although the PEG200 formulations recorded longer time than the Synperonic ™ PE/L-61 formulations. Nevertheless, all of them meet the BP specification, which is less than 15 minutes in the case of uncoated tablets [56].

Seeing rapid disintegration times through improving tablet dissolution profiles is important due to the fast division that is provided into surface fragments, reaching to higher surface areas for dissolution processes. Mentioning this would drive toward specifying the reasons of the fast disintegration, which relates to presenting both microcrystalline cellulose and carmellose sodium in high quantities in the

tablet dosage forms. In the same direction, PEG200 is demonstrated slightly longer disintegration time, which can be referred to the lower percentages of microcrystalline cellulose in the formulations.

In summary, the type of liquid vehicles, the quantity of the carrier and the quantity of the disintegrants are said to be the main factors controlling the time of the liquisolid tablet disintegration.

3.3.2. *In vitro* dissolution:

It is clear that the percentage of norfloxacin release in the acetate buffer dissolution medium is significantly higher than in the distilled water ($f2 < 26\%$ for all comparisons between each liquisolid and conventional formulations in the two dissolution media). The percentage of the drug release was over 85% in all liquisolid and conventional tablets after 90 minutes, whereas it was no more than 63% in distilled water dissolution medium.

Figure 3-10 shows the all classical PEG200 liquisolid tablets with conventional tablet in distilled water. In this profile, the conventional tablet shows the highest percentage of drug release comparing with the other liquisolid tablets. However, at the first 20 minutes, tablets with 40% w/w norfloxacin: PEG200 liquid medication with the both excipient ratios (R=10 and 20) record higher percentage norfloxacin release comparing with the conventional one. Then, the conventional dissolution profile continues raising over the both liquisolid tablets. On the other hand, when the percentage of norfloxacin: PEG200 liquid medication decreases, the dissolution profiles decrease significantly ($f2 < 35\%$ when comparing the PEG200 formulations 20% w/w and 40% w/w in Distilled water), reaching to only 30% after 90 minutes.

In Figure 3-11, all PEG200 liquisolid and conventional tablets record similar dissolution profiles with over 85% drug release in the first 30 minutes.

In the case of Synperonic ™ PE/L-61 dissolution profiles (Figure 3-12 and Figure 3-13), the drug release from conventional tablet is still higher than most of the Synperonic ™ PE/L-61 liquisolid tablets, except a slight increase in one dissolution profile, which drug: liquid medication percentage is at 40%w/w and the excipient ratio equals to 10, nevertheless it is not a significant increase in the drug release (f2= 61.41%). The liquisolid tablet (20%w/w, R=20) shows a significant decrease in comparison with the conventional tablet (f2=44.7%). In general, the all Synperonic ™ PE/L-61 profiles keep the same order of the PEG200 dissolution profiles, when comparing the liquisolid with the conventional tablets in both dissolution media (Figure 3-12 and Figure 3-13).

Finally, the comparisons between the dissolution profiles of the Synperonic ™ PE/L-61 liquisolid tablets and the PEG200 liquisolid tablets having the same composition determines that there is no significant differences in the all formulations, except the tablets having drug: liquid medication percentage equals to 20% w/w and R=10, where the Synperonic ™ PE/L-61 tablet has a significantly higher norfloxacin release (f2= 44.04% in distilled water and 40.98% in acetate buffer).

From the dissolution profiles, many points can be concluded. First of all, the enhancement of norfloxacin in two liquisolid formulations(40% w/w norfloxacin: PEG200 liquid medication, R=10 and R=20 (F3 and F4)) compared with the conventional tablets in distilled water dissolution medium can probably be explained by Noyes-Whitney equation : $\frac{dc}{dt} = \frac{DS(Cs-C)}{h}$ where dc/dt is the dissolution

rate of the drug particles, S is the surface area of the interface between the dissolving substance and the solvent, D is the diffusion coefficient, h is the thickness of the boundary layer of the solvent at the surface of the dissolving substance, Cs is the mass concentration of the substance on the surface and C is the mass concentration of the substance in the bulk of the solvent.

From this equation, only two factors could affect the enhancement of the drug release, which they are the drug concentration gradient in the diffusion layer (Cs-C) and the surface area of the interface between the dissolving substance and the solvent (S). This is due to the speed of the paddle is constant (50 rpm) and the dissolution medium (distilled water) that is the same for all the comparative tablet dissolution profiles. As a result, the thickness of the boundary layer (h) and the diffusion coefficient (D) are not included in this situation.

Regarding the surface area of the interface (S), it is directly proportional to the dissolution rate of the drug. Consequently, the drug dissolves in a water miscible liquid vehicle in the liquisolid tablets, which has good wettability. This enhances the wetting characteristics of norfloxacin particles, increasing the surface area of the interface between the liquid medication and the dissolution medium comparing with the surface area of the drug particles alone and the dissolution medium in the case of the conventional tablets, which leads to the increasing in the rate of norfloxacin release [72] & [11].

The second reason relates to the saturation solubility (Cs). At micro-environment, there is a high possibility that an infinite amount of liquid-vehicle is to diffuse away with norfloxacin molecule from liquisolid particles, since the liquid vehicle works as

co-solvent in order to improve the solubility of the drug, leading to increase the concentration gradient and the percentage of the drug release [6].

The third reason is the solubility of norfloxacin in PEG200, which is higher than the solubility of the drug in either Synperonic TM PE/L-61 or distilled water. Thus, a certain amount of PEG200 added to liquisolid tablet would increase the dissolution rate of the drug [14].

To sum up, three main factors are able to participate in enhancing the two PEG200 liquisolid formulations over the conventional in distilled water; the increase in the surface area of the interface between the dissolving liquid medication and distilled water, the increase of the saturation concentration at molecular level and the higher solubility of norfloxacin in PEG200 liquid vehicle compared with the solubility in distilled water and Synperonic TM PE/L-61 liquid vehicle.

An interesting point can be noticed from dissolution profiles is that the percentage of drug release of the conventional tablets are higher than most liquisolid tablets. This could be referred to the nature of norfloxacin solid particles. This drug has a unique solid structure that allows the pharmaceutical hydrate form to be more water soluble from the anhydrous form.

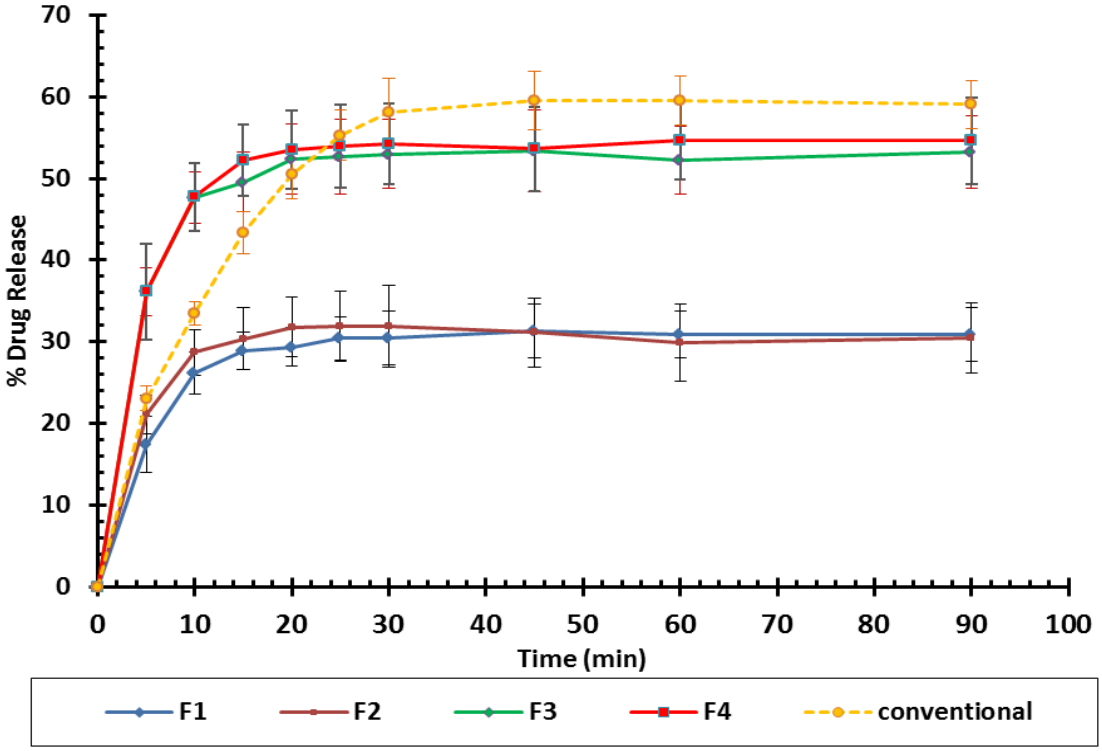


Figure 3-10: Percentage drug released from PEG200 liquisolid and conventional tablets in distilled water dissolution medium (for more information about the formulation components, see Table 2-2).

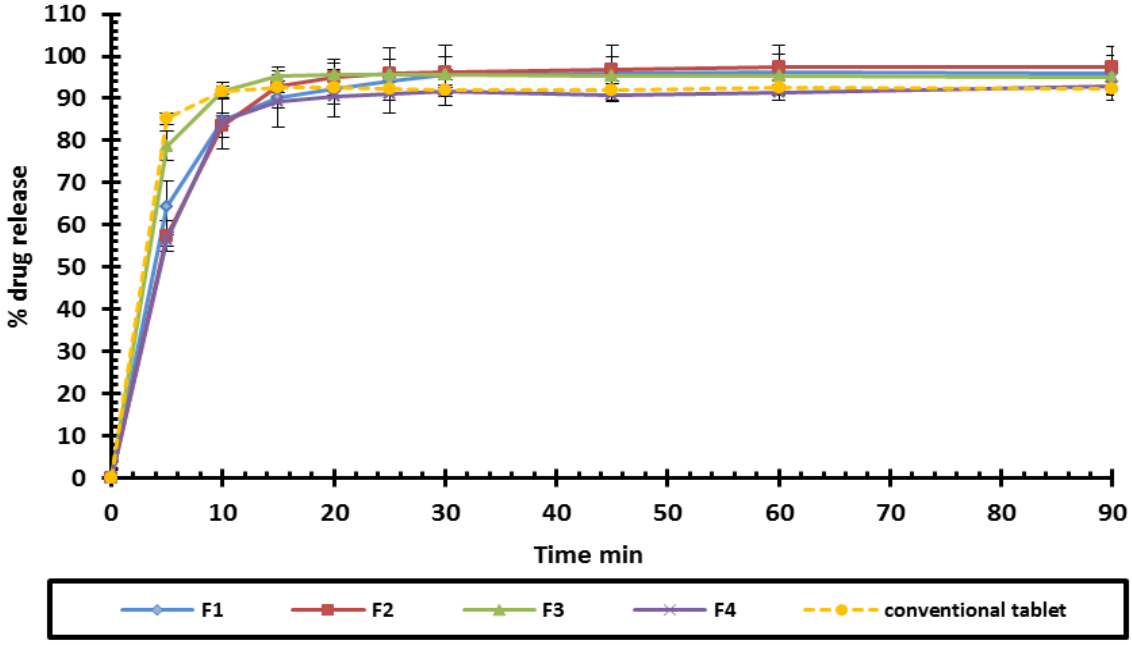


Figure 3-11: Percentage drug released from PEG200 liquisolid and conventional tablets in acetate buffer (pH=4) dissolution medium (for more information about the formulation components, see Table 2-2).

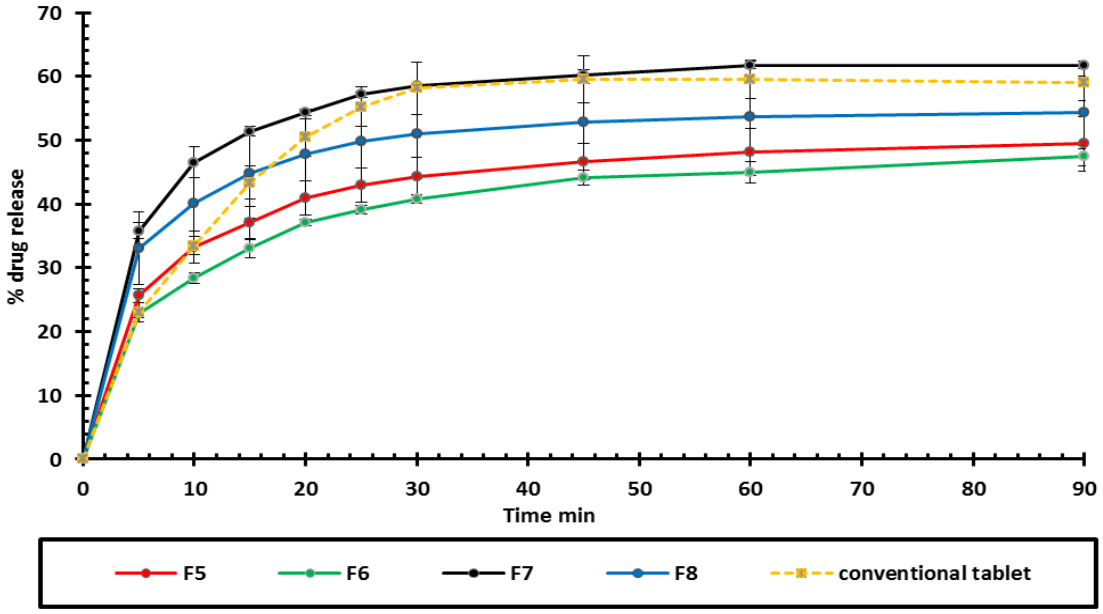


Figure 3-12: Percentage drug released from Synperonic ™ PE/L-61 liquisolid and conventional tablets in distilled water dissolution medium (for more information about the formulation components, see Table 2-2).

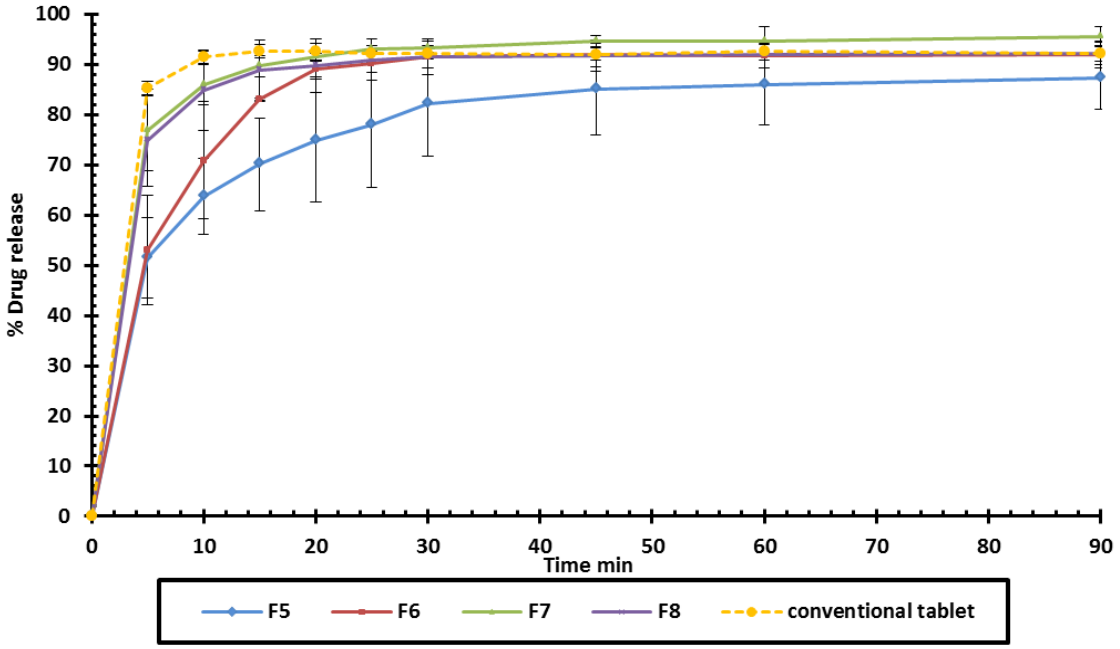


Figure 3-13: Percentage drug released from Synperonic ™ PE/L-61 liquisolid and conventional tablets in acetate buffer (pH=4) dissolution medium (for more information about the formulation components, see Table 2-2).

In general, the existence of water molecules in the solid state of drugs can decrease the solubility of the drug, because water molecules act to increase the thermodynamic stabilization of the solid structure by polar interaction. However, norfloxacin is an exception to this rule. This is due to that the hydrate formation of norfloxacin can occur in the anhydrous state [73]. In addition, the hydration can change the interactions between norfloxacin molecules from hydrogen bonding to ionic bonding by proton transfer process from the COOH group to the NH group in the solid state [73]. In other words, water molecules convert the drug from its neutral state to its zwitterionic state, which increases the percentage of ionization of the drug and the percentage of dissolution rate (Figure 3-14). Therefore, the tablet dissolution behaviour was adversely affected by the lower humidity. As a result, this phenomenon can explain the improvement of the conventional tablet dissolution profile over liquisolid tablet profiles because the drug particles in the conventional tablet are more exposed to water molecules in the liquisolid tablets.

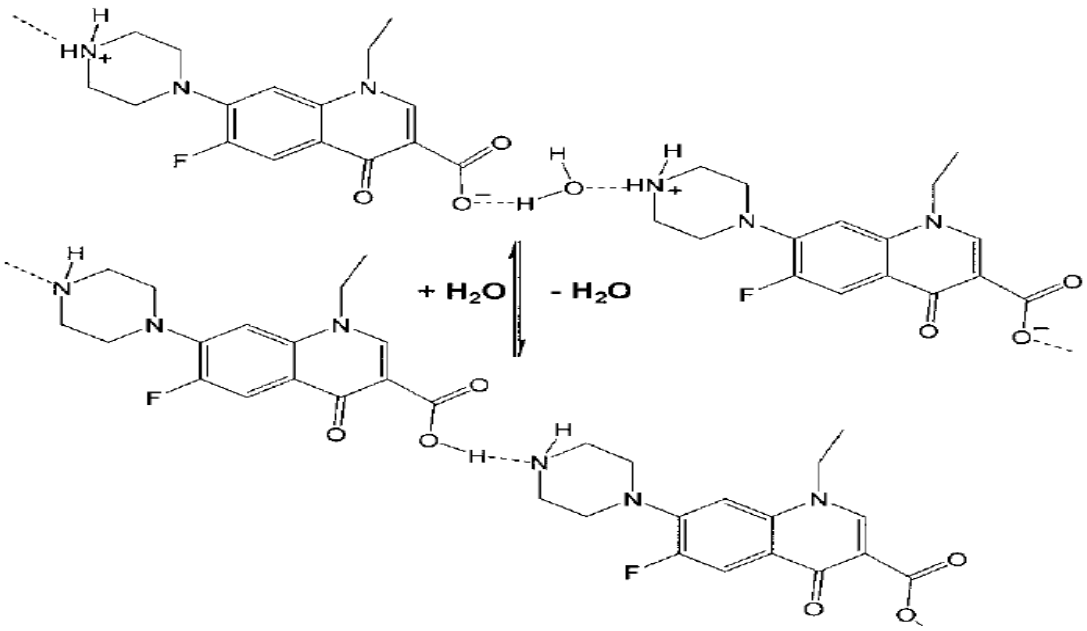


Figure 3-14: Equilibrium state when norfloxacin forms hydrogen bonds in the presence and absent of water molecules [71].

To support this conclusion, dissolution tests were applied to liquid medications consisting of either norfloxacin: PEG200 or norfloxacin: Synperonic ™ PE/L-61 alone without adding powder excipients. The same concentration of drug in the liquid vehicles that was used to prepare the liquisolid formulation was used in these tests. Also, the same dissolution conditions were applied, i.e. 750 ml distilled water maintained at 37 ^{o} C with a paddle speed of 50 rpm. The samples were measured at 15 and 30 minutes and the differences between the percentages of the drug release at the withdrawn time were calculated. The results are summarised in Table 3-4 and supported with images taken after 30 min of the beginning of the dissolution test Figure 3-15.

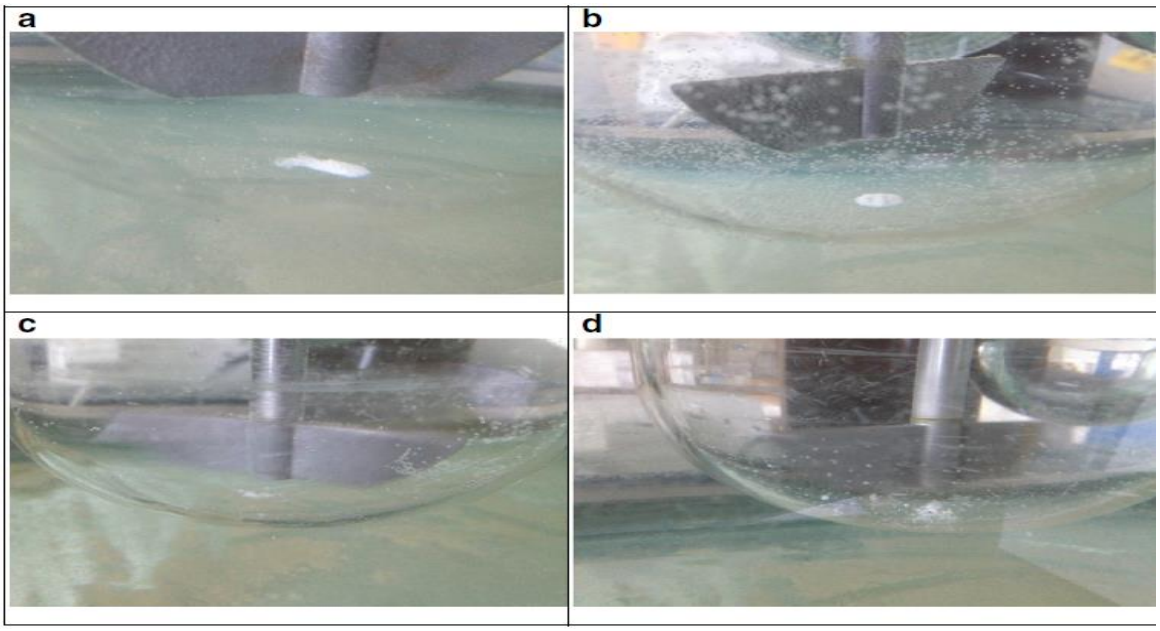


Figure 3-15: (a) Norfloxacin: PEG200 liquid medication (20%/w/w) after 30min in the mock dissolution test. (b) Norfloxacin: PEG200 liquid medication (40%/w/w) after 30min in the mock dissolution test. (c) Norfloxacin: Synperonic ™ PE/L-61 liquid medication (40%/w/w). (d) Norfloxacin: Synperonic ™ PE/L-61 liquid medication (20%/w/w).

Table 3-4: The percentage of drug release from the dissolution tests without powder excipients and the difference between them at 15 and 30 minutes.

Surfactant name	20%w/w (drug: liquid medication)					40%w/w (drug: liquid medication)				
	abs[1]	%R [2]	abs	%R	difference[3]	abs	%R	abs	%R	difference
	15 min	15 min	30 min	30 min		15 min	15 min	30 min	30 min	
PEG200	0.352	33.531	0.410	39.056	5.525	0.407	38.770	0.454	43.247	4.477
	0.431	41.056	0.495	47.153	6.097	0.457	43.533	0.570	54.297	10.764
	0.346	32.959	0.445	42.390	9.431	0.509	48.487	0.600	57.155	8.669
				Average=	**7.017**					**7.970**
				ST DEV[4] =	**2.109**					**3.201**
Synperonic TM PE/L-61	0.590	56.203	0.741	70.587	14.384	0.467	44.486	0.757	72.111	27.625
	0.379	36.103	0.575	54.774	18.671	0.586	55.822	0.832	79.255	23.434
	0.538	51.249	0.800	76.207	24.958	0.470	44.772	0.730	69.539	24.767
				Average=	**19.338**					**25.275**
				ST DEV =	**5.318**					**2.141**

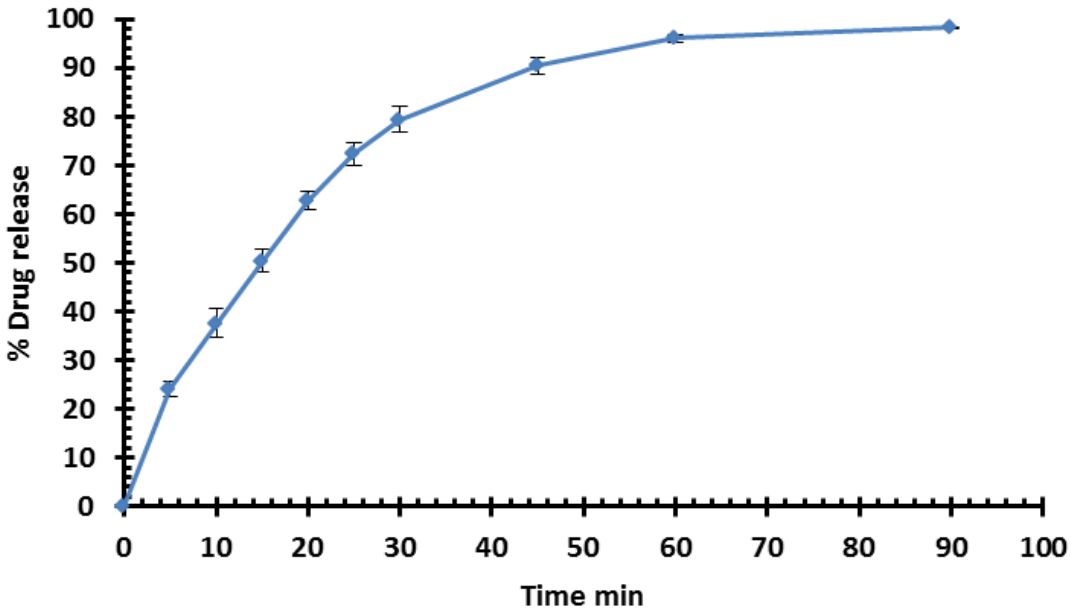


Figure 3-16: Dissolution profile of pure norfloxacin powder (20mg) in distilled water (pH=6.1).

[1] abs: absorbance at 321 nm wavelength

[2] %R : percentage of norfloxacin release in DW medium

[3] Difference: differences between the %R at 15 and 30 minutes.

[4] ST DEV: standard deviation of the difference

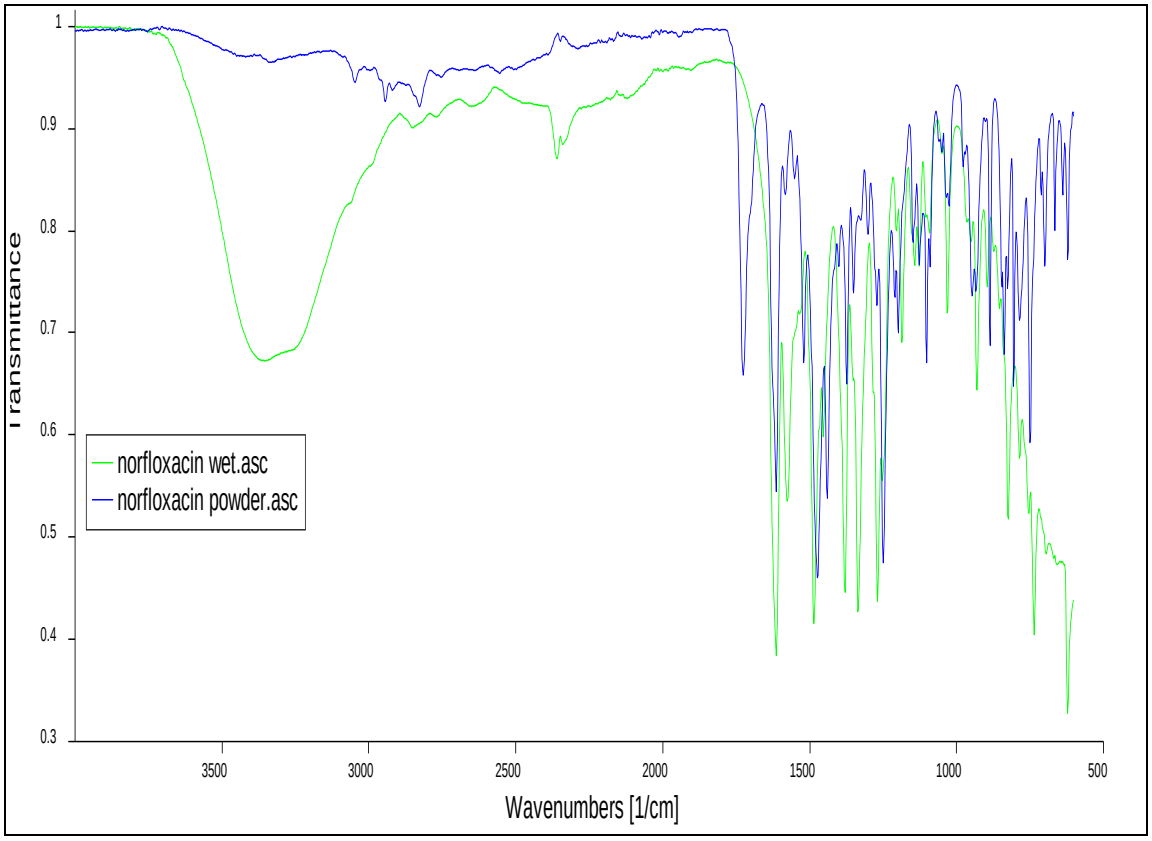
Table 3-4 and Figure 3-15 show clearly that there is a strong interaction between norfloxacin particles and PEG200, preventing water molecules to enter the solid framework of the drug particles, and reducing the percentage of norfloxacin released in dissolution medium from liquid medication compared to the conventional anhydrous form. This strong interacting layer is not seen in the case of the Synperonic ^{TM} PE/L-61 liquid medication (40% w/w), and a fragile layer, instead, was seen at concentration (20% w/w). As a result, the increased volume of liquid vehicle decreases the percentage of norfloxacin release, as the constituted interacting layer prevents water molecules to enter the liquid medication and induces the drug molecules to form ionic bonds like the case of the hydrated norfloxacin. Instead of this, hydrogen bonds are formed between the norfloxacin molecules themselves and the PEG200 and to some extent with Synperonic ^{TM} PE/L-61. One important point should be mentioned that the pure norfloxacin powder dissolution profile shows almost complete drug release in distilled water after 90 minutes (Figure 3-16); because the quantity of the drug is in sink condition and no liquid vehicles retard its dissolution.

The zwitterionic behaviour of the drug and the formation of interacting layers were confirmed by a FTIR investigation (see section 2.4.3). Figure 3-17 compares wet and dry norfloxacin powder FTIR spectra. In this figure, the assigned peaks of dry norfloxacin (anhydrous form) were similar to the previous work [74]. The wet norfloxacin spectrum shows a large broad peak at 3352 cm^{-1}, representing the hydroxyl group of water molecules. This peak is not identified in the dry norfloxacin powder. Another interesting peak that can be assigned is at 1576 cm^{-1}, which could represent the bend of $R_2NH_2^+$ in the structure of norfloxacin. It can be assigned in the both wet and dry IR spectra. The simultaneous appearance of two

bending vibration peaks (between 2700 cm^{-1}-2250 cm^{-1} and between 1600-1500 cm^{-1}) in the wet norfloxacin spectrum probably helps to confirm the existence of $R_2NH_2^+$ as a result of the proton transfer in the case of hydrated norfloxacin [60] & [73]. Moreover, the peak at 1730 cm^{-1} in the spectrum of the anhydrous form, which represents the C=O functional group in the anhydrous norfloxacin, moves to approximately 1630 cm^{-1} in the hydrated norfloxacin and become near to the peak at 1614 cm^{-1}. This phenomenon was assigned when norfloxacin forms a complex with metal ions [75]. One explanation is that the conjugated system results in the movement of electrons across the system from the lone pair of the nitrogen group on the same ring (see Figure 3-18). The electrons of the lone pair are shared in two ways.

Firstly they resonate into the ketone group and improve the electron density on the oxygen atom, strengthening the hydrogen bond to the hydrogen atom of the OH group (see the red arrows in Figure 3-18). This can be seen when the two FTIR peaks at 1630 cm^{-1} and 1614 cm^{-1} become nearer to each other (see the green line in Figure 3-17).

Secondly, the electrons can resonate with the (C=O) part of the carboxylic acid on the same ring (see the blue arrows in Figure 3-18), although this is not observed specifically on the IR spectrum. All in all, the presence of norfloxacin particles in water will lead to the formation of an ionic bond when the electron density on the ketone group increases, which interacts with the NH group of the next molecule via an incorporated water molecule between two norfloxacin atoms. Thus, the IR evidence supports proton transfer from the COOH group to NH group to form the zwitterion in the case of hydrated norfloxacin.



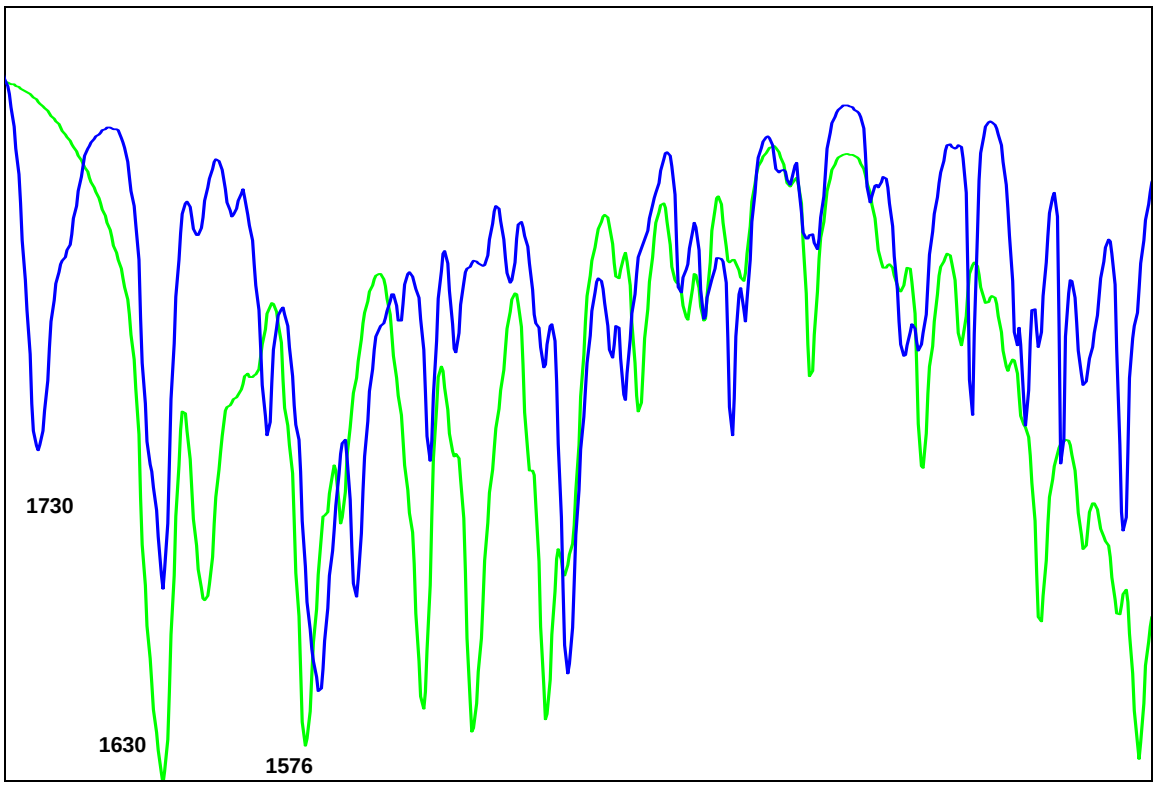


Figure 3-17: The upper part is a comparison between FTIR spectrum of norfloxacin dry powder (the blue line) and norfloxacin powder in distilled water (pH=6.1) (the green line), the bottom part is the maximization of the same spectra from wavelength 1730 cm^{-1} to 750 cm^{-1}.

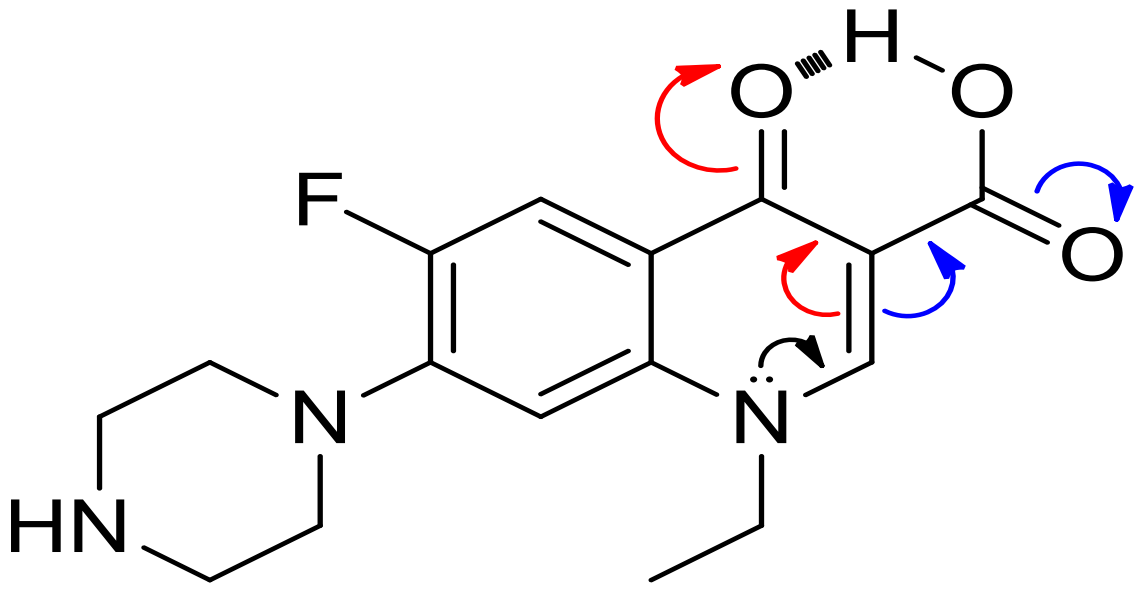


Figure 3-18: Chemical structure of norfloxacin with the possible conjugated systems.

Examining the spectra in Figure 3-19 helps to explain the formation of the interacting layer inside the DW dissolution medium, where the liquid medication consists of norfloxacin and the PEG200 liquid vehicle (20% w/w). The first assignment is that the peak at 2886 cm^{-1} in the PEG200 spectrum (green line, Figure 3-19) has disappeared in wet norfloxacin (black) and the liquid medication spectrum (red line, Figure 3-19). This can be used as evidence for the presence of an interaction between the drug and the liquid vehicle. Such an interaction is strong enough to resist the force of water flow in the dissolution vessel. Moreover, the large peak (3200-3500 cm^{-1}) decreased in the case of the liquid medication spectrum to represent a similar one in the PEG200 spectrum, suggesting that the content inside the interfacial layer is only norfloxacin and the surfactant and the water remain outside this layer.

The mixture of Synperonic ™ PE/L-61 with norfloxacin at 20% w/w made little change to the IR spectra of both components (Figure 3-20). The notable changes

were the reduction of the broad OH absorbance at 3200 cm^{-1} to 3300 cm^{-1} and the increasing of the fingerprint region peaks, which is consistent with the formation of an interfacial layer of Synperonic ™ molecules between the norfloxacin molecules. This slight change maintains the FTIR characteristic peaks of Synperonic ™ PE/L-61 in the spectrum of the mixture. The lack of change in the intense C-O absorbance at 1092 cm^{-1} of both Synperonic ™ EP/L-61 (red line, Figure 3-20) and the mixture with norfloxacin (green line, Figure 3-20) confirms the minimal role of C-O in the interaction. In conclusion, the formation of such a layer decreases the release of norfloxacin in the dissolution medium.

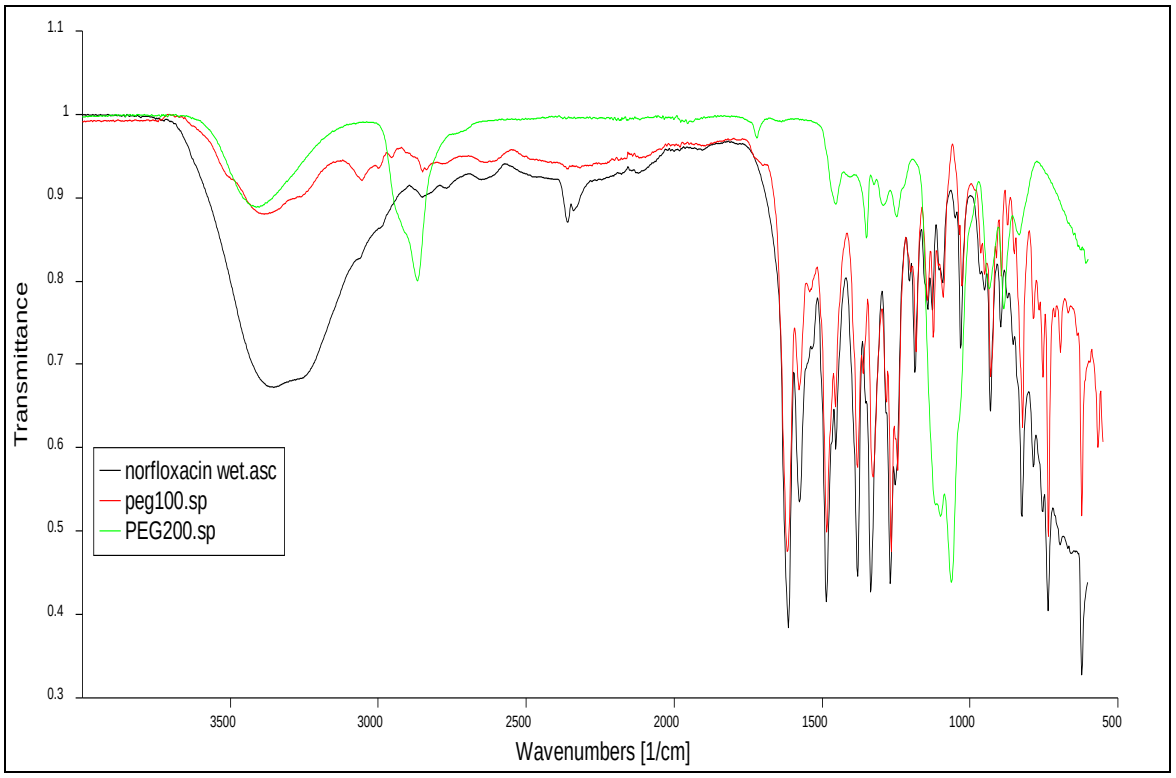


Figure 3-19: Comparison between wet norfloxacin (the black line), PEG200 (the green line) and the liquid medication consisting of norfloxacin and PEG200 at a concentration 20% w/w for 20 mg drug (the red line).

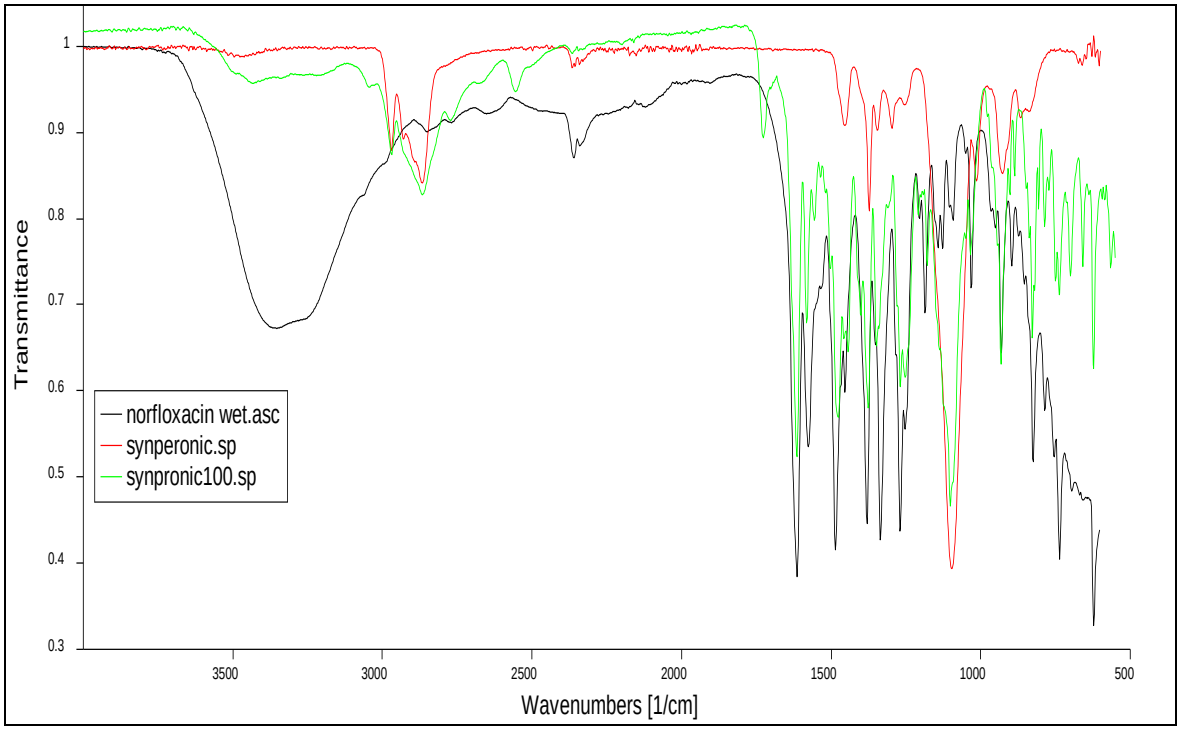


Figure 3-20: Comparison between wet norfloxacin (the black line), Synperonic ™ PE/L-61 (the red line) and the liquid medication consisting of norfloxacin and Synperonic ™ PE/L-61 at a concentration 20% w/w for 20 mg drug (the green line).

Moreover, all liquisolid and conventional tablets show a percentage of drug release less than 65% in distilled water. The reason of this in addition to the low percentage of norfloxacin ionization in distilled water is that the drug particles could precipitate inside the cavities of the porous carrier on contact with liquid medication with the release medium [13] . As a consequence of this, the drug release would retain. This can be noticed when the increase of the excipient ratio (R= 20). The higher percentage of Avicel® PH 101 leads to the lower percentage of the drug released in the dissolution medium. To overcome this problem, poly vinyl pyrrolidone (PVP) can be used as a crystallization inhibitor. Furthermore, PVP can also work as binder during compaction, which leads to an increase of the liquid load factor [13].

Finally, these factors affecting the percentage of drug release (e.g. Figure 3-10 and Figure 3-12) may enhance the oral bioavailability of these formulations. For

example, a solid dispersion formulation prepared at ratio (20:80) norfloxacin: PEG6000 presents better relative bioavailability (67%) when it is compared with powder of pure norfloxacin (49%) [76]. In the same study, which was carried out on male albinos' rabbits, the solid dispersion formulation showed maximum plasma concentration closer to the plasma concentration of norfloxacin acetic acid solution (pH = 4.5), which was recorded as 100% relative bioavailability [76], led to conclude that in our study, the liquisolid formulations of norfloxacin prepared with PEG200 are expected to enhance the drug oral bioavailability. Additionally, it is reported that aqueous solubility and the *in vitro* dissolution profile are not the unique explanation of the behaviour of the oral bioavailability of norfloxacin, although they help in indicating the physicochemical properties of the drug [76].

3.3.3. Kinetic model analysis of drug release:

Table 3-5 presents the values of the squared correlation coefficients for liquisolid and conventional tablets, using zero order, first order, Higuchi and Hixson-Crowell kinetic release models. Broader reporting, the highest R^2 values were recorded when applying Higuchi or Hixson-Crowell models for all types of tablets. Moreover, all liquisolid tablets containing Synperonic™ PE/L-61 have higher R^2 values than those including PEG200. In addition to this, the data which is considered to build the models are between 5 to 15 minutes, whereas the rest of the points (i.e. from 20 to 90 minutes) are excluded as the dissolution profiles reached to the steady state where the drug release gives a straight parallel line to the time axis. Paired t-test shows there is a slightly significant difference between R^2 values of both Hixson-Crowell and Higuchi models ($P=0.0051< 0.05$), where Hixson-Crowell recorded a slightly higher accuracy than Higuchi model. This situation is applied on all types of tablets, where all of them recorded R^2 values higher than 0.90.

Regarding Higuchi model, Fick's law consists of a fundamental diffusion background on which the release of norfloxacin into dissolution medium depends. This law states that a driving forces coming from a concentration gradient between the tablet and the bulk solution (C-Cs) diffuses the drug particles from tablet towards the dissolution medium [65]. As a consequence of this hypothesis, the dispersion of norfloxacin molecules in the liquid vehicles (PEG200 or Synperonic ^{TM} PE/L-61) would affect the increasing of the saturation solubility (Cs) and the relative concentration gradient (Cs-C) at different grades, allowing dissolving of the drug particles in the dissolution medium [14].

On the contrary, Hixson-Crowell release model does not take Fick's law in its assumptions. In other words, the diffusion of the drug particles from the tablet is not included here. Hixson-Crowell model states that there is a same effect of liquid agitation on the all parts of the surface, and no need to assume any particular shape of the drug crystal because the model consider all of them have a spherical shape through the solution. Consequently, the differences in the dissolution rate from different faces of the tablet are negligible, and the main effects of controlling the speed of the particle transformation are limited only to the proportional change of the surface with the time and the agitation. Therefore, the persistency of the drug particles to change its shape assumption as a cubic root relationship with the time gives the quantitative verification to the release model [66]. To some extent, the squared correlation coefficient values translate this assumption by dividing the tablets into two main groups; the first one includes all PEG200 liquisolid tablets which are less accurate, and the second includes the Symphonic PE/L-61 liquisolid and conventional tablets which are more accurate. As a result, the dispersion of the drug in the liquid vehicle may have the main effect in determining

the changing of the crystal shape during the dissolution test. Paired t-test signifies the difference in the accuracy of the Hixson-Crowell model when comparing with Higuchi model (P=0.0036< 0.05). This gives a further support to the Higuchi's assumption and explanations.

Table 3-5: Release parameters of norfloxacin liquisolid formulations (for more information about the formulation components, see Table 2-2).

Tablets/models	Liquid Vehicle	Zero	First	Higuchi	Hixson-Crowell
F1	PEG200	0.918725	0.926744	0.955216	0.924083
F2	PEG200	0.879475	0.885682	0.924325	0.883605
F3	PEG200	0.852812	0.863184	0.902309	0.859682
F4	PEG200	0.938769	0.953674	0.969966	0.948831
Conventional	-	0.999766	0.999173	0.996338	0.999802
F5	Synperonic PE/L-61	0.964378	0.971783	0.987057	0.969386
F6	Synperonic PE/L-61	0.997624	0.999196	0.999266	0.998764
F7	Synperonic PE/L-61	0.954916	0.968043	0.98105	0.963841
F8	Synperonic PE/L-61	0.984698	0.990493	0.997683	0.988700

3.4. Stability studies:

3.4.1. Content uniformity tests:

Table 3-6 represents a comparison between the percentage of norfloxacin in liquisolid and conventional tablets at the moment of making and after three months storage at 21 ^{o}C and 76% relative humidity. The all formulations show a high percentage of drug content (above 95%), indicating that there is no observed effect on the integrity of the drug. Moreover, comparison between the calculated values of the t-test for comparison of an experimental mean with a known value

shows that there is no significant difference between the average of the fresh and stored samples for each formulation at 99% confidence intervals (i.e. all absolute calculated t-test values are less than 9.92, which is the critical value of the t-test at 99% confidence intervals and degree of freedom =2).

Table 3-6: Averages , standard deviations and calculated T-test with degee of freedom (d.f =2) of the percentage of the fresh and stored norfloxacin content in the PEG200 and Synperonic™ PE/L-61 liquisolid tablets and conventional tablets.

Formula	Drug content uniformity (%) (number of replicates = 3)			
	Average % of Fresh samples	Standard deviations of % of fresh samples	% drug content after 3 months	Calculated values of T-test (d.f= 2)
F1	94.83	1.592	100.17	-5.809
F2	104.73	5.097	100.60	1.402
F3	94.90	3.164	104.72	-5.374
F4	96.74	7.510	96.39	0.080
F5	98.62	0.524	100.11	-0.557
F6	100.91	5.616	95.55	0.946
F7	100.49	5.052	98.31	0.891
F8	102.90	1.697	107.56	-7.218
Conventional tablet	99.94	2.279	101.55	1.027

3.4.2. Dissolution tests:

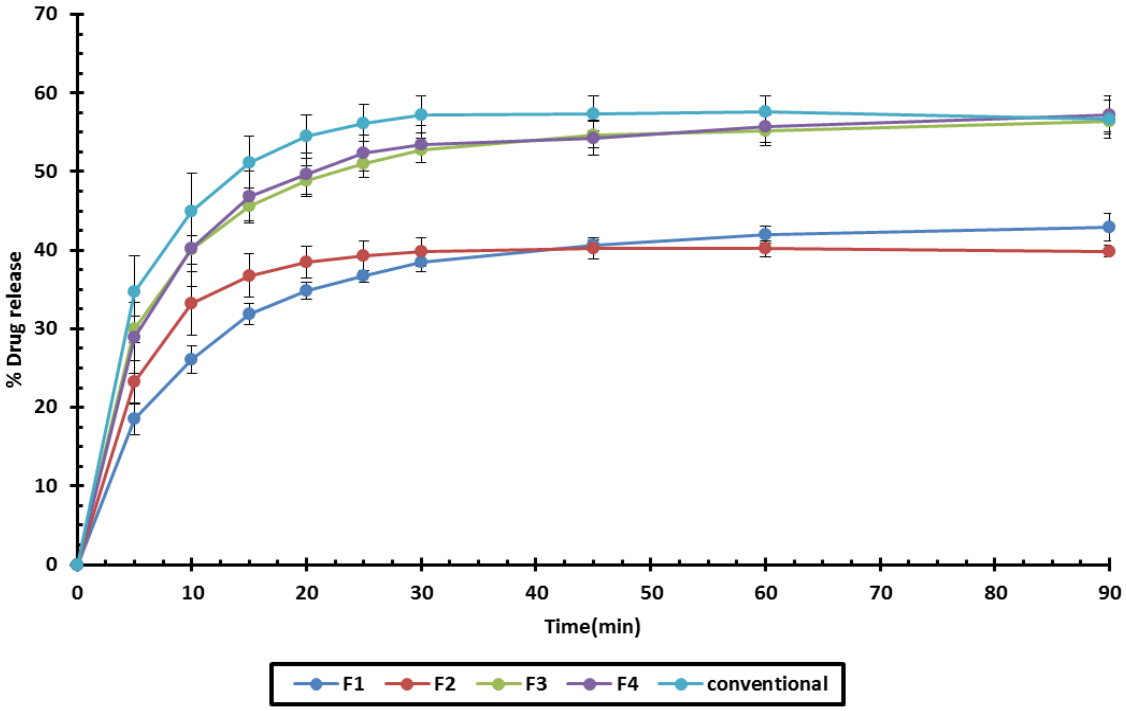


Figure 3-21: PEG200 and conventional tablets dissolution tests after 3 months in disilled water (pH=6.1).

The comparison between the dissolution profiles of the PEG200 liquisolid formulations at the moment of preparation (Figure 3-10) and after the storage (Figure 3-21) shows that there is no significant differences among them (similarity factor is always over 50% in these cases). However, the slight significant higher percentages over the conventional dissolution profile, which is noted in the fresh samples for the formulations R=10 and R= 20 at 40% w/w, disappears in the aging profiles. The similarity factor between the two liquisolid formulations and the conventional formulation is over than 50%. Nevertheless, the significant differences between the liquisolid formulations at 20% w/w and conventional and liquisolid formulations at 40% w/w remain the same after three month storage.

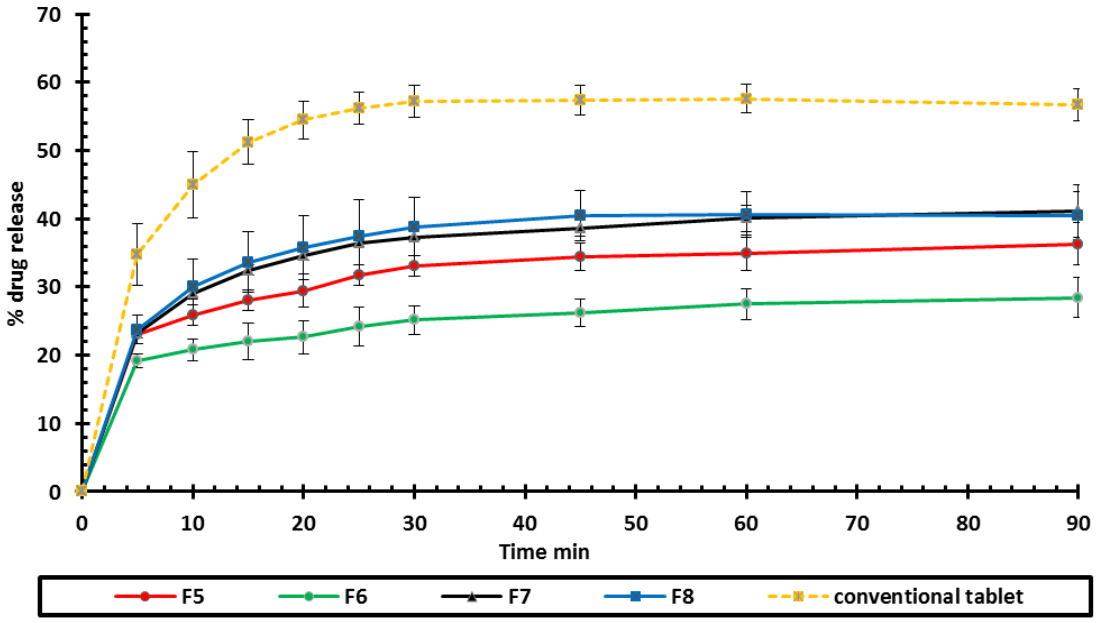


Figure 3-22: Synperonic™ PE/L-61 and conventional tablets dissolution tests after 3 months in distilled water (pH=6.1) .

Regarding the stability studies of the Synperonic ™ PE/L-61 liquisolid formulation dissolution profiles (Figure 3-22); there is a significant decrease in the drug release after 3 months storage. All Synperonic ™ PE/L-61 dissolution profiles recorded a percentage of norfloxacin release of less than 45%, whereas at the initial time, they ranged between 40% and 60% drug release [77]. The calculated similarity factors, comparing the initial trends (Figure 3-12) and after storage for the all classical Synperonic ™ PE/L-61 liquisolid formulations, show values less than 50%, showing significant decrease for all of these test samples. However, they keep the same arrangement comparing with the arrangement in the fresh samples (Figure 3-12).

The dissolution trends of the 40 %w/w of the Synperonic ™ PE/L-61 formulations were better than trends of the 20 %w/w of the Synperonic ™ PE/L-61 formulations both at time is zero and after three months. In conclusion, there is a significant negative effect of the presence of Synperonic ™ PE/L-61 in the liquisolid

formulation affecting the percentage of norfloxacin release in the DW dissolution medium.

3.4.3. Differential Scanning Calorimeter (DSC):

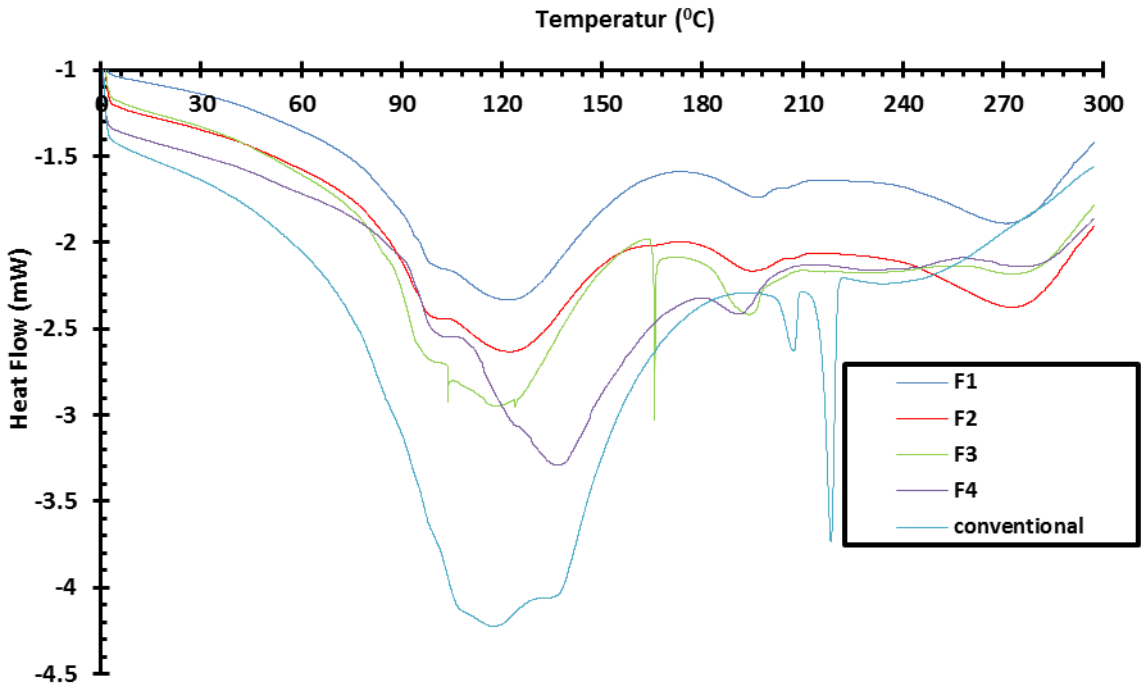


Figure 3-23: DSC thermographs for stored PEG200 liquisolid and conventional formulations.

Figure 3-23 represents all thermograms of the PEG200 liquisolid and conventional formulations after 3 months storage. The broaden peaks between 100 ⁰ C and 150 ⁰ C is clearer in the stored thermograms for all PEG200 liquisolid formulations. Moreover, small peaks can be noticed in the case of 40% w/w formulations at 191.6 ⁰ C, which completely disappears in the same fresh formulations (Figure 3-2). This may because the smaller amount of PEG200 in the formulation leads up to greater re-crystallization of the drug in the stored samples. Nevertheless, the effect of the PEG200 as a liquid vehicle on the crystalline nature of norfloxacin still can be indicated when comparing the conventional formulation with the liquisolid ones, regardless of the effect of the aging on the thermograms. For example, the

sharp endothermic peak at 218.51^{o}C in the conventional formulation, which represents the changing in the crystallinity of norfloxacin at its melting point, can be assigned in the both fresh and stored samples (Figure 3-2 and Figure 3-23). In general, PEG200 as a liquid vehicle keeps the liquisolid formulation stable thermally for at least three months.

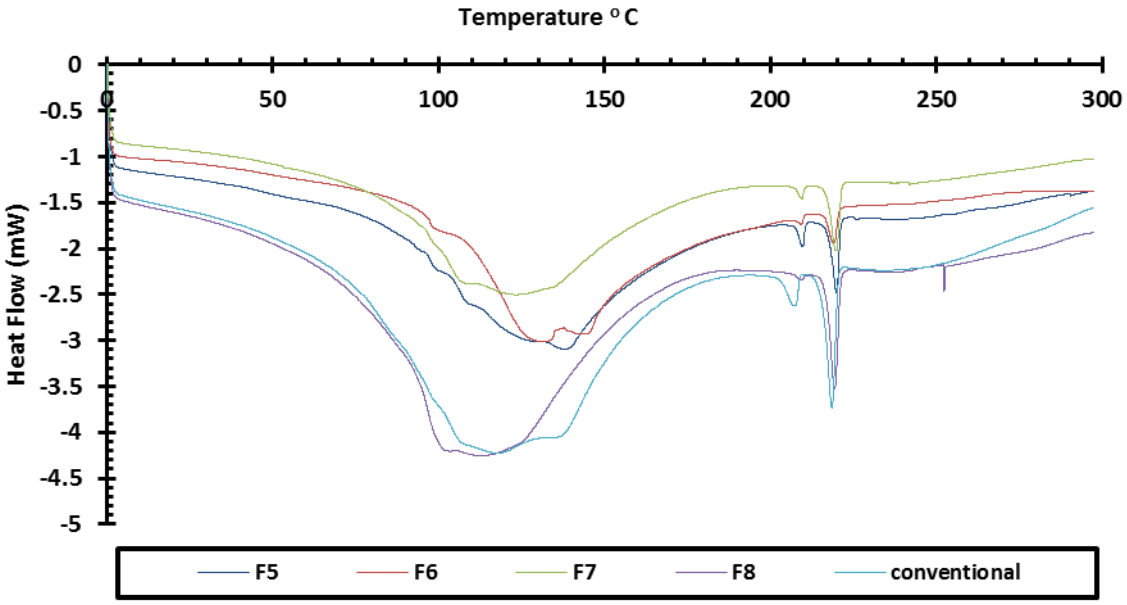


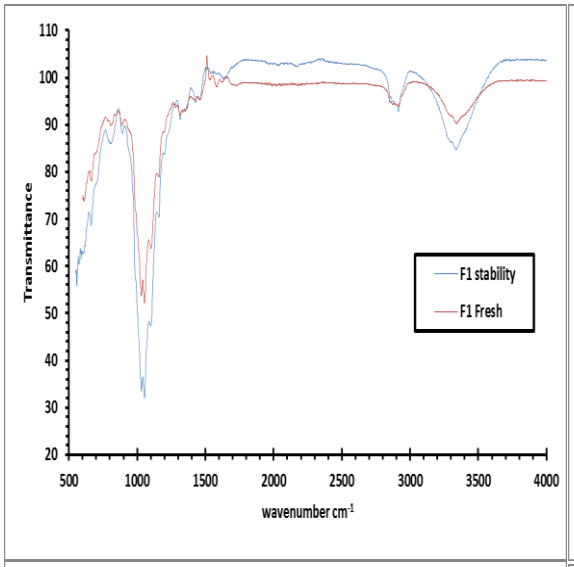
Figure 3-24: DSC thermographs for storage the Synperonic™ liquisolid and conventional formulations.

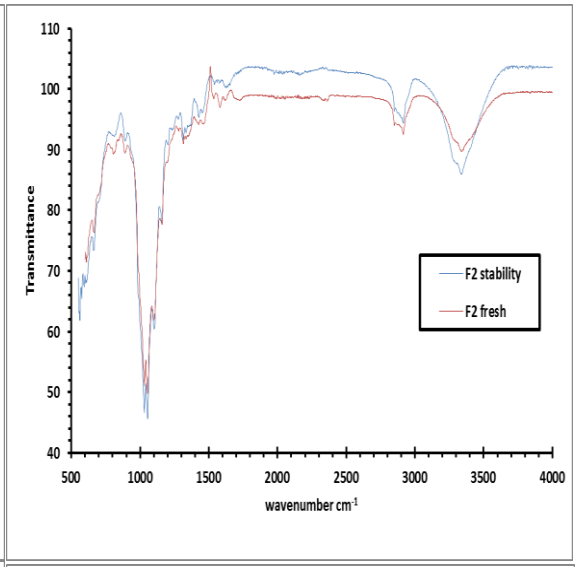
The broaden peaks that appears in PEG200 liquisolid formulations (Figure 3-23) can be also noted in Synperonic™ PE/L-61 liquisolid formulations in the both situations (Figure 3-24). However, these peaks have higher enthalpy values in the case of stored thermographs comparing with the fresh ones. In more details, the Synperonic™ PE/L-61 20% w/w has 49.13 J/g at R=10 and 66.57 J/g at R=20 with a temperature between 131 ^{o}C and 137 ^{o}C. Moreover, there is a decrease in the recorded temperature when the Synperonic™ PE/L-61 amount decreased to reach to 123.8 ^{o}C (85.97 J/g) at 40% w/w and R=10 and 112.2 ^{o}C (94.75 J/g) at the same amount of the liquid vehicle with R=20. In addition to this, tiny peaks were indicated at 219 ^{o}C in all classical liquisolid Synperonic™ PE/L-61 and

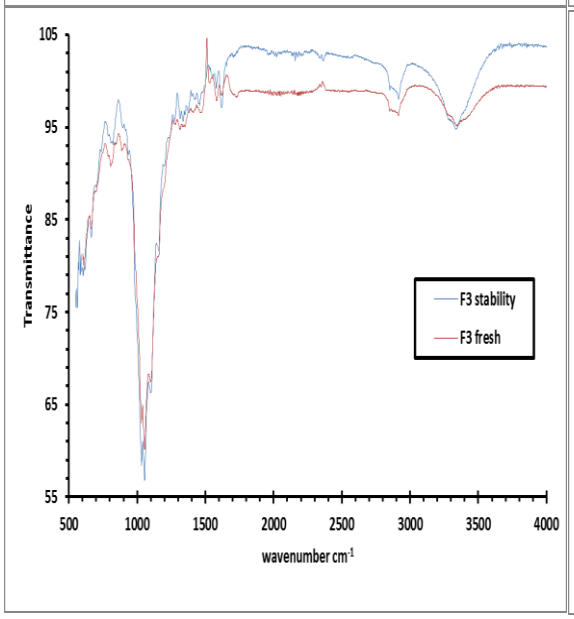
conventional stored formulations, which can be only assigned in the conventional fresh formulation, indicating partial interaction between the liquid vehicle and the drug affecting to some extent the dissolution. Finally, the enthalpy values of the endothermic peak at 221 ^{o}C are 2.107, 1.031, 2.625 and 2.847 J/g for the formulations from F5 to F8, respectively. These values indicated a slightly increase compared with the values for fresh formulations, which are 0.507, 0.6172, 1.110 and 1.024 J/g, respectively. This increase determines more crystallinity of the drug in the case of aged samples compared with the fresh ones.

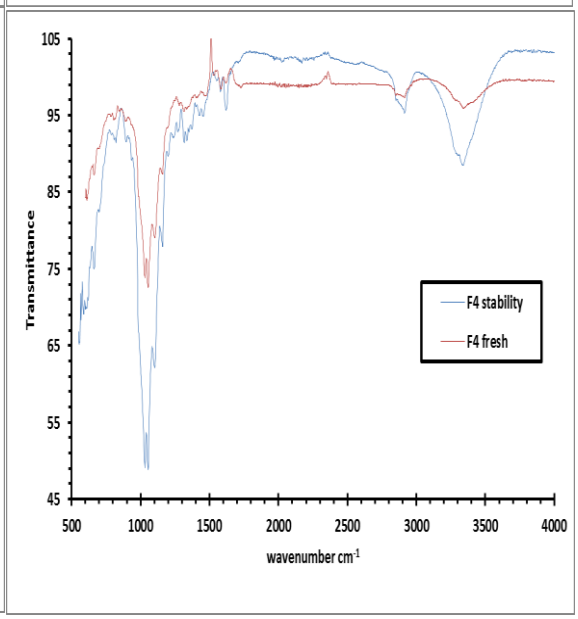
3.4.4. Fourier Transform Infrared (FTIR) analysis:

The studying of the all FTIR spectra before and after storage (Figure 3-25) shows that there is no difference in IR spectra between fresh and stored PEG200 liquisolid and conventional formulations. The differences in the value of the transmittance, noted in the spectra of the stored samples, could be referred to the contact between the sample and the beam in the device rather than recording any significant changes in the structure of the powder formulation due to the storage of the samples. These results correlate with the results of the content uniformity tests that show high percentages of the drug content in the stored samples.


Transmittance
wavenumber cm-1
F1 stability
F1 Fresh


Transmittance
wavenumber cm-1
F2 stability
F2 fresh


Transmittance
wavenumber cm-1
F3 stability
F3 fresh


Transmittance
wavenumber cm-1
F4 stability
F4 fresh

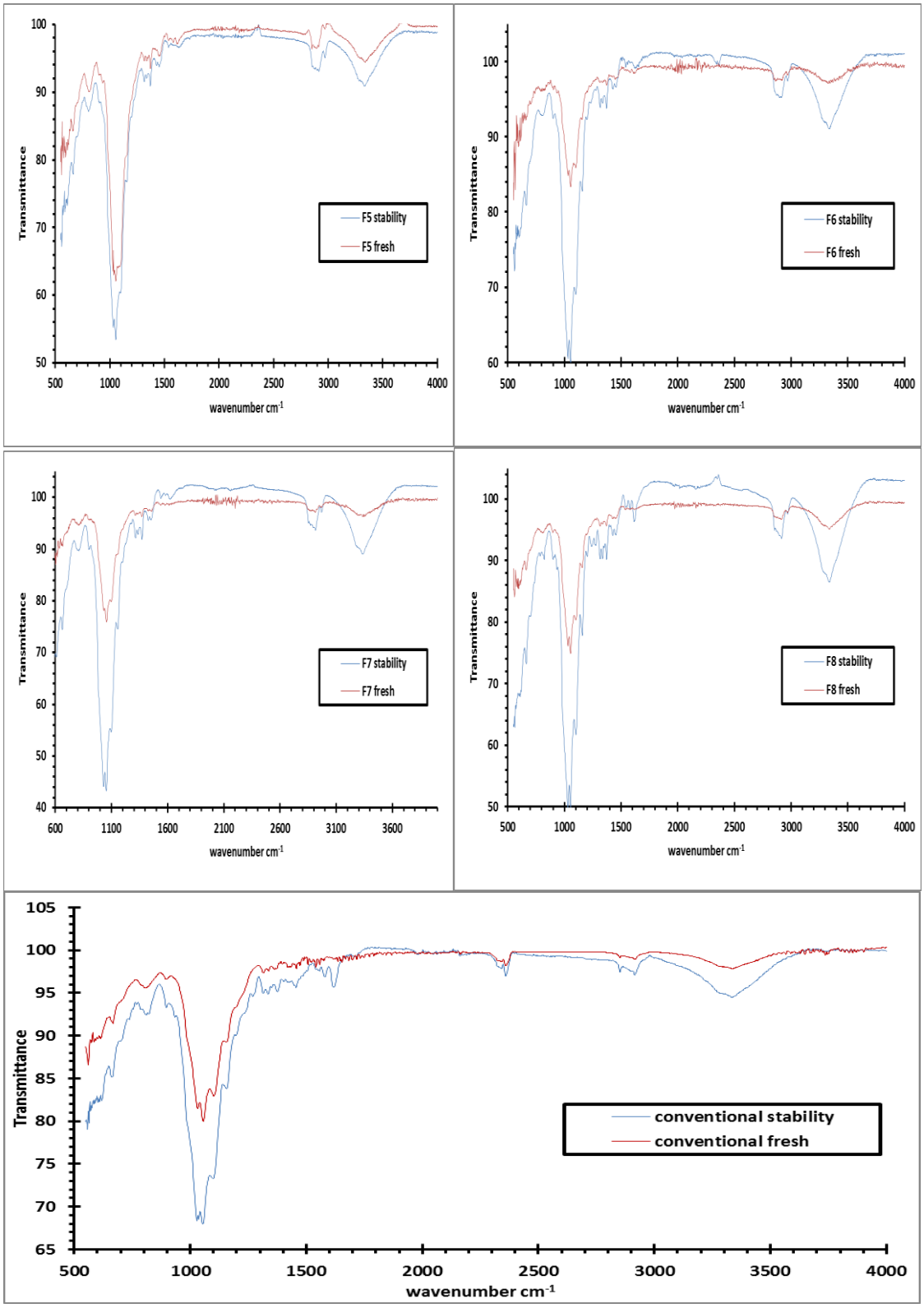


Figure 3-25: Comparison between the fresh and storage conventional and liquisolid (PEG200 and Synperonic ™ PE/L-61) formulations in terms of FTIR spectra.

3.5. Conclusion:

Norfloxacin releasing from the liquisolid tablets is not necessarily faster than conventional counterpart tablet. The chemical structure of the hydrophobic drug and its interaction with the liquid vehicle determines to large extent the dissolution behavior of the drug. Furthermore, this research represents that the solubility of the drug in the liquid vehicle is not necessarily considered as a main effect in liquisolid dissolution process.

On the other hand, using compressibility liquisolid test to indicate the optimum load factor in the case of Synperonic ™ PE/L-61 liquisolid formulations provide more consistent tablets comparing with PEG200 liquisolid tablets, which was prepared depending on the flowability liquid load potential of Avicel® PH 101 and Cab-O-Sil® M-5DP using angle of slide test, although the weight of the unite dose is lesser in the case of the PEG200 liquisolid formulations. Moreover, both DSC thermograms and the vibrational spectra of FTIR reflected the state of the crystallinity of the norfloxacin, which disappeared in liquisolid formulations, and the possible of hydrogen bond formation with liquid vehicle, respectively. Finally, it can be suggested that making further studies on using wet granulation in combination with liquisolid formulations so that it can work to enhance the flowability , compressibility and increase the percentage of norfloxacin release in distilled water dissolution.

Chapter Four: Water granulation for liquisolid tablets

4.1. Introduction:

The efficiency of the liquisolid technology comes from providing low-cost formulations, simulating production capability of conventional tablets, leading to enhancing the dissolution rate of hydrophobic drugs. However, these advantages could be restricted when the large amount of liquid vehicle needs to be applied or when using liquid vehicle with very low load factor (< 0.15) [77]. In these cases, the large amount of carrier and coating materials will be needed to reach to the dry, free flowing powders. An example of this problem was the liquid medication of norfloxacin with Synperonic ^{TM} PE/L-61, where the load factor was small and the amount of carrier/ coating system was high to prepare one unit dose.

Several studies suggested including extra additives in the liquisolid systems that not only increase the load factor, but also enhance and control the percentage release of hydrophobic drugs in aqueous dissolution medium. However, these works could only solve the problem related to improve the flowability behaviour of the liquisolid powder but they could not solve the problem related the tabletability so that it can reach to liquisolid tablets with acceptable crushing forces [16] & [31].

The present work aims to investigate the realm of combination between liquisolid technology and water granulation processes by calculating a new optimum load factor that provides acceptable compressibility, flowability and better dissolution profiles. Moreover, it compares between the classical (see chapter 3) and the new methods in order to determine the significant enhancement via this technology. Also, the study is supplemented with DSC, FTIR, stability and other quality control tests (content uniformity, friability, disintegration time and tensile strength tests) in

order to provide a comprehensive view about the water granulated liquisolid technology, compared with a classical liquisolid system.

4.2. Pre-formulation studies and characterisation of powder admixture:

4.2.1. Compressibility studies and determination of the new optimal compressibility load factor:

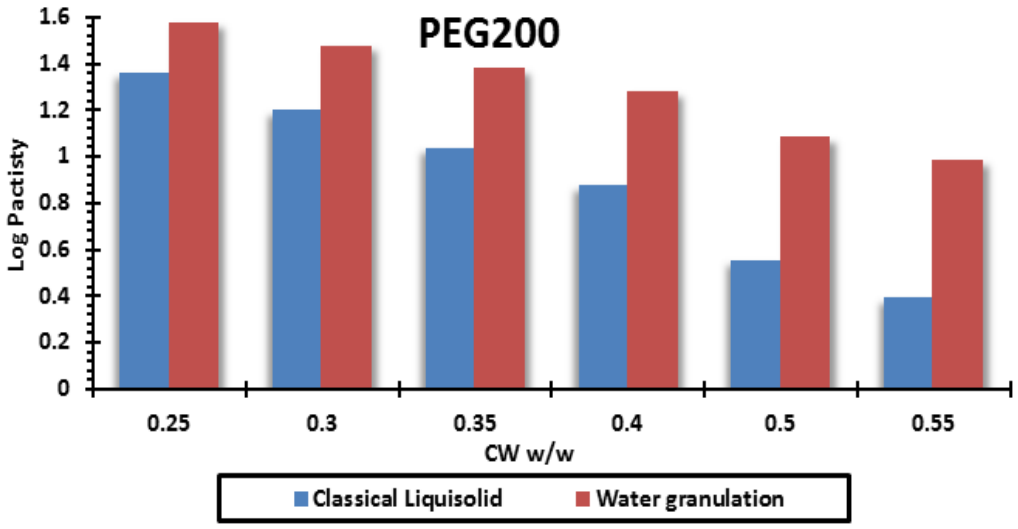


Figure 4-1: Log pactisity versus the (CW) in order to compare between classical and water granulated PEG200 liquisolid systems.

Figure 4-1 represents the relationship between Log pactisity, which is the logarithm of dividing the hardness of the tablet (KgF) by its weight (g), and the CW, which is the weight ratio of the liquid vehicle divided by the weight of the carrier and coating materials. Figure 4-1 also makes a comparison between water granulated liquisolid and classical liquisolid systems in term of using PEG200 as a liquid vehicle. It is clear that there is a significant difference between the classical liquisolid and water granulated liquisolid tablets (the probability of t-paired test is $0.00058 < 0.05$), although the decreasing trend of the log pactisity values with increasing amount of liquid vehicle does not change in the case of water granulation. Furthermore, it can be noted that when increasing the amount of

PEG200, the pactisity of the water granulation is more resistant to decrease than the classical formulations. A possible reason for this could be the ability of granulation to retain more liquid compared to the space provided from the same solid particles in the classical liquisolid formulations.

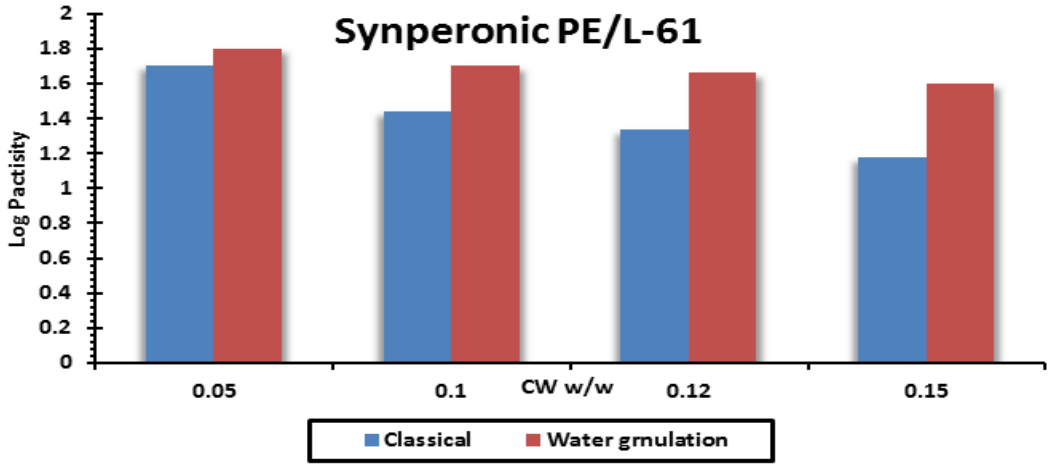


Figure 4-2: Log pactisity versus the CW in order to compare between classical and water granulated Synperonic ™ PE/L-61 liquisolid systems.

Similarly, Figure 4-2 represents the same comparison between the classical and the water granulated liquisolids, but using Synperonic ™ PE/L-61 as a liquid vehicle, and reflects the same conclusion compared with the PEG200 formulations (the probability of t-paired test is 0.0139 < 0.05), although it is a hydrophobic surfactant. This means that the water as a liquid binder does not affect the liquid vehicle. It only works on the solid particles in order to help form the granules, and hence it creates more capacity and space for the liquid vehicle. However, because of the chemical nature of the Synperonic ™ PE/L-61, the solid particles cannot accept as high an amount as PEG200, even though the water granulation powder system shows a significantly higher capacity.

In conclusion, the water granulation process provides a higher pactisity compared to the traditional process, and this improvement is seen regardless of the nature and the type of the liquid vehicle.

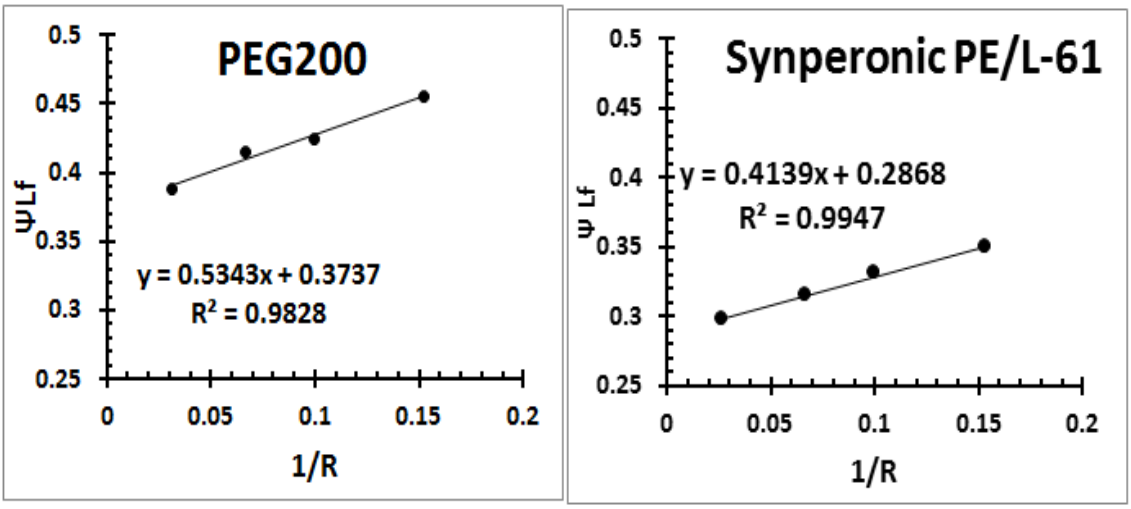


Figure 4-3: Linear models between the compressibility load factor (ΨLf) and reciprocal excipient ratio (1/R) for water granulated PEG200 liquisolid systems (left) and water granulated Synperonic™ PE/L-61 liquisolid systems (right).

Figure 4-3 shows the linear relationship between the compressibility load factor and the reciprocal R value of the water granulated PEG200 (left) and Synperonic ™ PE/L-61 (right) liquisolid powder systems. The compressibility load factor keeps its linearity with the reciprocal R value in water granulation liquisolid systems. In other words, the increased amounts of coating materials still results in increasing amounts of liquid vehicle retained inside the liquisolid system, whether PEG200 or Synperonic ™ PE/L-61 is used. The highest compressible load factor for PEG200 is approximately 0.454 at the minimum used R value, which equates to 6.59 in this example. The counterpart of the compressibility load factor for the same R values but in the traditional liquisolid is 0.309. This shows a significant improvement which is contributed by the water granulation process. Also, the load factor of Synperonic ™ PE/L-61 at R=10 is 0.33, whereas for the classical Synperonic ™

PE/L-61it equals 0.139. This means that the enhancement due to the water granulation process is more than double [77]. The probable explanation could be that there is a contribution between the carrier and the coating particles for making strong granules with higher resistance to crushing forces. This could be added to the factor of the formation of granulated carrier particles, which increases the capacity in order to retain the liquid vehicle inside its space.

From Figure 4-3, the slope of the linear equation for the PEG200 formulation is higher than the slope for the Synperonic ™ PE/L-61 linear equation. This means that the PEG200 formulations have more susceptibility towards change in the value of the coating materials comparing with the Synperonic ™ PE/L-61. This is particularly important for the industrial large scale production, because the ability to control the formation of the Synperonic ™ PE/L-61 batches is more difficult than the PEG200 liquisolid batches. In addition, as the Synperonic ™ PE/L-61 does not have the same binder properties compared with the PEG200, it could reach the compressibility acceptable plateau before the PEG200 formulations, meaning that the increase in punch forces will not increase the crushing strength. This phenomenon could not be detected in the classical liquisolid formulations, as the quantity of the solid powder system is high and so the single unit dose is divided into several smaller tablets. It is only noticed in the case of the Synperonic ™ PE/L-61 water granulated liquisolid system because the quantities of the solid particles have been reduced.

4.2.2. Flowability studies and the determination of angle of slide:

The angle of slide method was used to evaluate the flowability of the water granulated liquisolid systems. Figure 4-4 represents the average and the standard

deviations for a comparison between CW (w/w) and the relative angle of slide for the both liquid vehicles (PEG200 and Synperonic TM PE/L-61) in the classical liquisolid and the water granulated liquisolid powder systems.

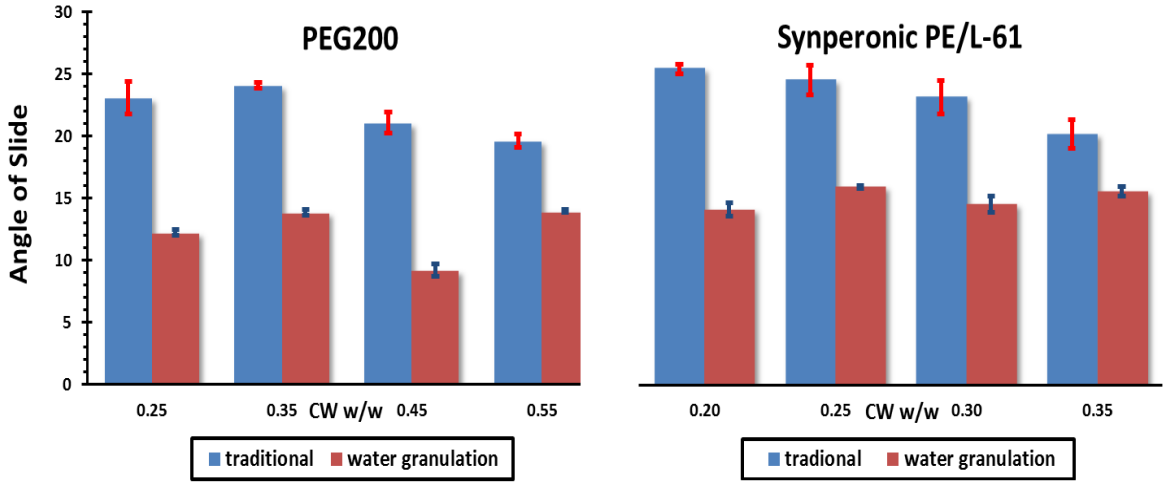


Figure 4-4: Comparison between water granulation and classical liquisolid systems in terms of angle of slide at different CW (w/w).

As expected, the significant decrease in the value of the angle of the slide is recorded with the water granulated liquisolid systems whether it contains PEG200 or Synperonic TM PE/L-61, compared with the classical ones (Figure 4-4). This improvement can be expressed statistically through the probability of the t-paired test, which is 0.0029 < 0.05 in the case of the PEG200 formulations and 0.0047 < 0.05 in the case of the Synperonic TM PE/L-61 formulations.

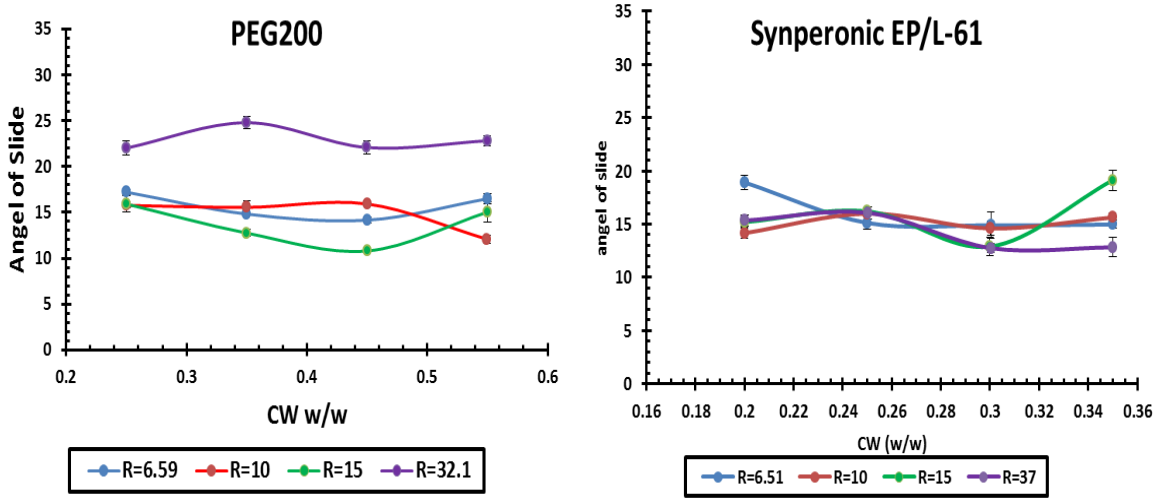


Figure 4-5: Comparison between water granulated PEG200 liquisolid systems (left) and water granulated Synperonic™ PE/L-61 liquisolid systems (right) at different R values in term of angle of slide with CW (w/w).

In addition, investigation of the R effect according to the relative CW values leads to the conclusion that, in the case of PEG200 water granulated liquisolid systems, there is a slight increase in the values of the angle of the slide when the R value increases, whereas this increase cannot be detected in the case of Synperonic ™ PE/L-61 water granulated liquisolid systems (Figure 4-5). This means that the percentage of the carrier to coating materials cannot change the angle of the slide because the spherical shape of the formed granules gives near the angle values with small variations compared to the classical formulations. Therefore, the linear correlation between the flowability load factor and the reciprocal R is not detected in the range of the optimum compressible load factor. In other words, the liquisolid systems may need larger quantity of liquid until the linear horizontal line between the CW and the angle of the slide becomes exponential (i.e. the angle value equals to 33^{o} or more). At this level, the relationship between the flowability load factor and 1/R could become linear to some extent [78]. However, the tablets will not be compacted at that amount of liquid vehicle.

4.2.3. Differential scanning calorimetry (DSC):

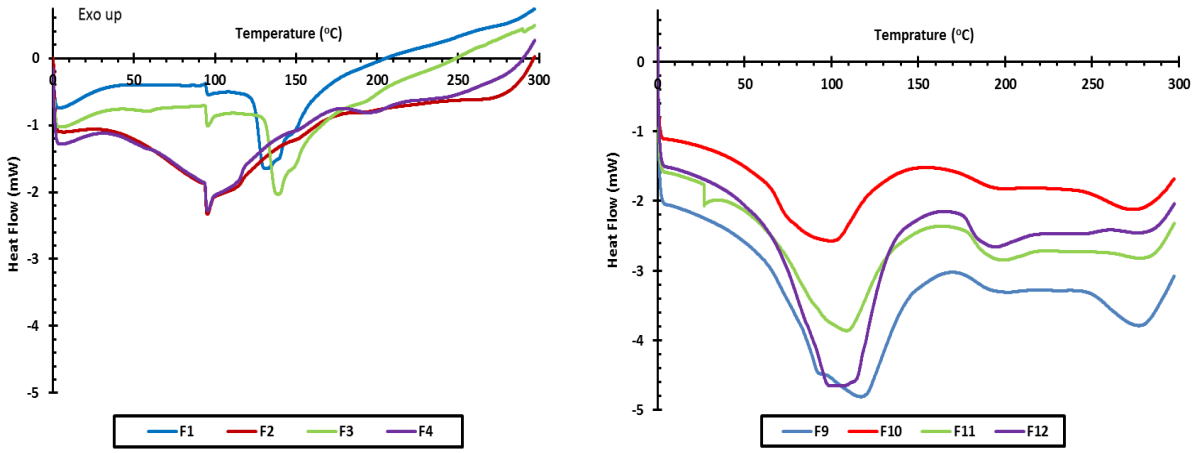


Figure 4-6: Comparison between classical PEG200 liquisolid systems (left) and water granulated PEG200 liquisolid systems (right) in terms of DSC thermographs (for formulation composition refer to Table 2-3).

As norfloxacin pure drug has a sharp endothermic peak at melting temperature (222 °C) with relatively high enthalpy value (107.7 J/g)(see Figure 3-2), the investigation of all of the water granulated liquisolid formulations should be in the range of the melting temperature of norfloxacin in order to assign the effect of wet granulation liquisolid formulations. Any changes in the endothermic peak or shifting of the melting temperature will appear as an effect of the non-volatile liquid vehicle as well as the effect of the water granulation on the active ingredient thermally.

The comparison between the thermographs of water granulated PEG200 liquisolid formulations (Figure 4-6, right) and the classical PEG200 liquisolid formulations (Figure 4-6, left) indicates two regions of particular interest.

The first one lies between 70 °C and 110 °C. The presence of these broad endothermic peaks could relate to the presence of PEG200 and Avicel® PH 101

[79] and [80]. However, these peaks appear to be deeper in the wet granulation formulations than in classical liquisolid formulations because they contain more water droplets, which lead to broader endothermic peaks. The second region is around 190 ^{o}C, which appears in both of the water and classical formulations. This could relate to the interaction between PEG200 and the crystals of norfloxacin, leading to a decrease and shifting back in the endothermic peaks of the pure drug. However, these peaks are clearer in the case of the water granulation formulations, due to the decrease in the weight of carrier and coating materials.

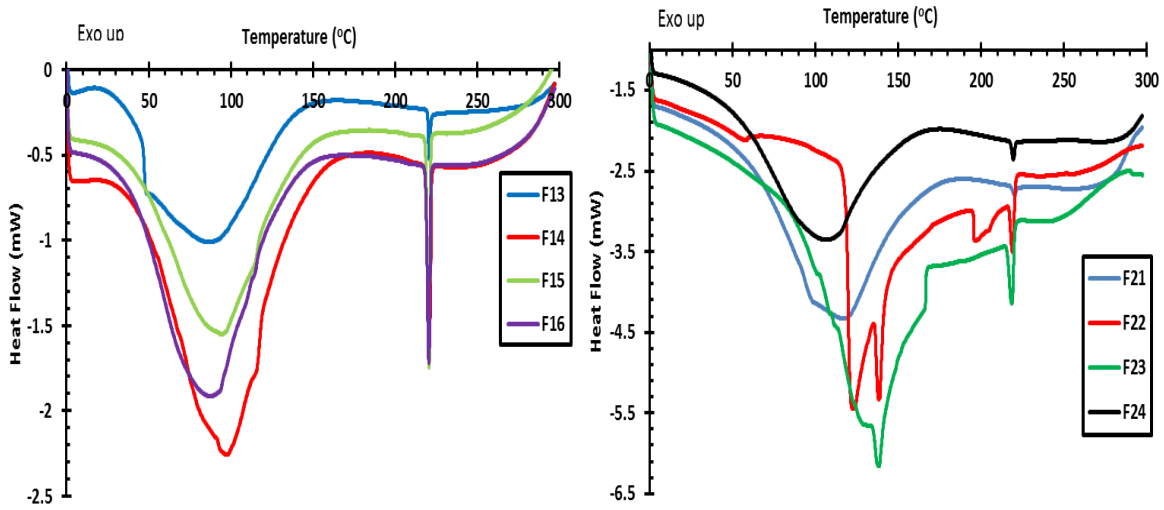


Figure 4-7: Comparison between classical Synperonic™ PE/L-61 liquisolid systems (left) and water granulated Synperonic™ PE/L-61 liquisolid systems (right) in terms of DSC thermographs (for more information about the formulation components, see Table 2-3).

In the case of the Synperonic™ PE/L-61 formulations (Figure 4-7), the distinctive peaks appear in the both types: water granulation and classical norfloxacin liquisolid systems. The first broad peaks, around 125 ^{o}C, come from the combination effects of the granules to take up more liquid vehicle compared to the classical formulations. This capability prevents the water to be evaporated easily especially if the liquid vehicle accumulates inside the cavity of the granules, reaching to the surface so that it covers the water molecules that present between

the solid particles. As Synperonic ™ PE/L-61 is a hydrophobic liquid vehicle and it is an immiscible liquid vehicle with water, in contrast with the PEG200, the water droplets need more heat to evaporate; this is seen in the formulations of Synperonic ™ PE/L-61 and not in the conventional powder without liquid vehicle, which is more similar to PEG200 formulations. The second region, at approximately 220 ° C, appears in the water-liquisolid granules as well as in the classical formulations, indicating that the drug is not soluble completely in the surfactant so that there is no complete interaction between them. The enthalpy values are 0.04497, 0.24, 0.0452, 0.09118 J/g for the formulations from F21 to F24, respectively. These enthalpies indicate that the crystallinity of the drug is still at its minimum values.

4.2.4. Fourier Transform Infra-red (FTIR) analysis:

Figure 4-8 and Figure 4-9 show a comparison between the FTIR spectra of the classical liquisolid and water granulation liquisolid norfloxacin formulations for both PEG200 and Synperonic ™ PE/L-61. As expected, there is no significant difference between the two types of formulations. The water as a liquid binder in this situation affects only the construction of granules without making any changes to the wavenumber or the peaks. Moreover, it is noted that most of the water molecules used in the granulation process evaporate during the drying process at 80 ° C without making bonds with PEG200 or Synperonic ™ PE/L-61. It does not make bonds with the pure norfloxacin particles, keeping the interaction only between the norfloxacin and the liquid vehicle (PEG200 or Synperonic ™ PE/L-61).

This could suggest water as a liquid binder with no negative effects in drug release in the neutral dissolution medium. In other words, added water in this situation will

not lead to crystallization. It just affects on the shape and capability of the carrier and coating materials to adsorb more liquid vehicle to its internal structure.

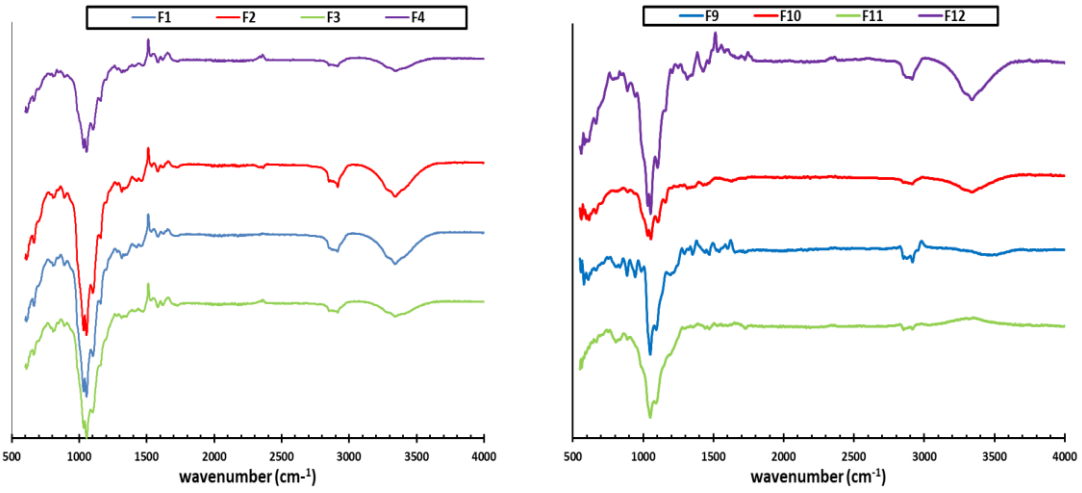


Figure 4-8: Comparison between the FTIR spectra (Y-axis is % Transmittance) of norfloxacin in classical PEG200 liquisolid systems (left) and water granulated PEG200 liquisolid systems (right) (for more information about the formulation components, see Table 2-3).

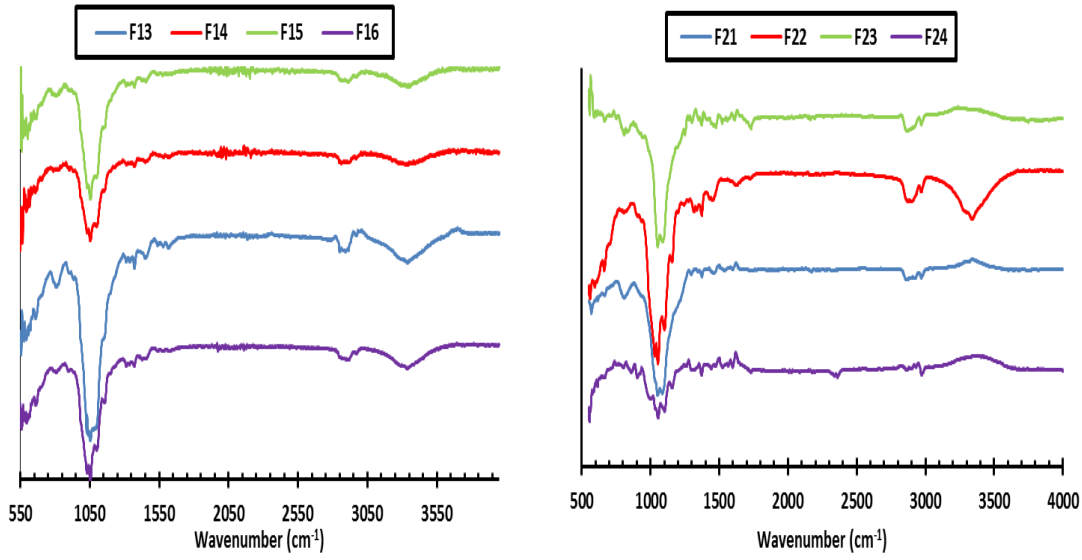


Figure 4-9: Comparison between the FTIR spectra ((Y-axis is % Transmittance) of norfloxacin in classical Synperonic™ PE/L-61 liquisolid systems (left) and water granulated Synperonic™ PE/L-61 liquisolid systems (right) (for more information about the formulation components, see Table 2-3).

4.2.5. Determination of flow properties:

Table 4-1: Comparison between classical liquisolid and water granulated liquisolid formulations for PEG200 and Synperonic™ PE/L-61 liquid vehicles in terms of compressibility index (CI%) and Hussner's ratio (H ratio) (for more information about the formulation components, see Table 2-3).

formula	flowability of classical liquisolid PEG200					
	Tapped density (g/cm^3)	bulk density (g/cm^3)	CI%	position	H ratio	position
F1	0.50	0.39	22.22	poor	1.29	passable
F2	0.58	0.44	23.64	poor	1.31	passable
F3	0.62	0.42	31.58	poor	1.46	very poor
F4	0.56	0.40	29.03	poor	1.41	poor
formula	flowability of water granulation liquisolid PEG200					
	Tapped density (g/cm^3)	bulk density (g/cm^3)	CI%	position	H ratio	position
F9	0.57	0.42	26.83	poor	1.37	poor
F10	0.51	0.36	29.17	poor	1.41	poor
F11	0.52	0.37	29.17	poor	1.41	poor
F12	0.47	0.33	29.63	poor	1.42	poor
formula	flowability of classical liquisolid Synperonic™ PE/L-61					
	Tapped density (g/cm^3)	bulk density (g/cm^3)	CI%	position	H ratio	position
F13	0.44	0.33	24.11	passable	1.32	passable
F14	0.45	0.36	21.21	passable	1.27	passable
F15	0.46	0.32	31.03	poor	1.45	poor
F16	0.56	0.36	35.38	very poor	1.55	very poor
formula	flowability of water granulation liquisolid Synperonic™ PE/L-61					
	Tapped density (g/cm^3)	bulk density (g/cm^3)	CI%	position	H ratio	position
F21	0.52	0.38	26.79	poor	1.37	poor
F22	0.46	0.34	26.47	poor	1.36	poor
F23	0.59	0.43	25.93	poor	1.35	poor
F24	0.50	0.35	28.57	poor	1.40	poor

The flowability of powder has effects on the feeding of the powder from the hopper to the punch in the tablet machine. As a consequence of this, it has a critical role in the tablet weight and drug content uniformity. Table 4-1 shows a comparison in flowability between the classical liquisolid and water granulated liquisolid formulations containing norfloxacin in both liquid vehicles; PEG200 and Synperonic™ PE/L-61. This table includes two methods: Hausner ratio and Carr's compressibility index from the relative values of the tapped and the bulk densities. According to the criteria of the British Pharmacopoeia [56], all formulations whether they are water granulated liquisolid or classical liquisolid have poor

flowability, except the first two classical Synperonic ™ PE/L-61 formulations where the quantity of the liquid vehicle is higher. Thus, it leads to the use of a higher amount of carrier and coating materials so that they partially improve the flowability of the powder bed. Apart from this, all formulations do not show a decrease in the value of the Hausner ratio or the Carr's index. The reason for this can be referred to the prevalent characterisation of Avicel® PH 101, which it has a documented poor CI% equals to 28.89 [81] & [82]. Although the poor flowability characteristic is the predominant feature of most of the formulations, it still differentiates between the classical liquisolid and water granulated liquisolid formulations. The water granulated liquisolid powders show less difference in the values of CI% compared to the relative classical liquisolid formulations. In the case of PEG200 formulations, the difference between the highest and the lowest CI% is less than 3%, whereas this difference increases to more than 9% in the classical liquisolid formulations. In the same manner, the difference between the highest and the lowest CI% in the case of water granulated Synperonic ™ PE/L-61 liquisolid formulations is only 2.1%, whereas this value raises to 14.17% in the classical liquisolid formulations. This phenomenon could be explained as follows; as the main effect of the significant differences in the classical formulations is from the quantity of the liquid vehicle (PEG200 or Synperonic ™ PE/L-61), the water granulation process seems to overcome this problem through creating more consistent bed powder in the term of flowability, decreasing the limit of the variation in the powder flow behaviour. Supporting this conclusion, the values of the angle of the slide for all water granulated liquisolid formulations come in the same range (Figure 4-5). As a result, the optimum load factor calculation becomes dependent on the compressibility load factor, mainly to indicate the exact amount

of the liquid vehicle that required tablets with acceptable compressibility characteristics.

4.3. Evaluation of water granulated liquisolid tablets:

4.3.1. Drug content uniformity, tablet dimensions, hardness, tensile strength, friability and disintegration tests:

Table 4-2: Content uniformity, friability, tensile strength, hardness and disintegration tests for norfloxacin tablets in classical liquisolid and water granulated liquisolid systems (for more information about the formulation components, see Table 2-3).

Classical PEG200	Content Uniformity (%)	Friability (%)	T-strength (MPa)	Hardness (N)	Disintegration Time (sec)
F1	97.43 +/- 2.922	0.474	0.97 +/- 0.209	51.98 **+/-** 3.756	105 +/- 24
F2	106.12 +/- 4.769	0.405	1.66 +/- 0.406	91.94 **+/-** 21.521	111 +/- 0
F3	96.85 +/- 0.980	0.842	0.85 +/- 0.103	45.36 **+/-** 4.189	49 +/- 8
F4	96.15 +/- 7.889	0.724	0.78 +/- 0.094	45.60 **+/-** 7.184	40 +/- 5
Water Granulated PEG200					
F9	108.03 +/- 0.512	0.260	1.07 +/- 0.178	72.57 **+/-** 12.677	347 +/- 39
F10	98.34 +/- 0.998	0.122	1.24 +/- 0.177	86.00 **+/-** 11.778	369 +/- 39
F11	98.31 +/- 1.836	0.639	0.75 +/- 0.088	27.36 **+/-** 3.184	165 +/- 4
F12	107.27 +/- 2.234	0.291	0.96 +/- 0.330	35.11 **+/-** 11.284	116 +/- 16
Classical Synperonic					
F13	97.91 +/- 4.189	0.304	1.29 +/- 0.092	46.85 **+/-** 3.014	197 +/- 28
F14	100.19 +/- 4.785	0.275	1.21 +/- 0.075	57.75 **+/-** 3.585	199 +/- 57
F15	103.44 +/- 1.128	0.167	1.33 +/- 0.072	48.27 **+/-** 2.933	81 +/- 9
F16	102.57 +/- 2.175	0.338	1.17 +/- 0.048	58.26 **+/-** 2.418	61 +/- 3
Water Granulated Synperonic					
F21	96.17 +/- 3.936	0.080	1.12 +/- 0.023	44.33 **+/-** 0.820	84 +/- 6
F22	96.77 +/- 2.438	0.000	1.13 +/- 0.019	44.13 **+/-** 0.693	113 +/- 12
F23	100.90 +/- 0.305	0.110	1.06 +/- 0.055	43.15 **+/-** 2.402	38 +/- 2
F24	100.59 +/- 1.075	0.209	1.23 +/- 0.050	46.68 **+/-** 1.487	50 +/- 9

Table 4-2 shows a comparison between norfloxacin tablets in the water granulated liquisolid and the classical liquisolid systems for PEG200 and Synperonic ™ PE/L-61 liquid vehicles of the content uniformity, friability, tensile strength, hardness and disintegration tests in terms of means and standard deviations.

The results of content uniformity tests show that the all formulations are within the British Pharmacopoeia specific limits (i.e. between 85% and 115%) [56]. Further investigation of the data shows that the values of the standard deviations in the water granulated liquisolid formulations have smaller values compared to the relative classical ones, although the steps of preparations in the case of wet granulation is more, leading to higher probability of errors and variations. This probably means that formation of the granules support the distribution of the liquid medication inside the solid structure framework, and the liquid binder (water) works compatibly with the liquid vehicle on this role.

Regarding the test of the tensile strength, statistical analysis confirms that there is no significant differences between the water granulated liquisolid and the classical liquisolid tablets for both types of liquid vehicles. The probability value from applying paired t test is 0.68 > 0.05 in the case of PEG200 formulations and 0.2 > 0.05 in the case of the Synperonic ™ PE/L-61 formulations. This could be expected because the design of the water granulated liquisolid formulations depend on the value of the pactisity which is related directly to the hardness and inversely to the tablet weight. Also, the tensile strength depends directly on the hardness and inversely on the thickness of the tablet, which is related directly to the weight of the tablet. As the compressibility load factor is calculated at the

optimum limit (i.e. 20 Kg F/1 g) for the all water granulated liquisolid formulations and all Synperonic TM PE/L-61 classical formulations, and as the selected flowability load factor in the case of the PEG200 classical liquisolid formulations should meet the criteria of acceptability [6], there should be no differences between them. The comparison between Synperonic TM PE/L-61 and PEG200 water granulated liquisolids supports this conclusion, and the probability of the t-paired test between Synperonic TM PE/L-61 and PEG200 water granulated liquisolid equals to 0.28 > 0.05, indicating that there is no significant difference between them in terms of tensile strength.

The hardness of the liquisolid tablets relates to the quantity of the liquid vehicle, the type of the liquid vehicle and the amount and the type of the carrier and coating [6]. The combination between wet granulation and liquisolid affects the hardness of the tablet [83] and [31]. In this study, there are no significant differences between classical and water granulated liquisolid for both types of liquid vehicles, due to the enhancement of the hardness that is provided by the granulation process in decreasing the amount of the coating and carrier inside the formulae, keeping the pactisity at the optimum level [6]. Instead of hardness test alone, the pactisity in these formulations could clarify the strength of the wet granulated liquisolid tablets.

The friability tests show an excellent resistance for the water granulated liquisolid tablets: no formulations reached 1% loss, meeting the demands of the British Pharmacopoeia criteria. Finally, the test of disintegration shows that significant differences in the case of PEG200 formulations when applying t-paired test (p-value = 0.031 > 0.005). As PEG200 has a binder property, increasing it in the formulation will prolong the time of the disintegration. Moreover, in the new water

granulation, the decreased amount of the carrier and coating accompanies a decrease in the tablet weight. Thus, the amount of disintegrant used in the formulation will be less than the amount used in the case of the classical liquisolid, although they have the same percentage in the unit dose (5%).

In the case of the Synperonic ™ PE/L-61 formulations, the liquid vehicle does not show binder properties like PEG200. Moreover, the quantity of disintegrant is high due to the lower values of the compressibility load factor in the classical formulation (Lf < 0.15), and does not decrease it to a limit that make a significant differences in the case of the water granulated Synperonic ™ PE/L-61 liquisolid preparations. Nevertheless, none of the formulations exceed 5 minutes disintegration time.

In conclusion, it can be said that water granulated liquisolid formulations show better drug distribution, low friability and short disintegration time with acceptable hardness and tensile strength.

4.3.2. *In vitro* dissolution Studies:

It is clear that the percentage of norfloxacin released in the distilled water dissolution medium has shown a significantly higher release from wet granulated liquisolid tablets (PEG200 and Synperonic ™ PE/L61) than the drug release in the same medium from classical liquisolid tablets. The highest percentage of the drug release was 83.1% in the case of PEG200 water granulated liquisolid after 90 minutes, whereas the highest percentage for the counterpart classical formulation was 54.2% after 90 minutes. Therefore, the critical questions that should be asked are: which formula is the optimum one? Moreover, what are the expected changes on the liquid vehicles when incorporating water as a liquid binder regarding the *in*

vitro dissolution? Finally, what is the effect of maximizing the values of the load factors (i.e. minimizing the weight of the tablets) on the percentage of the drug release?

In order to answer these questions, the changes in the trends of the dissolution should be investigated and comparisons made with the changes inside the formulations.

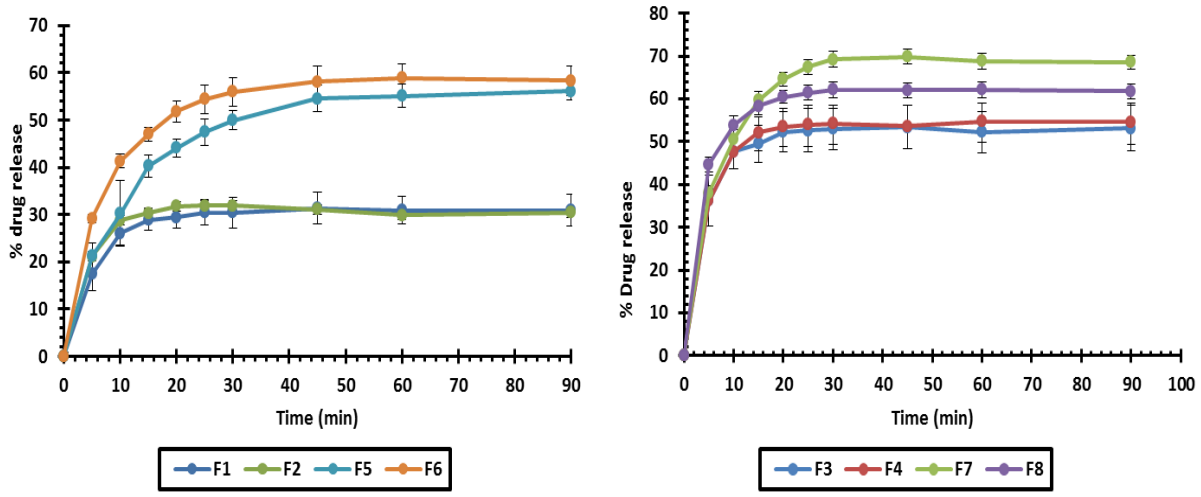


Figure 4-10: Comparisons between norfloxacin-containing classical PEG200 liquisolid tablets (left) and water granulated PEG200 liquisolid tablets (right) that prepared by the load factor that had been used in the classical PEG200 liquisolid tablets (for more information about the formulation components, see Table 2-3).

Figure 4-10 represents comparisons between norfloxacin dissolution trends. They are between the classical PEG200 liquisolid and the water granulated liquisolid tablets. The water granulated liquisolid tablets were prepared depending on the same load factors that are used for classical liquisolid formulations. The tablet containing a higher amount of the liquid vehicle (PEG200) showed greater improvements in the dissolution profiles (the similarity factor f2 is 32.61% for the comparisons between F1 and F5 and 32.92% for the formulations F2 and F6). Whereas comparison between F3 and F7 showed higher similarity factor reaching 44.14%, and the comparison between F4 and F8 formulations showed a value

above 50.00%, indicating that there were less significant differences between them. Nevertheless, there is an indication that the highest percentage of norfloxacin release was recorded at the F7 water liquisolid tablets, reaching to approximately 70% after 90 minutes. This could imply that the wet granulation technique has an important effect on enhancing drug release from liquisolid tablets when PEG200 is used as a liquid vehicle.

Using the new calculated compressibility load factor in order to prepare the water granulated PEG200 liquisolid for a smaller tablet weight size leads to formation of tablets with an improved norfloxacin drug release in distilled water dissolution medium. This applied to all formulations prepared, regardless of the value of the excipient ratios (R) or the concentrations of liquid medications. In more details, the best record for norfloxacin was at R=20 and 40% w/w liquid medication, reaching to 79.9% drug release (F12) (Table 2-3). This tablet formulation gave a similar dissolution profile with norfloxacin tablets, having R= 10 and 40% w/w liquid medication (F11). In the same way, the formulations having R= 10 or 20 and 20% w/w liquid medications show similar dissolution profiles (F9 and F10) (Table 2-3). As a consequence, the order of the dissolution profiles for the PEG200 classical liquisolid tablets stays the same as the water granulated formulations, but with higher percentages of drug release. This means that there is no effect on the *in vitro* drug release when incorporating the water granulation method into the PEG200 liquisolid formulation (Figure 4-11).

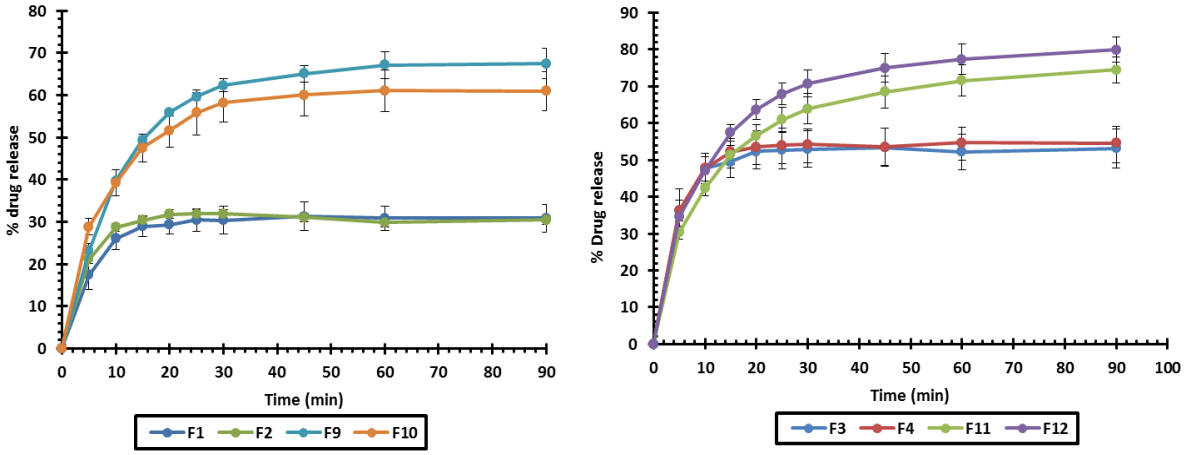


Figure 4-11: Comparisons between norfloxacin-containing classical PEG200 liquisolid tablets and water granulated PEG200 liquisolid tablets prepared by the new calculated load factor (for more information about the formulation components, see Table 2-3).

Regarding the comparisons between the water granulated PEG200 liquisolid tablets, using the classical (from F5 to F8) and the new load factor (from F9 to F12), a slight improvement on drug release was observed in all formulations prepared by the new calculated load factor (Figure 4-10 and Figure 4-11). The similarity factors are over 50 %, except in the comparison between F8 with F12 (f2 = 48.71) and the comparison between F5 with F9 (f2 = 48.70), yet the tablets prepared by the new load factors still provide higher drug release than from tablets prepared using classical load factors.

As a result, although the prepared formulations made only slight improvements to the dissolution profiles, they decreased the weight of the excipients used to prepare the tablets, they allowed increase of the weight of the active ingredients, using the advantage to keep the preparation at the same liquid medication, and greater ability to increase the weight of the liquid vehicle inside the powder formulations without destroying the rule of the liquisolid systems : improved dissolution with acceptable powder flowability and compressibility.

When changing the liquid vehicle to Synperonic ™ PE/L61, the dissolution behaviour becomes different. In more details, there was no significant effect on the percentage of the drug released when the water granulation technique was used as a liquid binder, comparing with the same dissolution profiles using PEG200 as a liquid vehicle (Figure 4-12). The recorded similarity factors were always over 50%.

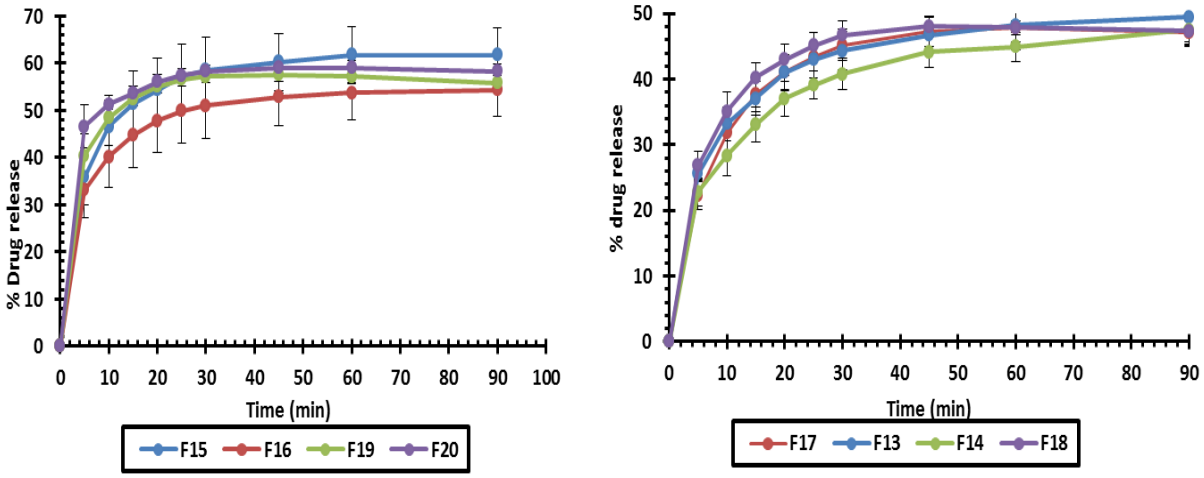


Figure 4-12: Comparisons between norfloxacin-containing classical Synperonic PE/L-61 liquisolid tablets and water granulated Synperonic ™ PE/L-61 liquisolid tablets prepared by the load factor that had been used in the classical Synperonic ™ PE/L-61 liquisolid tablets (for more information about the formulation components, see Table 2-3).

There are two probably reasons for this; the first one is related to the hydrophobic nature of the Synperonic ™ PE/L-61 which surrounds all the drug particles and prevents penetration by water in order to make further distribution to the drug particles inside the liquid medication [77], as happened in the case of PEG200, where the liquid vehicle and the liquid binder were miscible in the liquid medication system. However, this is doubtful because the solubility of the drug in water is higher than in Synperonic ™ PE/L-61, so the probability of the drug dissolving in the liquid binder is higher, especially during continuous mixing to the liquisolid system after adding the liquid binder. Nevertheless, the drug particles would go

back to react with Synperonic ™ PE/L-61 when the dry process completes. The DSC thermograms in Figure 4-7 show traces of water particles in the final wet granulated liquisolid system. These particles could simply help in forming the water granulation, rather than affecting the drug particles as they are present in a very small amount. The second reason could be that the high percent of the excipients used when applying such formulations leads to the same effect as happened in the classical liquisolid formulations (i.e. participating in preventing release of the drug particles into the dissolution system) [77].

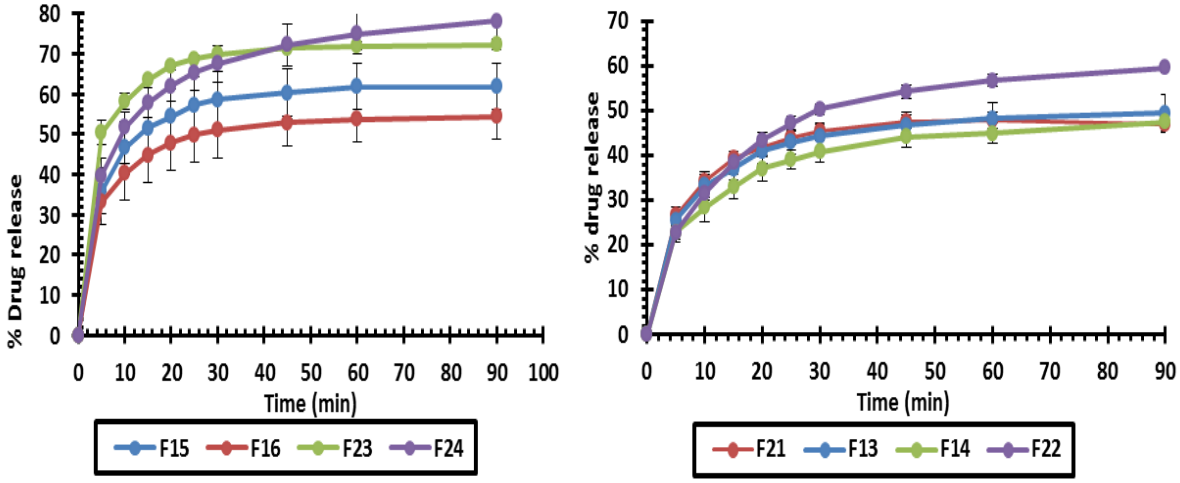


Figure 4-13: Comparisons between norfloxacin-containing classical Synperonic ™ PE/L-61 liquisolid tablets and water granulated Synperonic ™ PE/L-61 liquisolid tablets that prepared by the new calculated load factor (for more information about the formulation components, see Table 2-3).

This reason could be clarified when applying the new calculated load factor. In Figure 4-13, the comparison between classical liquisolid tablets and the smaller weight water granulated Synperonic ™ PE/L61 liquisolid formulations show that there is an increase in the percentage of norfloxacin release in the dissolution medium in all water granulated formulations. The percentage values of the similarity factor show that two out of four of the water granulated tablet formulations have values less than 50 % when compared to the classical liquisolid

formulations, leading to the conclusion that there is a significant increase in drug release. This enhancement could come from decreasing the amount of carrier and coating in the formulations, allowing the increase of the area of the diffusion layer between liquid medication and the dissolution medium at the molecular level. This happened with formulations F23 and F24, where the tablet weight decreased according to the new load factors. However, although this improvement is significant, it is still less than the improvement that happens in the case of PEG200 formulations, indicating that the role of the water granulation process retains the effect on the dissolution, but through the changing of the tablet weight this time.

4.3.3. Kinetic model analysis of drug release:

Table 4-3: Comparison between norfloxacin classical liquisolids and water grnulated liquisolids in terms of zero order, first order, Higuchi and Hixson-Crowell (H-C) kinetic dissolution models (for more information about the formulation components, see Table 2-3).

	Classical Liquisolid			
	zero	**First**	**Higuchi**	**H-C**
F1	0.9187	0.9267	0.9552	0.9241
F2	0.8795	0.8857	0.9243	0.8836
F3	0.8528	0.8632	0.9023	0.8597
F4	0.9388	0.9537	0.9700	0.9488
F13	0.9644	0.9718	0.9871	0.9694
F14	0.9976	0.9992	0.9993	0.9986
F15	0.9549	0.9680	0.9811	0.9638
F16	0.9847	0.9905	0.9977	0.9887
	Water Granulated Liquisolid			
	zero	**First**	**Higuchi**	**H-C**
F9	0.9770	0.9909	0.9942	0.9869
F10	0.9958	0.9995	0.9999	0.9987
F11	0.9934	0.9991	1.0000	0.9978
F12	0.9966	1.0000	0.9997	0.9997
F21	0.9869	0.9922	0.9985	0.9906
F22	0.9949	0.9985	1.0000	0.9975
F23	0.9898	0.9966	0.9994	0.9948
F24	0.9655	0.9803	0.9877	0.9757

Table 4-3 presents a comparison in the square values of the correlation coefficients (R^2) between the classical liquisolid and water granulated liquisolid for both PEG200 and Synperonic ™ PEL-61 liquid vehicle formulations. It compares four different types of kinetic models; the zero order, the first order, Higuchi and Hixson- Crowell (H-C) models. The important observation is that the water granulated liquisolid formulations which contain PEG200 show a significant increase in the R^2 values in all the kinetic models compared to the classical PEG200 liquisolid formulations (probability values for all kinetic models are less than 0.05 for the t-paired tests), (see Table 4-3/ formulations from F1 to F4 *vs.* formulations from F9 to F12). Consequently, the water granulated PEG200 liquisolid systems reach a value that nearly equals the water granulated liquisolid Synperonic ™ PE/L-61 formulations. All the R^2 values record over 0.95. However, the H-C values are less than others in the case of the water granulated PEG200 liquisolid formulations. For example, there is a significant decrease compared to the zero order, first order or Higuchi kinetic models (P= 0.0186, 0.0242 and 0.0288, respectively).

Regarding water granulated Synperonic ™ PE/L-61 liquisolid formulations, the all comparisons between the models show significant differences. This is very similar to the comparisons between the kinetic models in the case of the Synperonic ™ PE/L-61 classical liquisolid formulations, which could be expected as the water granulation process does not reflect a significant improvement in the dissolution trends, especially at the first 15 minutes when the points have been selected for this study.

In summary, the three kinetic models (the zero, first and Higuchi models) show the highest accuracy. In other words, they have characteristics that applied to the water granulated liquisolid formulations.

The enhancement in the R^2 values in the case of zero order can be identified in the case of the water granulated liquisolid formulations due to the enhancement of the distribution of the liquid medication inside the solid granules, which is, in this case, less than the classical one. As a consequence, the chance to form the interacting layer between the drug and the liquid vehicle is less in this situation, which reflects positively on the percentage of the drug release and the accuracy of this model.

For the first order kinetic model, the relationship between the drug release and the time is exponential [64], which can be noticed in all the water granulated formulations in the selected time; (i.e. between 5 and 15 minutes). This may be expected because the tablet contains disintegrant, as well as a reduced amount of carrier and coating materials, which leads to fast exponential release in the dissolution medium.

On the other hand, the Higuchi model deals with the drug release from a different perspective, because it depends on Fick's law of diffusion. In fact, the drive forces, which come from the concentration gradient between the tablet matrix and the bulk solution, play an important role in diffusing the drug into the dissolution medium [65]. This force considers the dispersion of drug particles in the liquid vehicles (PEG200 or Synperonic ™ PE/L-61). The water granulation process enhances such dispersion via providing a fair distribution of the liquid medication inside the solid granules. It eliminates the negative rule of the retardation that could happen

in the case of the classical liquisolid formulations. As a result of this, the model accuracy is improved.

Regarding the H-C model, it depends on the assumption of the spherical shape for all particles inside the dissolution medium, so that they have the same effect on all part of their surface through the liquid agitation. It ignores other factors that could be found in Fick's law of diffusion, keeping one factor that control the speed of the transformation of the particles towards the dissolution medium by a proportional change of surface with time and agitation [66].

Water granulation improves the H-C assumption via supporting the sphericity of the particles inside the dissolution medium. It provides a fair distribution of the liquid medication inside the solid particles, and decreases the crystallinity of the drug particles via providing more liquid vehicle, so that it increases the wettability by increasing the value of the load factor. As a result, the assumption of this H-C model is still accepted in this case.

4.4. Stability studies:

Table 4-4: Drug content uniformity comparison in percentage between fresh and stability after 6 months samples for the water granulated PEG200 and Synperonic™ PE/L-61 liquisolid tablets of norfloxacin (for more information about the formulation components, see Table 2-3).

Formula	Fresh			After six months		
	Average (%)		St Dev	Average (%)		St Dev
F9	108.028	+/-	0.512	96.460	+/-	1.233
F10	98.337	+/-	0.998	102.515	+/-	3.943
F11	98.305	+/-	1.836	94.247	+/-	3.796
F12	107.268	+/-	2.234	97.358	+/-	4.032
F21	96.168	+/-	3.936	87.405	+/-	1.270
F22	96.774	+/-	2.438	95.128	+/-	5.672
F23	100.903	+/-	0.305	95.814	+/-	1.692
F24	100.593	+/-	1.075	99.418	+/-	6.011

Table 4-4 compares the percentage of norfloxacin in water granulated liquisolid tablets at the moment of making and after six months storage at 21 ^{o}C and 76 % relative humidity. All formulations show a high percentage of drug content, yet there are some evidences that there is a decrease in some formulations. For example, formulations F9 and F21 loses about 10%, although the tablets still in the acceptable BP levels. However, this loss could be due to the stability conditions or just due to variations in the tablets. A more probable reason could be because other formulations do not show that decrease in the percentage of the drug, which could be supported from the dissolution behaviour of these formulations, showing no significant differences in the percentage of drug released between fresh samples and stored ones for the all formulations (Figure 4-14 and Figure 4-15). The similarity factor percentages in the case of formulations F9 and F21 are 65.32% and 70.87%, respectively.

Furthermore, the DSC thermographs in Figure 4-16 and Figure 4-17 do not lead to a similar conclusion. The endothermic peaks have the same melting temperature values in the stored formulations, especially the ones near to the melting point of the norfloxacin where there is no significant change in this region. Moreover, the enthalpy values for the endothermic peaks at 220 ^{o} C in the case of the water granulated Synperonic PE/L-61 (i.e. from F21 to F24) are 0.174, 0.1034, 0.9206 and 1.314 J/g, respectively, which are less than the counterpart values in the case of classical Synperonic PE/L-61 formulations. This means that the weakness in the case of classical Synperonic ^{TM} PE/L-61 liquisolid formulations after 3 months storage is overcome in the counterpart water granulated liquisolid tablets after storage, and the new prepared formulations do not only withstand stressful

conditions, but also provide a longer resistant time compared with the classical formulations.

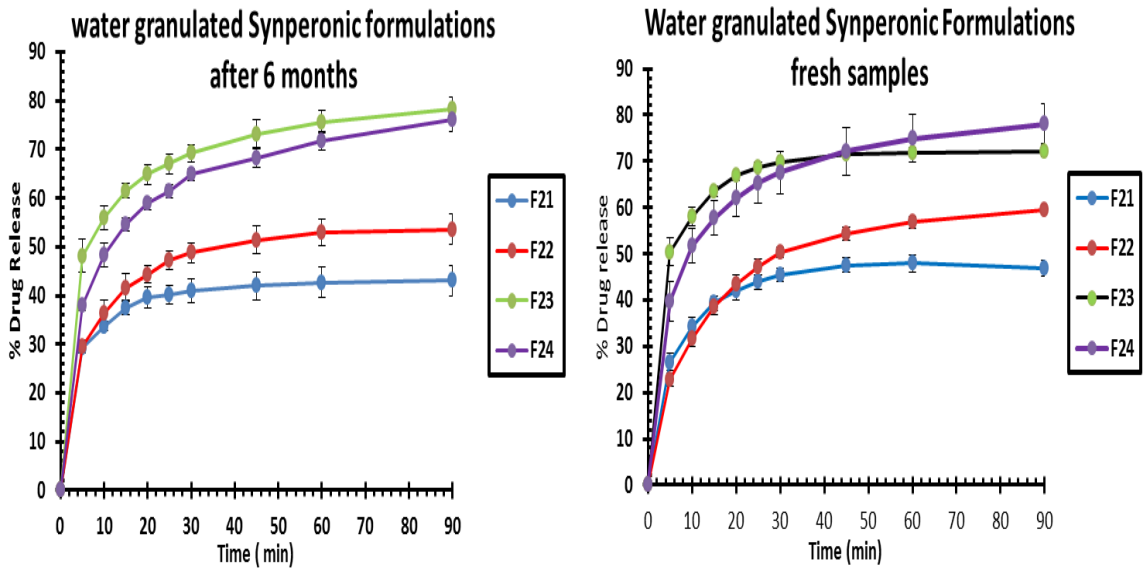


Figure 4-14: Comparison of the dissolution profiles between fresh and samples stored for 6 months in terms of water granulated Synperonic™ PE/L-61 liquisolid tablets of norfloxacin (for more information about the formulation components, see Table 2-3).

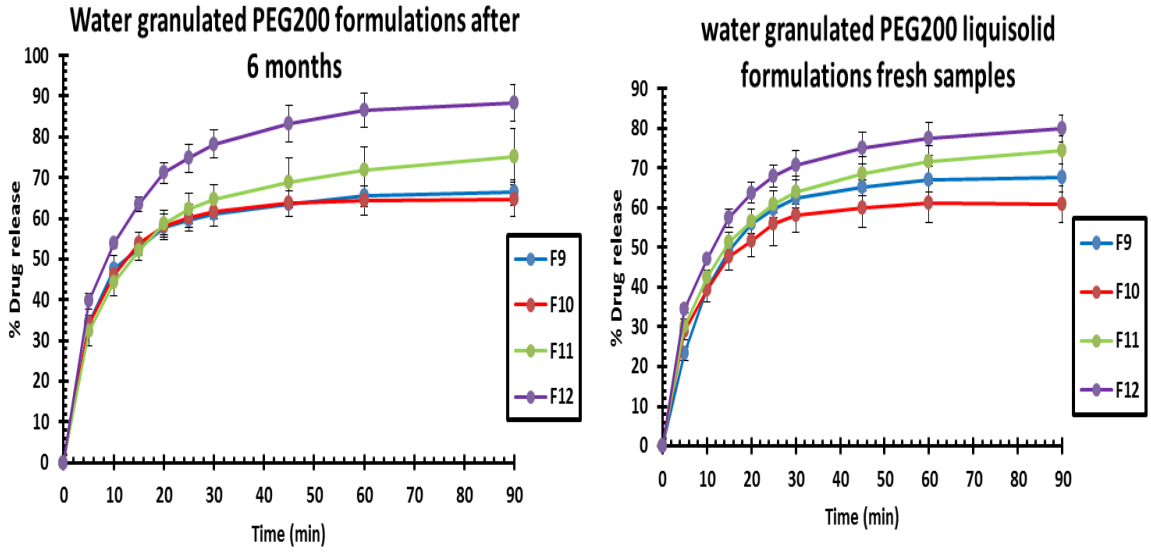


Figure 4-15: Comparison of the dissolution profiles between fresh and samples stored for 6 months in terms of water granulated PEG200 liquisolid tablets of norfloxacin (for more information about the formulation components, see Table 2-3).

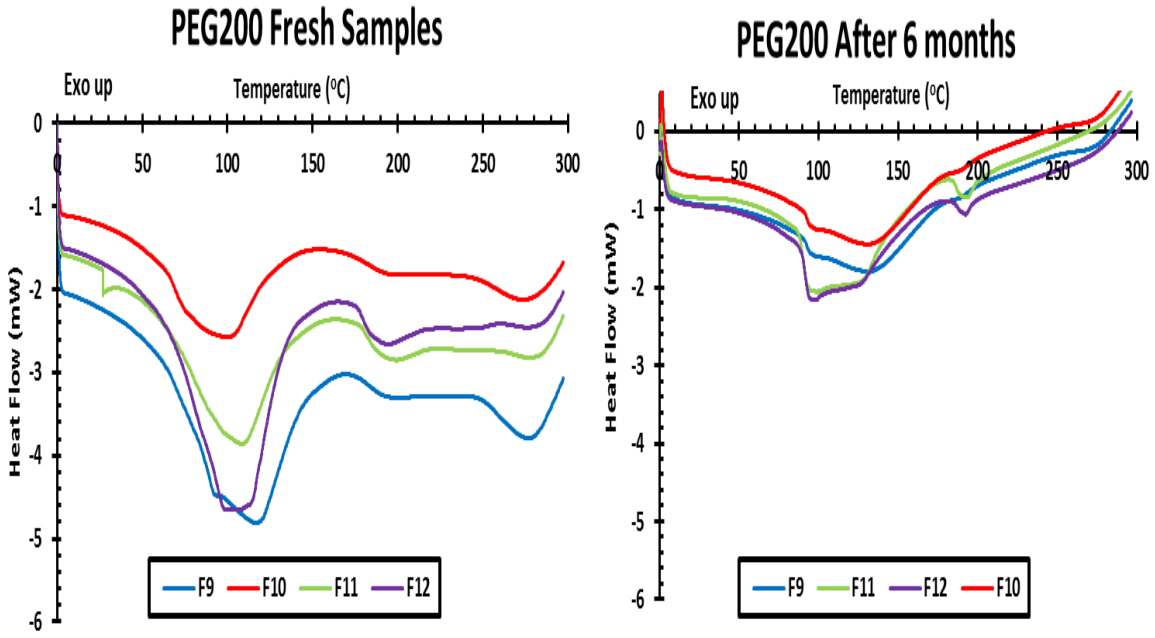


Figure 4-16: Comparison of the DSC thermographs between fresh and samples stored for 6 months in terms of water granulated PEG200 liquisolid tablets of norfloxacin (for more information about the formulation components, see Table 2-3).

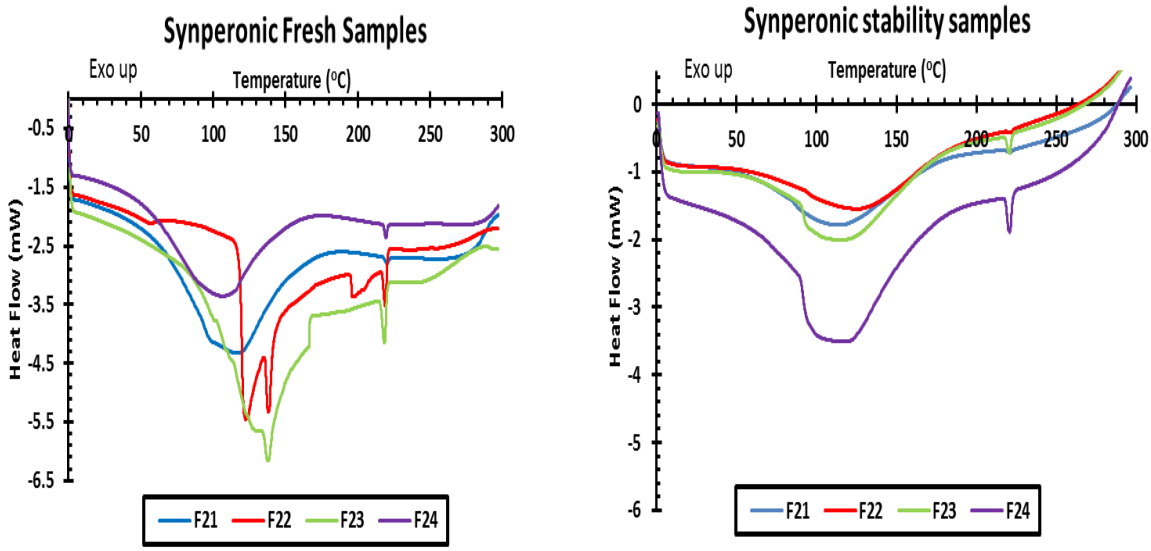


Figure 4-17: Comparison of the DSC thermographs between fresh and samples stored for 6 months in terms of water granulated Synperonic™ PE/L-61 liquisolid tablets of norfloxacin (for more information about the formulation components, see Table 2-3).

4.5. Conclusion:

Liquisolid formulation technique has always been challenged by the size of the tablets. A large quantity of excipients was used in order to reach acceptable

flowing and compressible powder systems. The work in this chapter aimed to enhance this method via incorporation of water into the granulation process during liquisolid tablet preparation. The new calculated optimum load factor decreases significantly the size of the prepared tablets, which helps the industry to produce acceptable tablet size. The added water as a liquid binder affects the compressibility and the flowability of the liquisolid formulations, whether containing Synperonic™ PE/L61 or PEG200 as liquid vehicles. The *in vitro* dissolution profiles, studying norfloxacin as a model of very slightly water soluble drug, show that there is a significant increase in the percentage of the drug released, compared to the classical liquisolid formulations, although in the case of water granulated Synperonic™ PE/L61 formulations, the significant increase appears only after applying the new compressibility load factor. The PEG200 formulations show the dissolution enhancement regardless of applying the classical or the new calculated load factor, allowing more flexibility during preparation of larger batches. This novel method for the preparation of liquisolid tablets continues studying the differences when applying different liquid binders, different liquid vehicles and different hydrophobic drugs in order to investigate their suitability, as well as applicability, in terms of enhancing flowability, compressibility and the percentage of the drug released in aqueous dissolution medium.

Chapter Five: Comparing water and 10 %w/w PVP solution as liquid binders in wet granulated liquisolid tablets

5.1. Introduction:

The preparation of the water granulated liquisolid process provided good solutions for the large quantities of the carrier and the coating that could be faced when preparing the classical liquisolid formulations. Although these kinds of formulations enhance the dissolution of the hydrophobic drug in neutral dissolution media, the norfloxacin release is still under the accepted limit for the immediate release drug (i.e. 85% of drug release in the first 30 minutes [56]). Therefore, it is worthy to investigate another type of liquid binder.

The suggested binder solution is Polyvinyl Pyrrolidone (PVP) due to its good physicochemical characteristics in terms of water solubility and wettability so that they improve the percentage of the drug release during the dissolution test. Other aspects could affect the drug release is the chains of the used PVP structure and the ratio of the PVP to the drug.

Therefore, studying PVP effect on the wet granulated liquisolid preparations, and comparing this effect with water granulated liquisolid formulations not only in the dissolution profiles, but also, in flowability, compressibility, load factor calculations, DSC thermograph, FTIR spectra, and other quality control tests are the main goals of this chapter.

5.2. Pre-formulation studies and characterisation of powder admixture:

5.2.1. Flowability studies and determination of angle of slide:

The aim of applying this test is to investigate the powder flow and how it would affect if there would be any changes in the type of the liquid binders. Figure 5-1 compares water and PVP-K17 as binder solutions in terms of changing the angle

of slide when using Synperonic ™ PE/L-61 and PEG200 as liquid vehicles. In the both situations, there are no significant changes on the angle values when the concentration of PVP changes. All different concentrations including the water record values between 14 and 16 degrees approximately. This could be expected in the case of PEG200 formulations as PVP in water makes polar solution, which it can be immiscible with the hydrophilic liquid vehicle. However, this conclusion can also be seen in the case of Synperonic ™ PE/L-61, where there is no homogeneity due to the hydrophobicity of the liquid vehicle. As a result, PVP can candidate both type of formulations (PEG200 and Synperonic ™ PE/L-61) to the industrial applications for powder preparations, such as hard gelatine capsule filling.

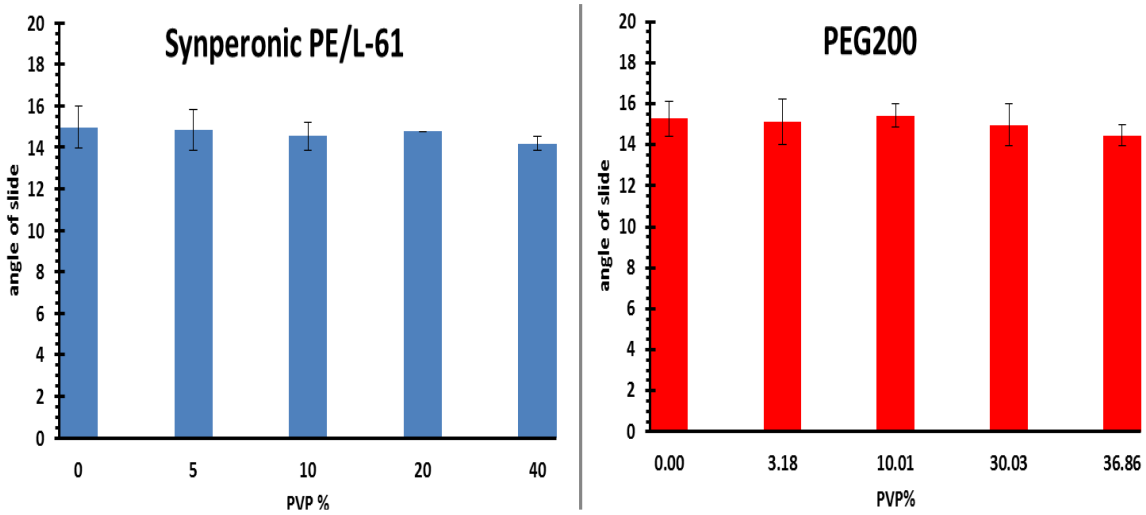


Figure 5-1: Comparison the averages and standard deviations of the angle of slide values for different wet granulated liquisolid formulations having the same R value and the same CW value but different PVP % concentrations for Synperonic ™ PE/L-61 (left) and PEG200 (right) as liquid binders.

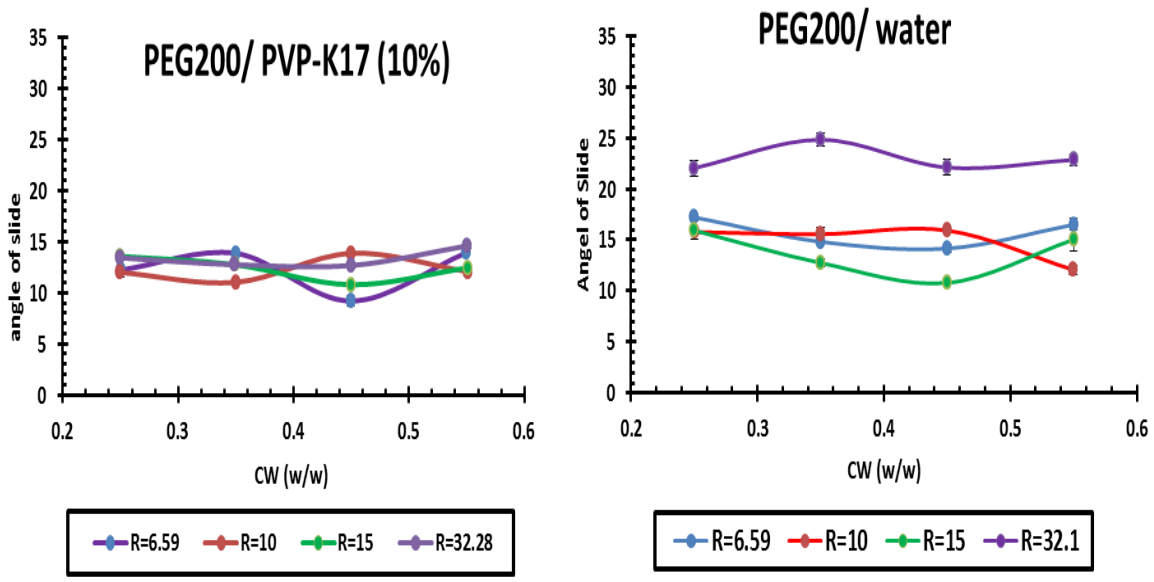


Figure 5-2: Comparison the averages and standard deviations of the angle of slide values for different wet granulated liquisolid formulations at several R values and CW values for the same liquid vehicle (PEG200) , using PVP-K17 (10%) (Left) and water (right) as liquid binders.

In the same way, the records when changing the R values were at a minimum level of changing the angle of slide in the case of PVP-K17 solution (Figure 5-2, left). In fact, it provides more consistent results compared to the same formulation but using water as a liquid binder instead (Figure 5-2, right). The recorded values of the angle of slide were in a low range between 10 and 15 degrees in the case of the PVP formulations, and this continued with no significant changes when increase the value R, whereas the angle of slide increases with larger R value in the case of the water formulations. As a result, the application of PVP as a binder solution provides an acceptable powder flow properties regardless the ratio of carrier and coating materials (R) and whether using Synperonic ™ PE/L-61 or PEG200.

5.2.2. Compressibility studies and determination of the new optimal compressibility load factor:

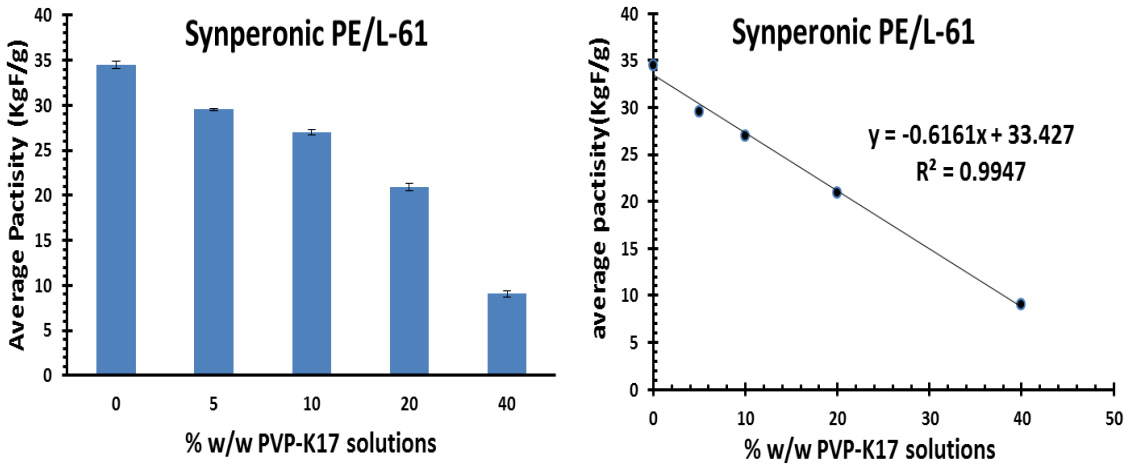


Figure 5-3: The effect of PVP-K17 solutions on the average pactisity for liquisolid formulations using Synperonic™ PE/L-61 at a specific R value (15) and a specific CW value (0.2).

The aim of applying this study is to investigate the compressibility of the liquisolid tablet formulations in terms of average pactisity when using PVP solutions as a liquid binder. When applying different concentrations of PVP-K17 solutions to the liquisolid formulations containing Synperonic TM PE/L-61 as a liquid vehicle, the average pactisity start decreasing when the concentration of PVP increases (Figure 5-3). Water without PVP powder records the highest amount of pactisity whereas the lowest amount is at 40 % w/w PVP solution. As stated in Figure 5-3, the inverse correlation between the average pactisity and the percentage concentration of PVP-K17 seems to be linear with regression coefficient is more than 0.99. The expected reason for this result could be referred to the opposite hydrophobic nature of the liquid vehicle and the liquid binder, where the first one (Synperonic TM PE/L-61) is hydrophobic surfactant and the second one is a polar water soluble solution (PVP), so that both of them cannot mix together and they

form a heterogeneous mixture. Although water shares the polarity characteristics with PVP solution but in the wet granulation process it will evaporate after drying process and it would stay in the minimum levels, whereas the PVP crystals would precipitate on the powder surface of the liquisolid formulations after drying process, occupying a space inside the granules that could be filled with Synperonic TM PE/L-61 in the case of water granulated liquisolid formulations. Consequently, a smaller space in the granules retains a smaller amount of liquid vehicle, decreasing the compressibility load factor and the relative average pactisity. Moreover, due to the contrasting in the hydrophilicity nature, there could be a shifting outside the granules for Synperonic TM PE/L-61, which could lead to squeeze it out and weaken the prepared tablet. Both explanations can be determined from the linearity relationship, representing in Figure 5-3 where the largest pactisity has been recorded in the case of the water granulated liquisolid formulation. For these reasons, the preparations of liquisolid Synperonic TM PE/L-61 formulations have been stopped in the presence of PVP solutions.

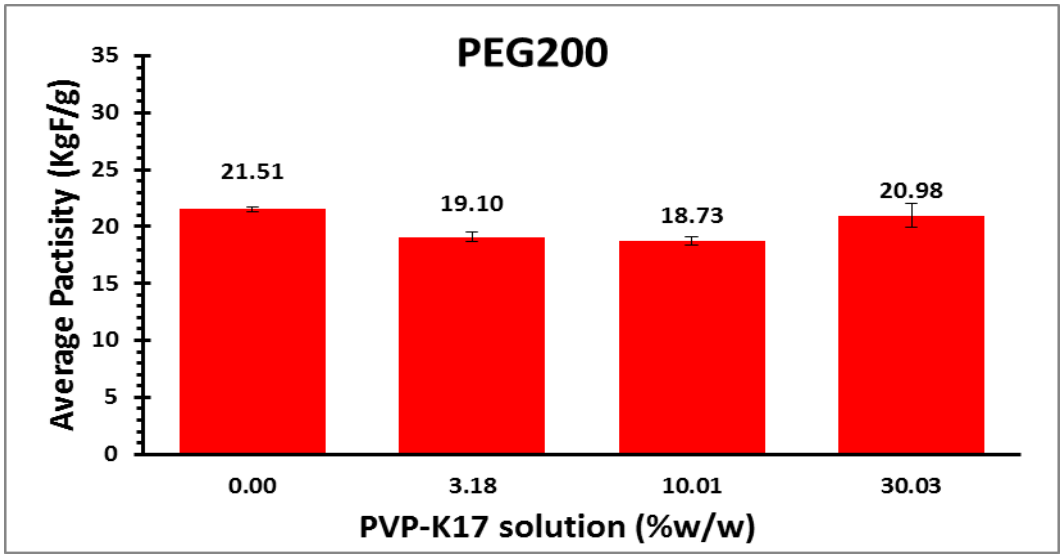


Figure 5-4: The effect of PVP-K17 solutions on the average pactisity for liquisolid formulations using PEG200 at a specific R value (15) and a specific CW value (0.35).

On the contrary to the PVP wet granulated Synperonic ™ PE/L-61 liquisolid formulations, PVP granulated PEG200 liquisolid formulations show closer values in the average pactisity with change in the concentration of the PVP (Figure 5-4). Moreover, the addition of PVP solutions with different concentrations instead of water does not make a significant change in the pactisity from range of 0 to 30 % w/w PVP. All pactisity values are around 20 KgF/g. Therefore, the superiority of the formulations having water as a liquid binder in the case of the Synperonic ™ PE/L-61 formulations (Figure 5-3) cannot be recognized in the case of the PEG200 formulations (Figure 5-4). The same hypothesis could explain this result. As the PEG200 has a hydrophilic nature, thus it can form a homogeneous mixture with either water or PVP solutions. Therefore, the liquid vehicle has the ability to retain in the granules after the drying process and there are no particles could affect its occupancy inside the powder admixture.

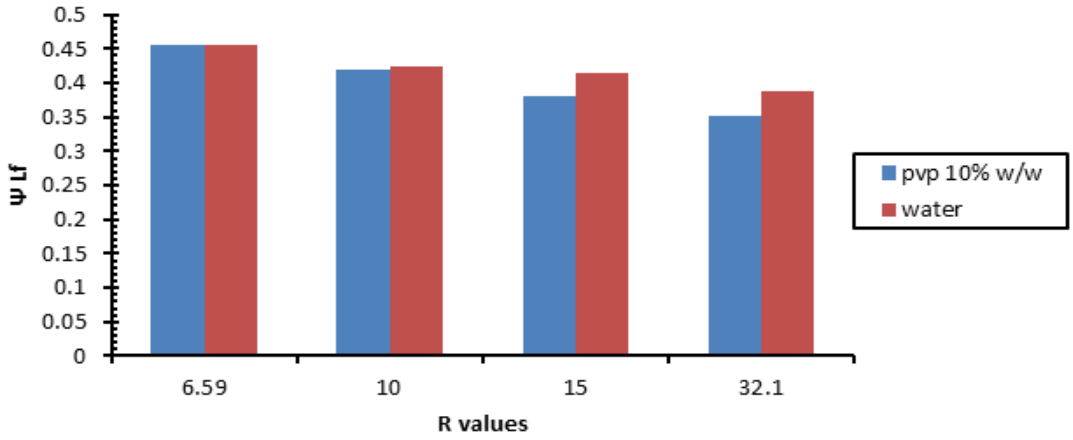


Figure 5-5: Comparison between the compressibility load factors (ΨLf) of the water and 10 % PVP-K17 granulated PEG200 liquisolid tablet formulations at different R values.

After investigation the role of the PVP concentration as a liquid binder at specific R and CW values, it is worthy to demonstrate the differences between water and a specific PVP concentration (10% w/w) on the values of the compressibility load factors. Figure 5-5 shows the compressibility load factors for water and 10% PVP

solution over the used ranges of R values. It can be noticed that when R values are small (e.g. at 6.59 and 10), the differences between water and PVP formulations in terms of the load factor is not significant. However, when R values increase, the differences start increasing, and water prepared formulations show higher values than relative PVP prepared formulations. This phenomenon could be referred to the role of the coating material (silica) and its sensitivity to form granules and its help in providing strong tablets. In other words, when the quantity of coating material is large in the smaller R values, the effect of PVP on the pactisity does not appear. However, when less amount of coating material used in larger R values, the decreasing effect of PVP solution on the pactisity start to be significant.

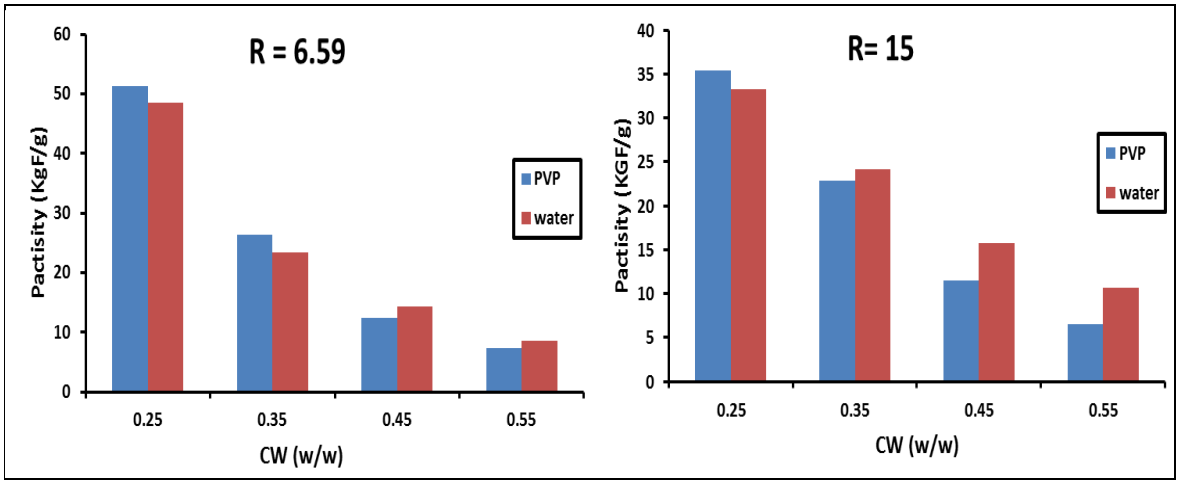


Figure 5-6: Comparison the pactisity (KgF/g) of PVP and water wet granulated PEG200 liquisolid tablet formulations with a range of CW between 0.25 and 0.55 (w/w) for R= 6.59 (left) and R = 15 (right).

More investigation into the differences between the water and the PVP liquisolid formulations when PEG200 is the liquid vehicle clarifies several results (Figure 5-6). First of all, the coating material at low R is more sensitive to the change of the CW in the PVP solutions compared to the water formulations. In other words, the decreasing in the pactisity of the PVP formulations takes place to large extent

compared to the water formulations when the amount of the liquid vehicle (PEG200) increases and when the coating materials is relatively predominant in the formulations (Figure 5-6,left).

In the same manner, the PVP sensitivity to the change of the CW still higher than water when the carrier material predominating (Figure 5-6, right).

This means that binder characteristics of the PVP solution have negative effects on the pactisity only when the CW becoming large regardless the value of the solid ratio (R) in the PEG200 liquisolid formulations.

Also, when R =6.59, the values of the pactisity decreases massively when increasing the CW for both type of formulations (i.e. water and PVP). However, this is not indicated when the R values increase.

This investigation is important for the industrial application when the liquid vehicle and the liquid binder are added gradually to make these kinds of formulations.

Finally, the exponential relationship between CW and the pactisity does not change whether applying PVP or water as binder solutions or whether using small or large R values. As a result, it is possible to predict the linear relationship between the compressibility load factor (ΨLf) and the reciprocal solid ratio (1/R) in the case of 10 % w/w PVP-K17 granulated PEG200 liquisolid formulations. The regression coefficient ($R^2 > 0.99$) was relatively high (Figure 5-7).

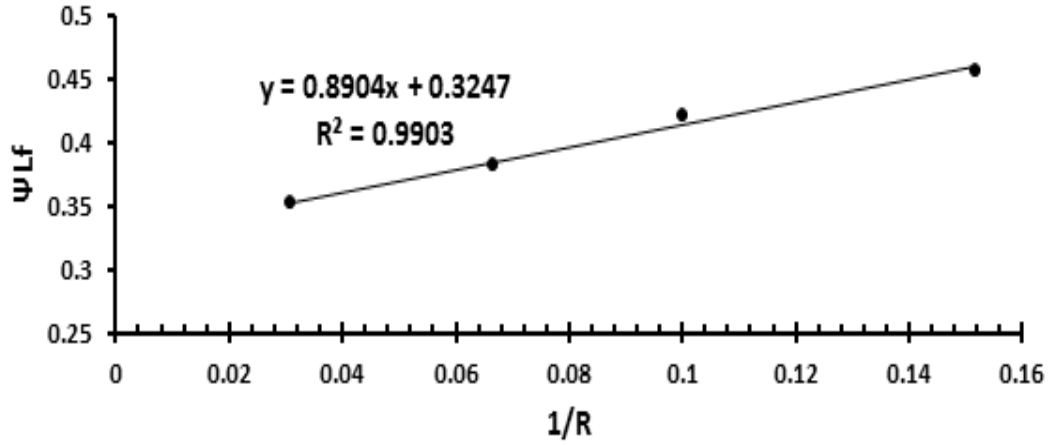


Figure 5-7: The linear model between compressibility load factor (Ψ Lf) and the reciprocal solid ratio (1/R) with R^2 = 0.9903.

5.2.3. Differential Scanning Calorimetry (DSC) analysis:

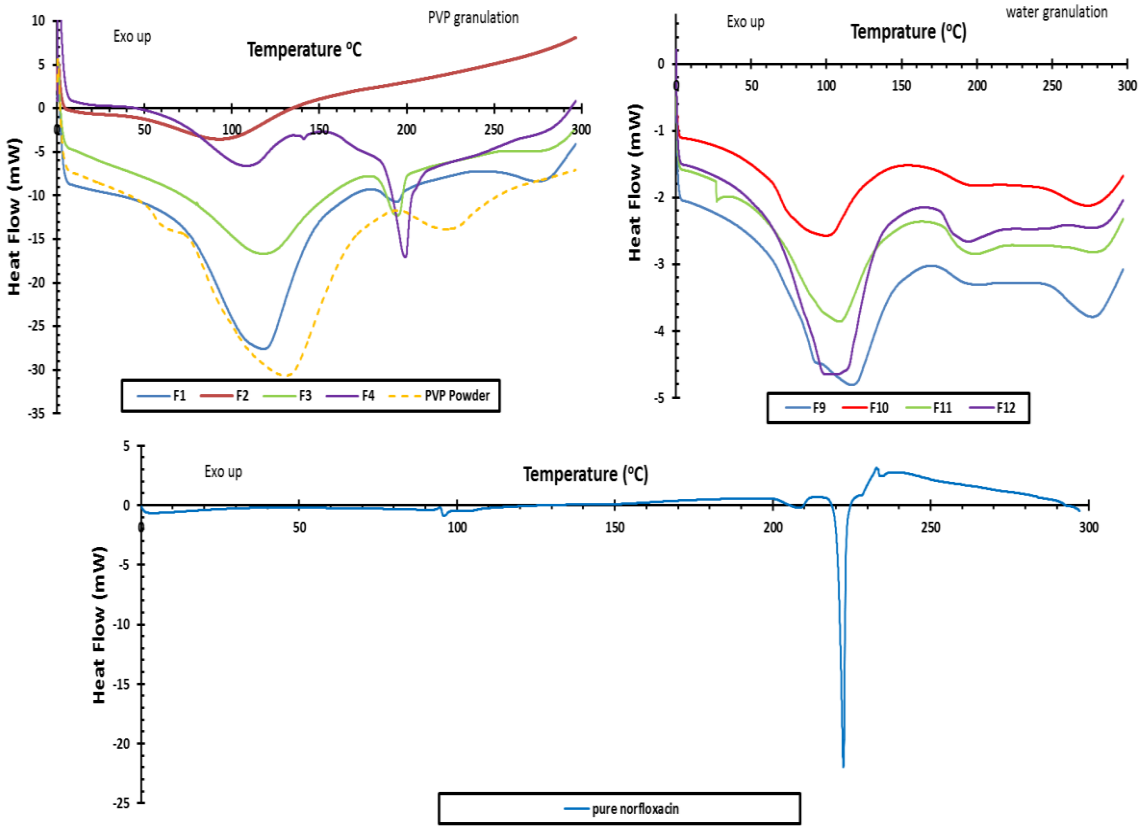


Figure 5-8: DSC thermographs for PVP (left) and water (right) granulated liquisolid formulations when using PEG200 as a liquid binder. it includes DSC thermographs for PVP-K17 pure powder (left) and for pure norfloxacin (bottom) for comparison purposes (for formulation compositions, refer to Table 2-4).

Figure 5-8 represents a comparison between DSC thermographs of the pure norfloxacin powder (Figure 5-8, bottom), PVP-K17 pure powder and PVP granulated liquisolid formulations (F1 to F4) (Figure 5-8, top-left) and water granulated liquisolid formulations (Figure 5-8, top-right) (F9 to F12), using PEG200 as a liquid vehicle. The endothermic peak of pure norfloxacin at 222 ^{o}C shifts in the case of three PVP granulated formulations (F1, F3 and F4), whereas it disappears in the case of formulation F2. This leads to conclude that there is an interaction between the drug itself with the PVP particles, and this interaction decreases the crystallinity of the pure drug, enhancing the drug solubility and the drug dissolution in the aqueous medium, as will be shown later.

In more details, the investigation of the DSC thermographs of the PVP granulated liquisolid formulations and their counterparts of the water granulated liquisolid formulations shows that endothermic peaks due to crystallinity of the drug are smaller in the case of the water granulated formulations. The probable reason for this is that there is one interaction between PEG200 and norfloxacin in the case of the water granulation, whereas there are two interactions in the case of the PVP formulations; one with PEG200 and the other with the PVP. The similar situation can be noticed in the case of acetaminophen, where there was a comparison among three different granulation methods, using the same type of PVP as a binder solution [84]. Although there is a slight shift in the endothermic peaks in all granulation methods, there were questions about the reason of such shifting whether it comes from the drug interaction with PVP or comes from the interaction with other excipients [84].

Furthermore, the decrease of the powder quantities (i.e. carrier and coating materials) in the all formulations allow these small endothermic peaks to appear in

the both types of (PVP and water) formulations, and when the solid powder becomes large, such as in the case of formulation F2, these small peaks disappear, due to the dilution effect.

One thing could be noticed in the water and PVP granulated liquisolid formulations is the broader endothermic peaks around 100 ^{o}C. As it can be referred the reason of these peaks to the evaporation of water droplets, it can also be indicated in the case of the thermograph of PVP pure powder (see Figure 5-8, top-left). It indicates that this binder is adsorptive to humidity on its surface, and this broader peak increases with the increase of the molecular weight of the used PVP [85].

5.2.4. Fourier Transform Infra-red (FTIR) analysis:

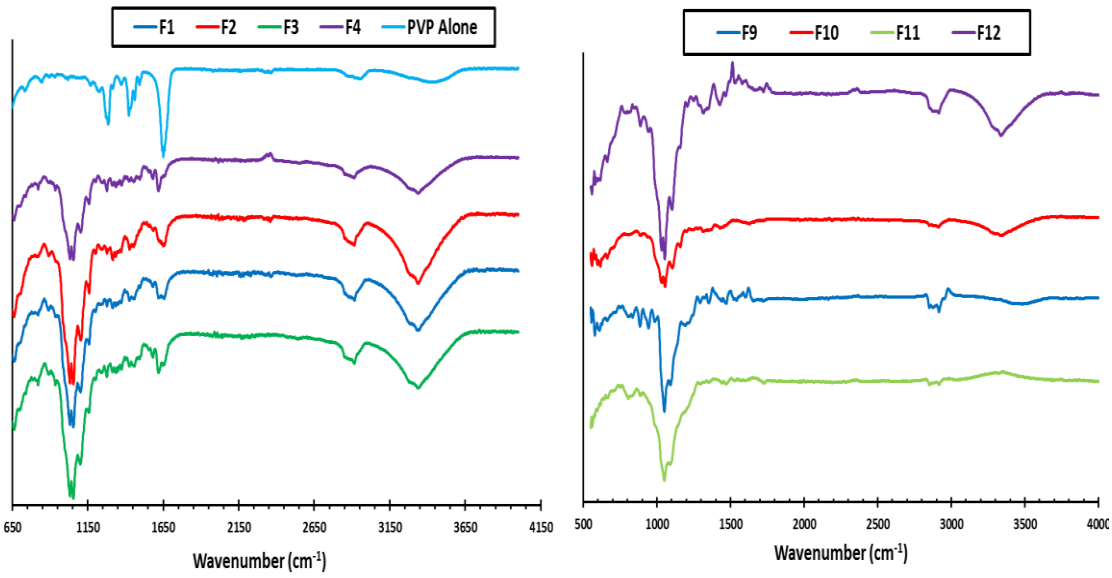


Figure 5-9: FTIR spectra for the PVP granulated liquisolid formulations, the spectrum for PVP powder alone (left) and water granulated liquisolid formulations (right) (for formulation compositions, refer to Table 2-4).

Figure 5-9 shows a comparison between FTIR spectra of the PVP and water granulated PEG200- norfloxacin liquisolid formulations. It also includes the spectrum of PVP powder alone in order to examine its existence in the formulation

after drying process. Four significant assigned peaks can be noticed in the all spectra of the PVP formulations as well as in the spectra of the PVP alone, which are at 1418 cm^{-1}, 1644 cm^{-1}, 2954 cm^{-1} and 3360 cm^{-1} wavenumbers. While the first two assigned peaks could be related to C-N, C=O stretching in the PVP structure [86], the third and the fourth assigned peaks, which they could be for asymmetric stretching of CH_2 and OH stretching, respectively [86], do not relate directly to the PVP structure because they could be noticed in the case of the water granulated liquisolid formulations. Thus, they could relate to other excipients existing in the formulations. In conclusion, the granulation process does not affect the PVP particles and does not lead to any interaction with norfloxacin.

5.2.5. Determination of flow properties:

Table 5-1: Comparison between PVP granulated liquisolid systems and water granulated liquisolid systems for PEG200 liquid vehicle in terms of compressibility index (CI %) and Hausner ratio (H ratio) (for formulation compositions, refer to Table 2-4).

Formula	Flowability of PVP granulated liquisolid PEG200					
	Tapped density (g/cm^3)	Bulk density (g/cm^3)	CI%	Position	H ratio	Position
F1	0.47	0.34	28.13	poor	1.39	poor
F2	0.43	0.33	23.53	passable	1.31	passable
F3	0.47	0.32	30.77	poor	1.44	poor
F4	0.44	0.33	23.81	passable	1.31	passable
Formula	**Flowability of water granulated liquisolid PEG200**					
	Tapped density (g/cm^3)	Bulk density (g/cm^3)	CI%	Position	H ratio	Position
F9	0.57	0.42	26.83	poor	1.37	poor
F10	0.51	0.36	29.17	poor	1.41	poor
F11	0.52	0.37	29.17	poor	1.41	poor
F12	0.47	0.33	29.63	poor	1.42	poor

Table 5-1 represents the values of tapped powder density, bulk powder density, the percentage of compressibility Carr's index and Hausner ratio for PVP granulated and water granulated PEG200 liquisolid formulations. It also includes the position of the formulations according to the criteria of the British Pharmacopoeia where the all formulations whether they are water granulated liquisolid or PVP granulated liquisolid have poor or passable flowability [56]. Thus, all formulations do not show any significant decrease in the values of the Hausner ratio or the Carr's index when using PVP solution as a liquid binder compared to water alone. They reflects the poor flowability characteristics of Avicel® PH 101, which it has 28.89 CI% [81] & [82] as the predominant carrier excipient for all of the included formulations.

5.3. Evaluation of PVP granulated liquisolid tablets:

5.3.1. Drug content uniformity, tablet dimensions, hardness, tensile strength, friability and disintegration tests:

Table 5-2: Content uniformity, friability, tensile strength, hardness and disintegration tests for PVP granulated liquisolid and water granulated liquisolid systems (for formulation compositions, refer to Table 2-4).

PVP Granulated PEG200	Content Uniformity (%)	Friability (%)	T-strength (MPa)	Hardness (N)	Disintegration Time (sec)
F1	101.91 +/- 4.870	0.100	1.1 +/- 0.038	38.64 +/- 1.240	204 +/- 8
F2	106.33 +/- 4.227	0.378	1.2941 +/- 0.092	42.12 **+/-** 3.554	399 +/- 8
F3	111.5 +/- 5.320	0.299	1.0947 +/- 0.097	38.25 **+/-** 3.521	108 +/- 25
F4	111.33 +/- 1.962	0.275	1.2231 +/- 0.058	44.42 **+/-** 1.964	167 +/- 11
Water Granulated PEG200					
F9	108.03 +/- 0.512	0.260	1.07 +/- 0.178	72.57 +/- 12.677	347 +/- 39
F10	98.34 +/- 0.998	0.122	1.24 +/- 0.177	86.00 +/- 11.778	369 +/- 39
F11	98.31 +/- 1.836	0.639	0.75 +/- 0.088	27.36 +/- 3.184	165 +/- 4
F12	107.27 +/- 2.234	0.291	0.96 +/- 0.330	35.11 +/- 11.284	116 +/- 16

Table 5-2 provides information about several quality control tests, which include drug content uniformity test, friability test, tensile strength test, hardness test and disintegration test for the both PVP and water granulated PEG200 liquisolid tablet formulations. The aim of making this comparison is to investigate any possible effect due to using PVP solution as a liquid binder on the physicochemical characteristics of the prepared tablets. The results of content uniformity tests show that the all formulations are within the British Pharmacopoeia specific limits (i.e. between 85% and 115%) [56]. In addition to this, the statistical t-paired test between the average values of the percentage of the drug inside the PVP formulations and the water formulations shows that there is no significant

differences between these two groups (p-value is 0.326 > 0.05). Furthermore, the changing in the quantities of the liquid vehicle, carrier, and coating in the presence of PVP or water binder solutions does not have any significant effect on the uniformity of the drug in these formulations. As a consequence, the wet granulated formulations whether using water or PVP solution as liquid binders do not affect the distribution of the drug inside the PEG200 liquisolid bed systems although granulation has several processes that could affect the quantity of the drug during manufacturing, such as sieving and drying.

Also, the difference in tensile strength between the PVP and water formulations seems to be not significant. The calculated probability (p-value) from applying t-paired statistical test between the average results equals to 0.1116 > 0.05, although there is a slightly improvement in the case of F3 compared with F11. The reason for the similar results is because of the near values of the T-strength in the all of the PVP and water formulations. As the diameters for all tablets have approximately the same values, the expected variations may come from the thickness and the hardness, where the crushing forces is directly proportional to the T-strength and the thickness is inversely proportional to the T-strength; thickness does not show any significant differences due to the effect of using PVP and water as a binder solutions.

The hardness results still meet the criteria of the compressibility load factors. The recorded averages of the crushing force in (KgF) of the all PVP batches are very near to the assigned weight of the tested tablet in (g) multiplying by 20 [6].

The friability tests do not show any exceptions. The PVP formulations have an excellent resistant to any expected damage could come from the cohesive forces

among the tablets or from adhesive forces with the wall of the friability tester. All PVP formulations do not reach to 0.5 % loss in the tablet weights, meeting the criteria specified by the British Pharmacopoeia [56], and keeping the differences between the water and PVP formulations at their minimum levels with probability (p-value) equals to 0.639 > 0.05. The friability test shows an excellent resistant in the case of the water granulated liquisolid tablets, no formulations reach to 1% in the loss weight, meeting the demand of the standard of British Pharmacopoeia. Finally, the disintegration test shows that the all PVP formulations do not exceed 7 minutes to complete disintegration. The variations among the PVP formulations in these situations refer only to the variations in the weight of the tablets, and the PVP solution does not make a significant difference over the water granulated formulations. The probability (p-value) from t-paired test equals to 0.326 > 0.05.

In nut shell, all applicable quality control tests confirm the conclusion that adding PVP solution at 10 % concentration does not make any significant differences over the water formulations when the liquid vehicle is PEG200. In other words, 10% PVP solutions keep the differences with water to the minimum levels so that the effectiveness on the flowability and compressibility stays low, directing the effectiveness only towards the dissolution results. It also support the hypothesis that PEG200 as a liquid vehicle helps stability in the flowability and compressibility in these formulations, allowing the possibility to mix it with 10 % PVP solution and to apply in the manufacturing processes.

5.3.2. *In vitro* Dissolution Studies:

In chapter 4, the dissolution profiles tried to answer the questions related to the assignment of the optimum formula and how the water as a liquid binder affects

the role of the liquid vehicle, whether PEG200 or Synperonic ™ PE/L-61, in term of enhancing the dissolution of norfloxacin in neutral aqueous medium. In this chapter, the research study continues trying to investigate the role of the wet granulation in the presence of PVP K-17 at concentration of 10% w/w on the PEG200 liquisolid tablet formulations, compared to the effect of water for the same tablet formulations. In other words, what are the differences between using PVP-K17 and using water as liquid binders and how do they affect the drug release?

Furthermore, there is another comparison between the formulations prepared according to the classical load factors [77] and the new calculated load factor after granulation (Figure 5-10).

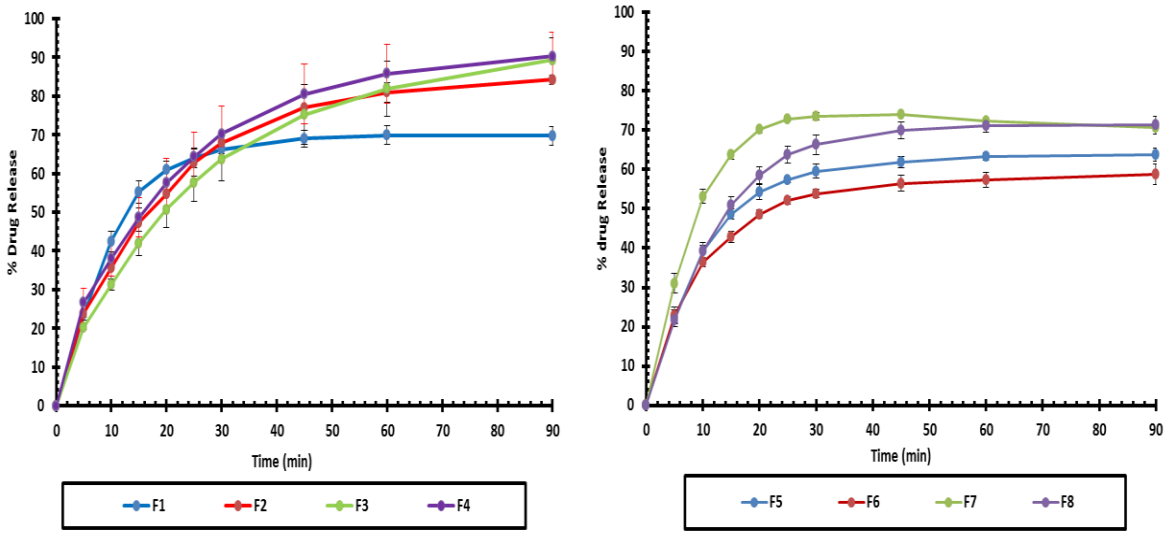


Figure 5-10: Dissolution profiles of the PVP -K17 wet granulated PEG200 liquisolid formulations prepared according to the new compressibility load factors (left) and to classical compressibility load factor (right) (for formulation compositions, refer to Table 2-4).

The percentage of norfloxacin records a higher release in the wet granulated liquisolid tablets, with significant increasing in formulation F2, F3, and to some extent F4 compared to classical tablets for the same formulations (Figure 5-10). The similarity factors for these formulas are 41.3, 40.2 and 52.2 %, respectively. The interesting note about these percentages are that all of them for the whole

dissolution profiles (i.e. from 5 minutes to 90 minutes), whereas there is no significant changes in the first 30 minutes. This indicates that the PVP as solubilizing enhancer appears after the period of the immediate release (i.e. after 30 minutes) in order to enhance the distribution of the drug particles in the aqueous dissolution medium. However, this role needs to be in smaller quantities of solid particles (i.e. small amounts of carrier and coating materials when the new compressibility load factors calculated).

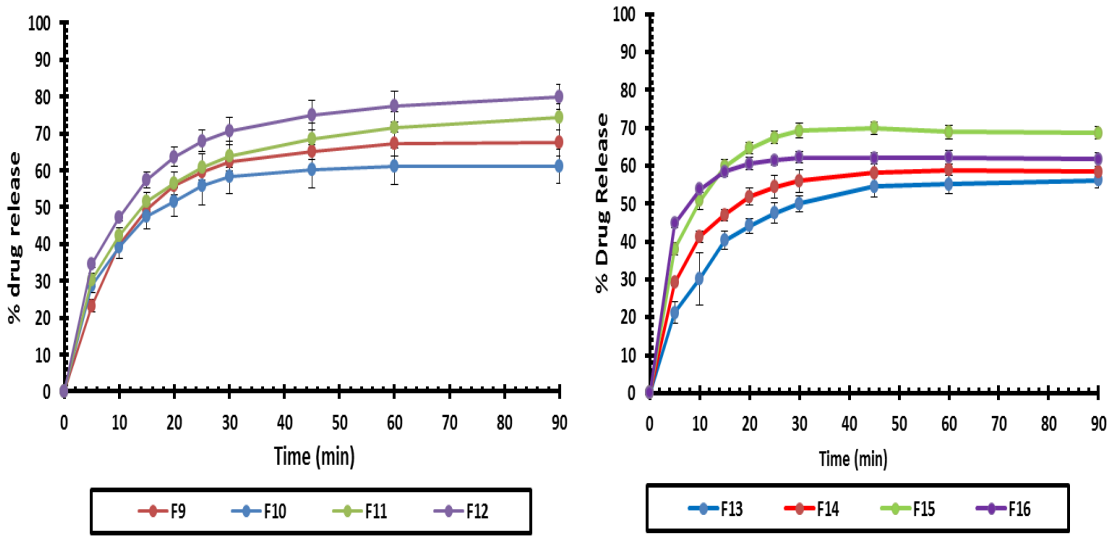


Figure 5-11: Dissolution profiles of the PEG200 water granulated liquisolid formulations prepared according to the new compressibility load factors (left) and to classical compressibility load factor (right) (for formulation compositions, refer to Table 2-4).

The comparison between the effect of the adding the water or adding the PVP solution to PEG200 liquisolid formulations leads to that there is a similarity in the dissolution profiles (f2 > 50%) with a slightly improvement in dissolution profiles containing PVP-K17 in formulations F2 and F3 and F4, where the differences between the formulations are 23.2%, 14.84% and 10.26% at 90 minutes, respectively (Figure 5-10 and Figure 5-11). From these results; it is possible to determine the role of the PVP over water as a liquid binder. It affects the dissolution profiles from 30 minutes onward, where the water granulated

dissolution profiles stop releasing the drug and the PVP granulated formulations continue increasing in the drug release gradually. The conclusion from this is that the PVP-K17 has a positive effect on the dissolution profile [13], but still small in these conditions, keeping the main effect in improvement of dissolution profile comes from the wet granulation process itself rather than the type of the used liquid binder. One reason for this conclusion is that PEG200 is a miscible liquid vehicle with the liquid binder, water or PVP-K17 solution.

Finally, the comparison between the water and PVP granulated liquisolid formulations when using the classical load factor in the preparations shows that the differences between the dissolution profiles become less significant when it compares with the new calculated load factors, although the PVP formulations still show slightly enhancement in the drug release. The highest recorded difference does not exceed 10 % in the case of formulation F4, whereas it decreases in the case of formulation F2 to about 0.48%. This means that as the quantities of the carrier and coating decreases in these formulations, the role of the PVP as a solubilizing enhancement becomes more obvious. Consequently, the importance of re-determine the load factors after incorporation wet granulation does not stop at parsimonious purposes, but it extends to enhance the drug dissolution profiles and norfloxacin could be considered as a good example.

5.3.3. Kinetics model analysis of drug release:

The kinetic models representing in Table 5-3 show a comparison of square regression coefficients (R^2) between PVP and water granulated PEG200 liquisolid formulations for two periods; the first one from 5 to 90 minutes (i.e. the all dissolution profiles) and the second one is from 5 to 20 minutes (i.e. the expected

immediate release for the relative formulations).The aim of selecting these cycles is to investigate the role of PVP as a liquid binder in the immediate and post-immediate dissolution time and how this role will reflect on the theory for the selected kinetic models (zero order, first order, Higuchi and Hixson-Crowell models).

Table 5-3: Comparison between PVP granulated liquisolid and water granulated liquisolid in terms of zero order, first order, Higuchi and Hixson-Crowell (H-C) kinetic models from 5 to 90 minutes and from 5 to 20 minutes (for formulation compositions, refer to Table 2-4).

		Regression Coefficients R^2 from 5 to 90 minutes			
Formula	**Binders**	**Zero**	**First**	**Higuchi**	**H-C**
F1	PVP	0.485	0.575	0.663	0.545
F2	PVP	0.758	0.897	0.896	0.856
F3	PVP	0.846	0.983	0.953	0.950
F4	PVP	0.799	0.956	0.924	0.913
F9	Water	0.563	0.656	0.736	0.494
F10	Water	0.560	0.616	0.736	0.517
F11	Water	0.710	0.825	0.860	0.640
F12	Water	0.664	0.799	0.823	0.603
		Regression Coefficients R^2 from 5 to 20 minutes			
Formula	**Binders**	**Zero**	**First**	**Higuchi**	**H-C**
F1	PVP	0.946	0.977	0.981	0.992
F2	PVP	0.989	0.997	0.997	0.993
F3	PVP	0.997	0.999	0.997	0.990
F4	PVP	0.997	0.999	0.997	0.989
F9	Water	0.958	0.984	0.989	0.977
F10	Water	0.967	0.982	0.992	0.977
F11	Water	0.970	0.988	0.994	0.983
F12	Water	0.980	0.996	0.997	0.992

The investigation of the data for the period of time from 5 to 90 minutes confirms that most of PVP formulations have higher R^2 values compared to its counterparts in the water formulations. In fact, the all PVP formulations show higher values except for F1. The investigation for the dissolution profiles (Figure 5-10 and Figure 5-11) can clarify the reason for such results as the formulations having PVP continue releasing the drug in the dissolution media after the immediate time (the first 30 minutes), whereas the water formulation gives straight horizontal lines parallel to the time axis and hence no further releasing for the drug.

In the second period of time from 5 to 20 minutes, both water and PVP formulations record R^2 values higher than 0.94. The reason could be referred to the action of both wet granulation processes that make liquid vehicle (PEG200) is better distributed in the solid powder.

Regarding the zero and first order kinetic models, both models depend on the fast increasing in the release of the drug in the first 30 minutes of the dissolution studies. The zero order suggests a linear dissolution rate, whereas the first order model goes to the exponential drug release [64]. As both types of formulations attain the equations for the fast releasing in the first 30 minutes, the second period of time(form 5 to 20 minutes) shows higher accuracy for these types of models, whereas the first period of time has lower accuracy, it still declares the superiority of the PVP formulations over the water counterparts.

In addition to this, when considering the Higuchi model, the Fick's law diffusion controls any assumption, where the driving forces due to concentration gradient between the tablet matrix and the bulk dissolution are the main corner in building this model to simulate the drug release [65].

As the wet granulation process enhances drug distribution in the liquisolid tablets and prevents the accumulation of the drug particles in the bottom of the dissolution tank, PVP as a binder solution shows less contact angle between the drug particles and the surface, increasing the wettability and preventing recapping or recrystallization [16]. Thus the driving forces will continue until complete drug release. This assumption can be supported from the Table 5-3 where the values of R^2 for F3 and F4 reaches to over 0.90 in the cycle time from 5 to 90 minutes.

Finally, the assumption related to sphericity shape of the particles, keeping the speed of transforming these particles to the dissolution medium and proportioning the surface with the time and agitation [16]. In this model, there is no indication that PVP as a liquid binder crafts the shape of the granules more than water during the preparation. However, PVP as a material preventing the re-crystallization, it helps keeping the speed of the transferring into the dissolution medium in a constant rate. Thus, the assumption of the relation between the surface decreasing with the time and agitation still exists and the R^2 for all PVP formulations have values similar to the water formulations and reaching over 0.90 in the case of formulations F3 and F4 for the period of time from 5 to 90 minutes.

5.4. Stability studies:

Table 5-4: Comparison between fresh and 3 months stored samples of the 10 % w/w PVP K17 granulated PEG200 liquisolid tablets (for formulation compositions, refer to Table 2-4).

	Fresh			After 3 months		
Formula	**Average %**		**Standard deviation**	**Average %**		**standard deviation**
F1	101.9	+/-	4.866	98.4	+/-	0.639
F2	106.3	+/-	4.227	100.1	+/-	4.505
F3	111.5	+/-	5.319	100.8	+/-	2.800
F4	111.3	+/-	1.962	100.6	+/-	4.897

Table 5-4 compares between the percentage of norfloxacin in PVP granulated liquisolid tablets at the moment of preparation and after three months storage at 21 ^{o}C and 76 % relative humidity. All formulations show a high percentage of drug content, and the tablets are in the acceptable BP levels. Moreover, the similarity factor percentages for all formulations mentioned in Figure 5-12 have a value higher than 50 %, indicating that there are no significant differences between the dissolution profiles before and after the stability test.

Furthermore, the DSC thermographs in Figure 5-13 have the same conclusion. The endothermic peaks of the stability test have the similar trends and the endothermic peaks that appear in fresh samples. The only notice could be mentioned here that the stored samples have enthalpy values larger than the fresh samples (broad peaks) due to adsorption water droplets on the surface of the stored tablets.

Finally, the comparison in terms of the FTIR spectra between the fresh and stored formulations gives the same spectra characteristics (Figure 5-14), complying with the results from content uniformity, dissolution and DSC results. This means the new PVP prepared formulations do not only show withstand to the stressful conditions, but also they improve that the PVP is a good liquid binder when it incorporates with PEG200 in the wet granulated liquisolid formulations.

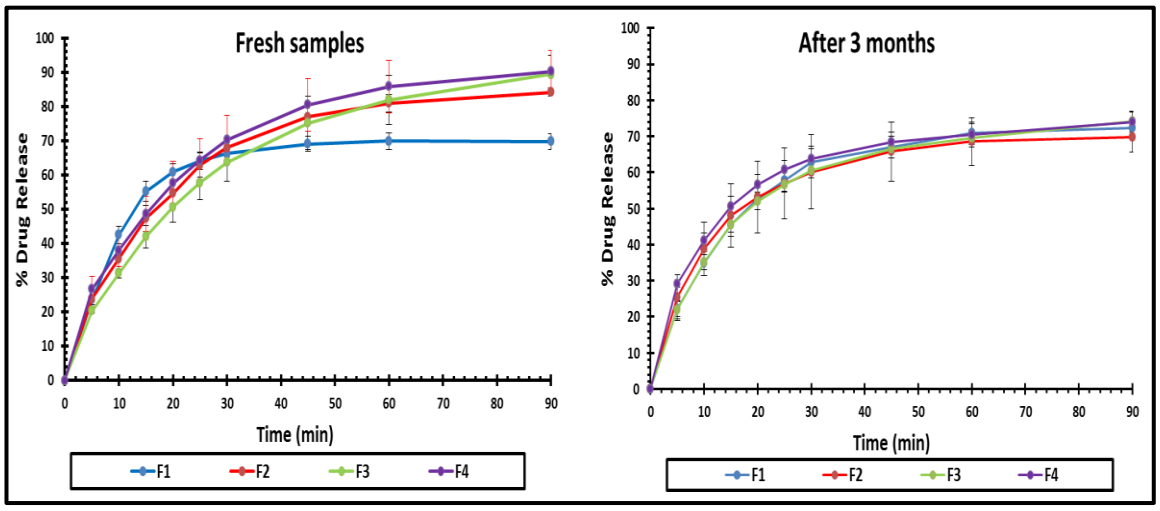


Figure 5-12: Comparison the dissolution profiles between fresh and stored for 3 months using10% w/w PVP K17 granulated PEG200 liquisolid tablets (for formulation compositions, refer to Table 2-4).

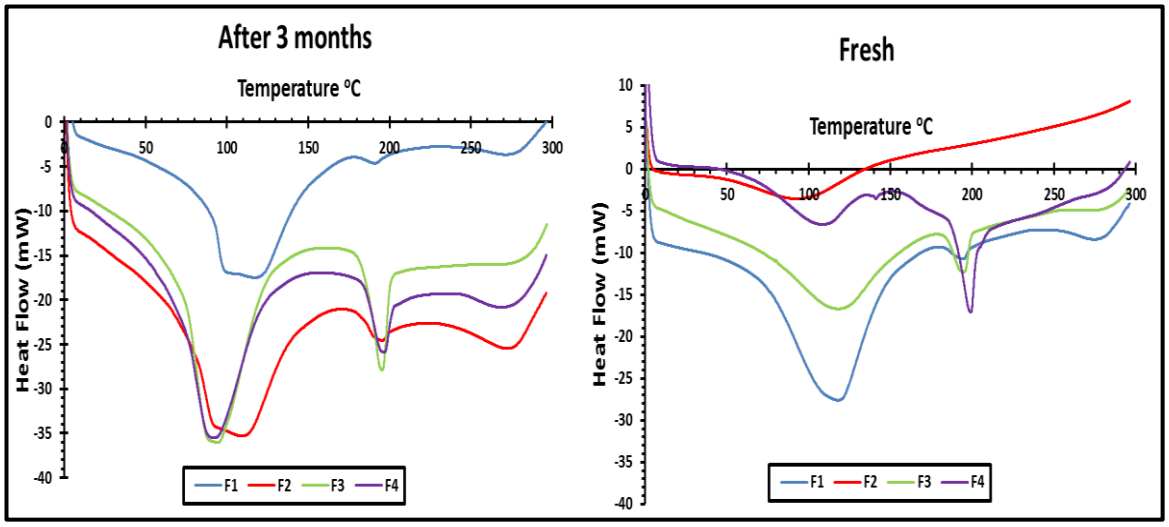


Figure 5-13: Comparison the DSC thermographs between norfloxacin fresh and samples stored for 3 months in terms of 10% w/w PVP K17 granulated PEG200 liquisolid tablets (for formulation compositions, refer to Table 2-4).

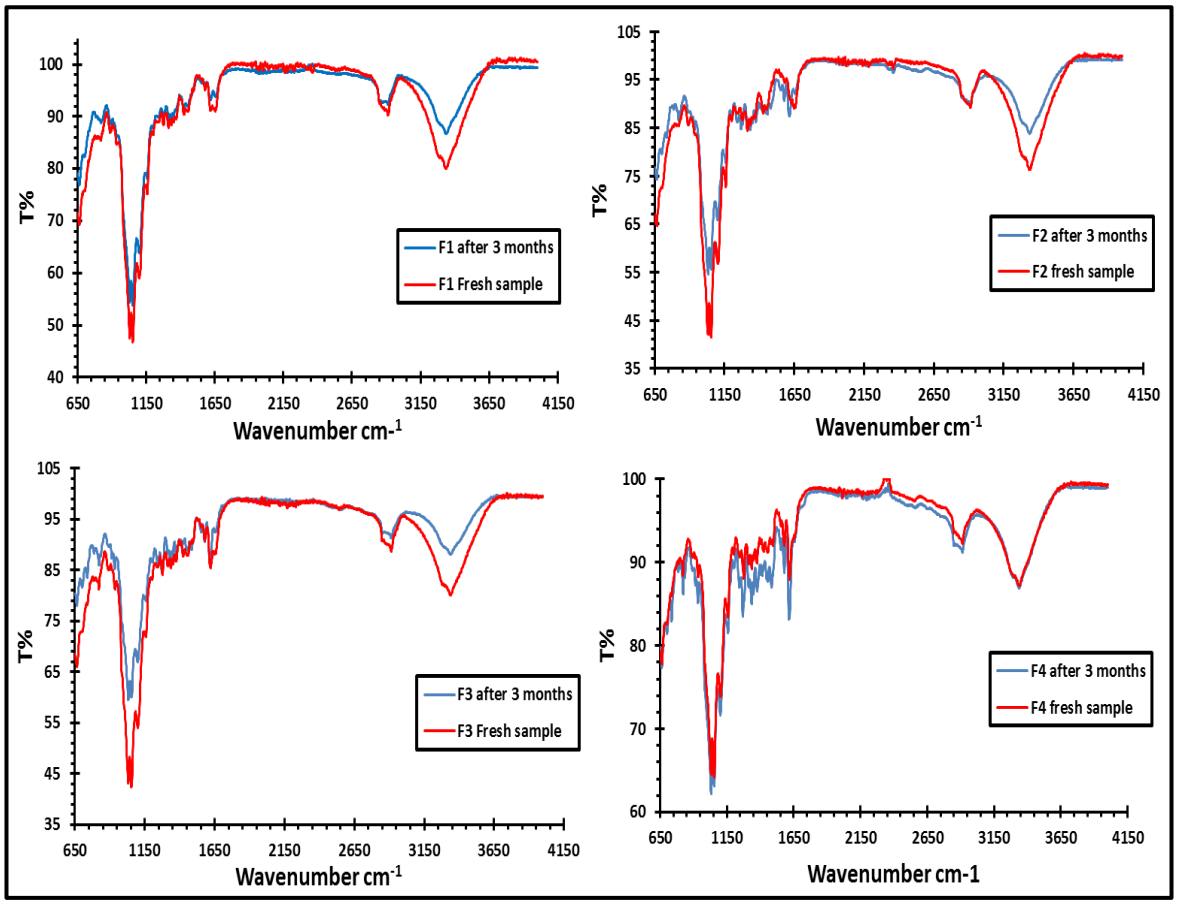


Figure 5-14: : Comparison the FTIR spectra between fresh and samples stored for 3 months for 10 % w/w PVP-K17 granulated PEG200 liquisolid tablets (for formulation compositions, refer to Table 2-4).

5.5. Conclusion:

The aim of this study is to investigate the role of PVP solution as a liquid binder and compare the role of the water in the wet granulated liquisolid formulations with the role of the PVP solution. The study of the angle of the slide provided good application for the PVP formulations to be used for powder filling. The compressibility studies, on the other hand, showed the incorporation of PVP solution with Synperonic ^{TM} PE/L-61 was not good approach for the tablet preparations. However, the mixing of PVP solution with PEG200 liquid vehicle provided good compressibility characteristics with acceptable compressibility load factor.

The comparison between the water and the PVP formulations in terms of the values of the compressibility load factor showed that the significant decrease only happened with the higher amount of the solid ratio (R values). As a result, the dissolution profiles for the PVP preparations had slightly higher percentages of the drug release compared to the water preparations. This happened when the quantities of carrier and coating decreased.

The content uniformity and other quality control tests presented similar results with the water formulations and all of them were in the acceptable specifications.

Finally, the stability for 3 months for PVP formulations did not show significant differences from the fresh preparations, indicating that PVP as a liquid binder could be a good candidate for wet granulated PEG200 liquisolid formulations.

Chapter Six: Studying the solubility and dissolution behaviors of cinnarizine via SEDDS systems

6.1. Introduction:

The aim of this chapter is to enhance the solubility and the dissolution in aqueous medium of cinnarizine, which can be considered as a model for hydrophobic drugs. It is classified as a medication derivative of piperazine, which is an organic water-soluble compound that consists of a six-membered ring containing two nitrogen atoms at opposite positions in the ring. However, its structure is considered as a very hydrophobic drug because its nitrogen atoms on the piperazine ring connect with Diphenyl methyl from one side and phenylprop-2-enyl from the opposite side (Figure 6-1).

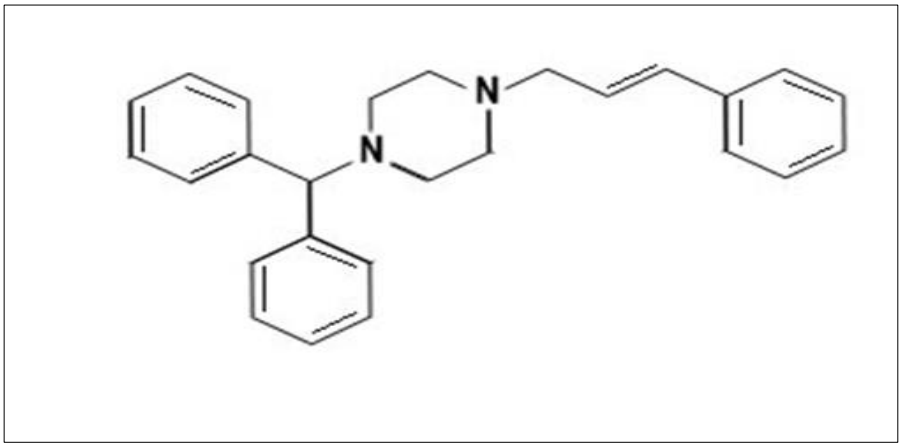


Figure 6-1: Chemical structure of cinnarizine.

Pharmacologically, the drug is considered as an antihistamine medicine that has been prescribed for treatment of vertigo, motion sickness, nausea and vomiting [87]. Furthermore, it is also known to promote cerebral blood flow, and so it is used to treat cerebral apoplexy, post-trauma cerebral symptoms, and cerebral arteriosclerosis [88]. This drug is usually taken orally and once it reached to stomach, the tablet disintegrates and the drug dissolves completely because it is freely soluble in the low pH solutions. Then, it permeates to the blood circulation quite rapidly so that it reaches to the maximum concentration during 1 to 3 hours

post-administration [89]. However, this does not prevent the drug to be classified as a lipophilic one with low bioavailability and variable dissolution so that it is administrated as frequent doses because of its short half-life (3- 6 hours) [90] & [91]. Moreover, the solubility of the drug in the acidic medium make the absorption site from the stomach not from small intestine, which it has a relative larger area as a site of absorption.

A recent study shows that given the drug intravenously as a lipid emulsion instead of taken orally would help to improve its bioavailability due to the higher recorded AUC and the lower clearance than the solution form, allowing for better therapeutic effect [92].

As a result of this, it could be possible to formulate this drug as a liquisolid tablet via dissolving through liquid vehicle having the same characteristics of the lipid emulsion.

Therefore, this chapter tries to determine the most suitable liquid vehicle that enhances the solubility and *in vitro* dissolution profile of cinnarizine in an aqueous medium, where the pH values of the liquid in the small intestine.

6.2. Calibration curves and Solubility studies:

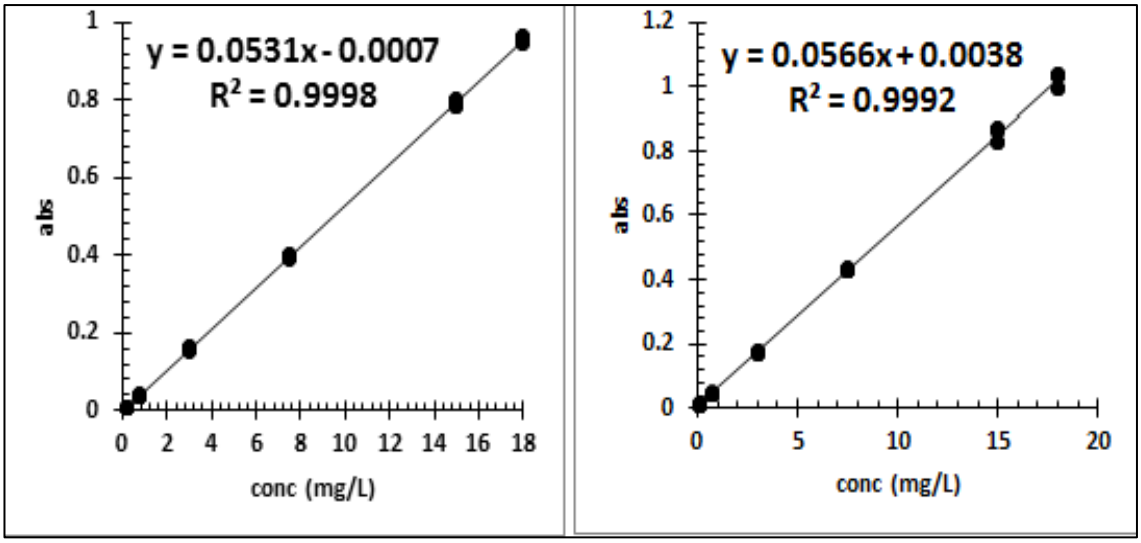


Figure 6-2: Calibration curves for cinnarizine in acetonitrile solvent at 249 nm as a maximum wavelength (left) and in 0.1 M HCl at 253 nm as a maximum wavelength (right) (repeated three times).

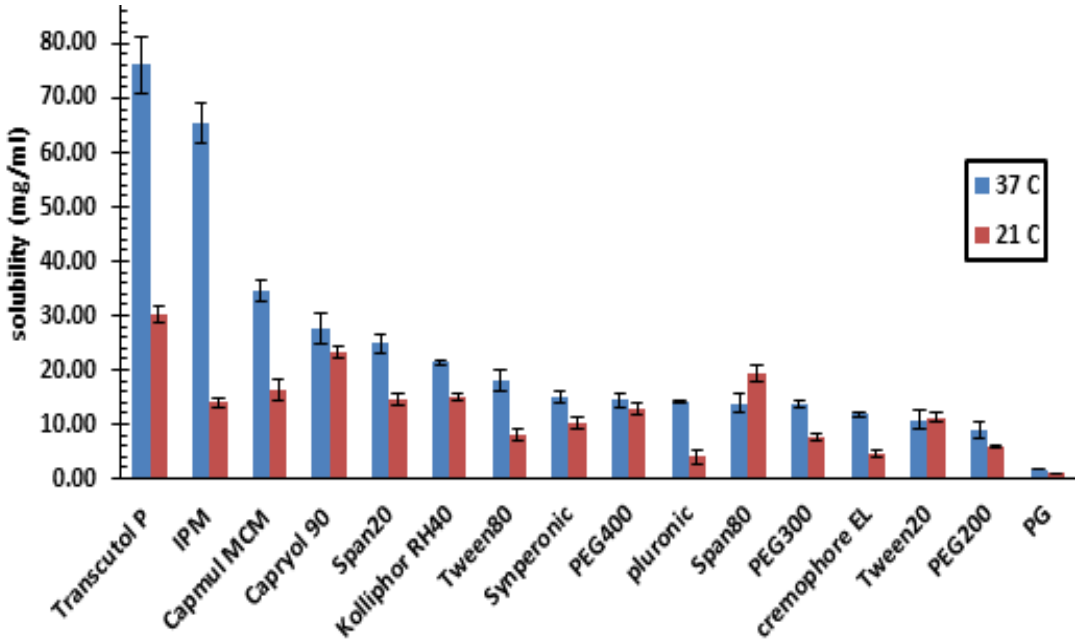


Figure 6-3: The solubility of cinnarizine in different types of surfactants/ lipids at 21 ° C and 37 ° C. The data are represented as mean of and standard deviation values.

The linear equation constituted from serial dilutions of cinnarizine in acetonitrile solvent and shown in Figure 6-2 (left) was used in order to determine the solubility

of the pure drug in the selected surfactants (Figure 6-3) by substituting the UV absorbance at 249 nm wavelength to calculate the relative cinnarizine concentration . The consideration of acetonitrile as a polar organic solvent allows being the main candidate in these solubility studies. Moreover, it has a capability to dissolve the all selected surfactants completely and make clear solutions. Thus, it ends any possibility to make interference in the absorbance due to less transparency.

Cinnarizine can be classified as a drug practically insoluble in water at neutral pH level. Previous studies determined approximate value for its solubility in water (16.95×10^{-6} mg/ml) [87]. Therefore, the incorporation of cinnarizine in different types of surfactants is important as it gives an indication how this drug dissolves in water and how it acts during the dissolution studies.

The investigation of Figure 6-3 assigns that the solubility of cinnarizine can be classified into three groups; the first one includes the surfactant that records solubility over 30 mg/ml at the body temperature (37 ^{o}C), which they are Transcutol® P, IPM and Capmul® MCM EP. Although some of these surfactants shows a certain of sensitivity to the change of the temperature, such as Transcutol® P which records 30.9 mg/ml solubility at 21 ^{o}C, all of them records high solubility values by increasing the temperature.

The second group includes Capryol™ 90, Span 20 and Kolliphor® RH40. These surfactants record solubility values between 20 and 30 mg/ml at 37 ^{o}C. Furthermore, Kolliphor® RH40 and Capryol™ 90 show less sensitivity of temperature change when compared to the surfactant in the first group. Therefore, they can be considered as good candidate for further investigations.

The last group contains the rest of surfactants that record solubility less than 20 mg/ml at body temperature. This group contains surfactants with different physicochemical characteristics. For example, PEG200, PEG300, PEG400 and Pluronic L-35 have HLB values more than 18, whereas the HLB value for Synperonic ™ PE/L-61 equals to 3.

Furthermore, they have different sensitivity to the temperature change. In more details, Propylene Glycol (PG), PEG200, PEG300, PEG400 and Tween20 show more stability towards the changing in the temperature, whereas Pluronic L-35, Cremophor® EL and Tween80 show less heat stability, and the solubility of cinnarizine in span80 at 21 ^{o}C records a higher value than its solubility at 37 ^{o}C.

In general, the conclusions that can be drawn from this solubility studies are the incorporation of cinnarizine as a pure drug with surfactants at higher temperature shows larger solubility values and a relative enhancement when compared with the solubility of the drug in distilled water. Also, surfactants that show higher drug solubility values or less sensitivity towards the change of heating could be good candidates for further investigations and dissolution studies.

6.3. Screening *in vitro* dissolution studies:

The aim of these studies is to determine surfactants that show the best percentage of cinnarizine release in the aqueous dissolution media, whether distilled water at pH 6.1 or phosphate buffer at pH 7.2. Moreover, it is designed to determine the conditions that could participate in increasing the percentage of drug release, such as heating, changing the type of the carrier, the effect of changing the type of surfactant, the quantity of surfactant, the type of dissolution media and the effect of combination between two or more surfactants.

Several surfactants with different HLB values have been incorporated with cinnarizine at 20% w/w in order to assign the best dissolution profiles. Figure 6-4 represents the percentages of the drug release from these liquid medications. Although, all of them provide no more than 6 % of drug release, there is a possibility to divide them into three groups.

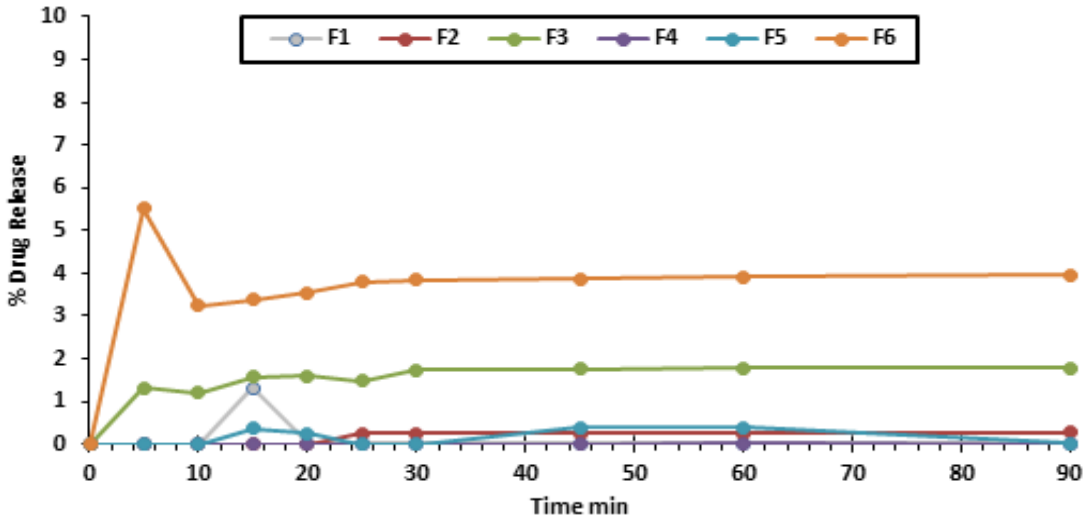


Figure 6-4: Percentage of Cinnarizine release in DW (pH 6.1) from several liquid medications (20% w/w) with PEG200, Synperonic™ PE/ L-61, Tween 20, PG, PEG400 and Cremophor® RH40. (See Table 2-5).

The first one contains PEG200, PEG400 and PG, which they do not reach to 0.5% drug release after 90 minutes. When the liquid medication of the first group is incorporated inside the dissolution medium, there is a separation between the surfactants and the drug that leads to dissolve the surfactant inside the aqueous dissolution medium and precipitate the drug particles at the bottom of the dissolution vessel. These surfactants have HLB values over 11, which is more hydrophilic surfactants. In other words, their affinity to dissolve and make hydrogen bonds with water is higher than making strong bond with cinnarizine. The second group could consist of Synperonic™ PE/L-61 (formulae F2, Figure

6-4), Span 20 and Span 80 (data not shown); which they have HLB values equal to 3.0, 8.6 and 4.3, respectively. These surfactants show practically no drug release in distilled water. This could be expected as they are hydrophobic surfactants, tend not to dissolve in water. Consequently, they will keep their bonds with the cinnarizine away from the dissolution medium on the bottom of the dissolution vessel.

The third group could include Cremophor® RH40 (HLB value is between 14 and 16) and to some extent Tween 20 (HLB value is 16.7). In this group, there is a slightly increase in the percentage of the drug release but cannot be considered as a significant increase. The similarity factor between the third group and the other groups is still over 60 %. In conclusion, the HLB value as an indicator factor does not play very vital role in enhancing the dissolution behaviour in water dissolution medium in the case of cinnarizine.

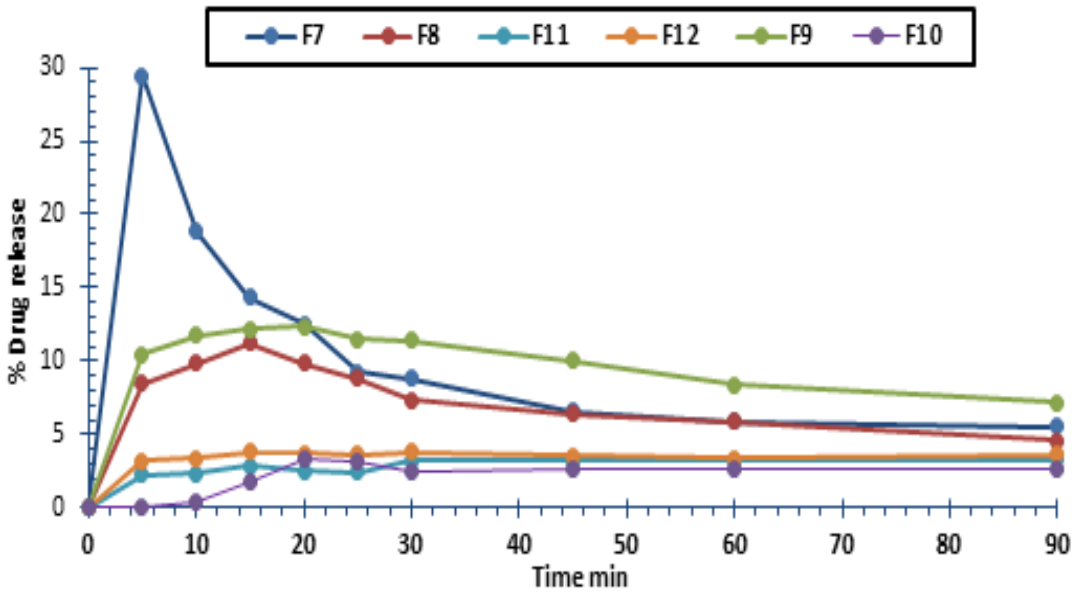


Figure 6-5: The dissolution profiles for cinnarizine with Solutol® HS 15, Cremophor® RH40, and Cremophor® EL with Solutol® HS 15, Cremophor® RH 40 with Cremophor® EL, and the combinations among them with applying heating until dissolving the drug particle in the surfactant, keeping the percentage at 20%w/w drug/ liquid medication (See Table 2-5).

The factors that investigated in Figure 6-5 are heating and the combination between surfactants. Regarding heating, when apply a certain degree of temperature on the liquid medication, the dissolution enhanced markedly. In the case of formulation F8, the heating was for a limited time, which was not enough to make all the drug dissolve completely, but the enhancement of the dissolution was determined; after 15 minutes, it reaches to 12.22% while in the case of no heating, it was 3.39% at the same time (see Figure 6-4, F6). Another example is the formulation F7, where Solutol® HS 15 was used as a liquid medication. Here, the applying of heating was kept until reaching to make cinnarizine completely dissolve in the surfactant. This leads to obtain about 29.43% drug release after 5 minutes. However, the Solutol® HS 15 liquid medication started decreasing gradually until reach to 8.87% after 30 minutes and 4.85 % after 90 minutes. These lead to conclude that the Cremophor® RH40 has more stability in its dissolution profile comparing with Solutol® HS 15, although both of them provide a marked enhancement when applying heating. Finally, the combination of liquid medications among Solutol® HS 15, Cremophor® EL and Cremophor® RH40 did not show an expected enhancement comparing with the individual relative liquid medication when applying heating.

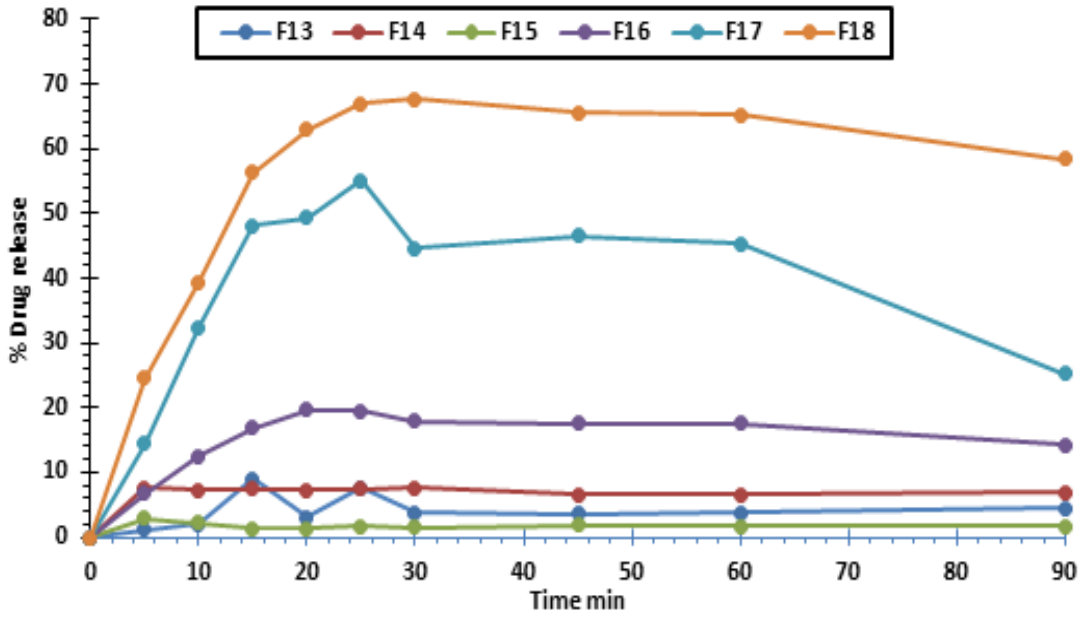


Figure 6-6: The dissolution profiles for liquisolid formulations using lactose as a carrier with Solutol® HS 15, Cremophor® RH40 and PEG200. Liquid medication of Cremophor with 120 mg, 200 mg and 400 mg surfactant weight in phosphate buffer dissolution media pH= 7.2. (See Table 2-5).

Another factor has been investigated is the type of carriers that could be used in cinnarizine liquisolid formulations. The selected carrier was lactose. The dissolution profiles for Cremophor® RH40, Solutol® HS 15 and PEG200 liquisolid formulations, using lactose as a carrier (Figure 6-6), do not show significant enhancement of the percentage of the drug release, comparing with the same quantities of liquid medications without addition of powder. The highest recorded points for the three liquisolid formulations were less than 10% drug release after 15 minutes. Moreover, the similarity factor shows more than 84% between formulation F1 and formulation F15 when using PEG200 as a liquid vehicle. The similar results have been noticed in the case of Cremophor® RH40 without applying heating; the similarity factor between F6 and F14 is over 70%. Furthermore, the heating of Solutol® HS 15 in formulation F7 still shows a better dissolution profile from the one used liquisolid formulation with lactose as a carrier

material. In other words, the type of carrier shows no significant effect on the dissolution profile of cinnarizine in neutral dissolution media.

On the other hand, when increasing the quantities of the Cremophor® RH40, the significant enhancement in the cinnarizine dissolution profiles is noticed. The similarity factors between F8 from one side and F16, F17 and F18, which represent different formulations containing increased amount of Cremophor® RH40, are 52.30%, 23.23% and 14.58%, respectively. The highest percentage is recorded at 67% drug release after 30 minutes in F18 formulation, where the quantity of the liquid vehicle is 400 mg. However, the differences between F17 and F18 are only 10% drug release in the first 25 minutes, although the difference in quantities of surfactants is 200 mg. However, when increasing the quantity from 120 mg to 200 mg, the enhancement in the dissolution profile is more 26%. This means that the enhancement of the percentage of the drug release reaches to plateau level after adding specific amount of the liquid vehicle.
As a result of this, the quantity of the Cremophor® RH40 surfactant plays an important role in determination the enhancement of the dissolution profile of cinnarizine.

Another aspect has been investigated is the type of the dissolution media. In more details, when applying the same formulations but in distilled water dissolution medium (Figure 6-7: F19, F20 and F21) instead of phosphate buffer solution at pH 7.2 (Figure 6-6: F16, F17 and F18), there is no significant differences between dissolution profiles, especially when applying higher quantities of the surfactants (i.e. at 200 and 400 mg).The similarity factors recorded between F16 and F19, F17 and F20 and F18 and F21 are 50.14%, 60.04% and 58.31%, respectively. This

indicates that the type of the dissolution media in neutral range does not have a major effect on the enhancement of the dissolution profiles.

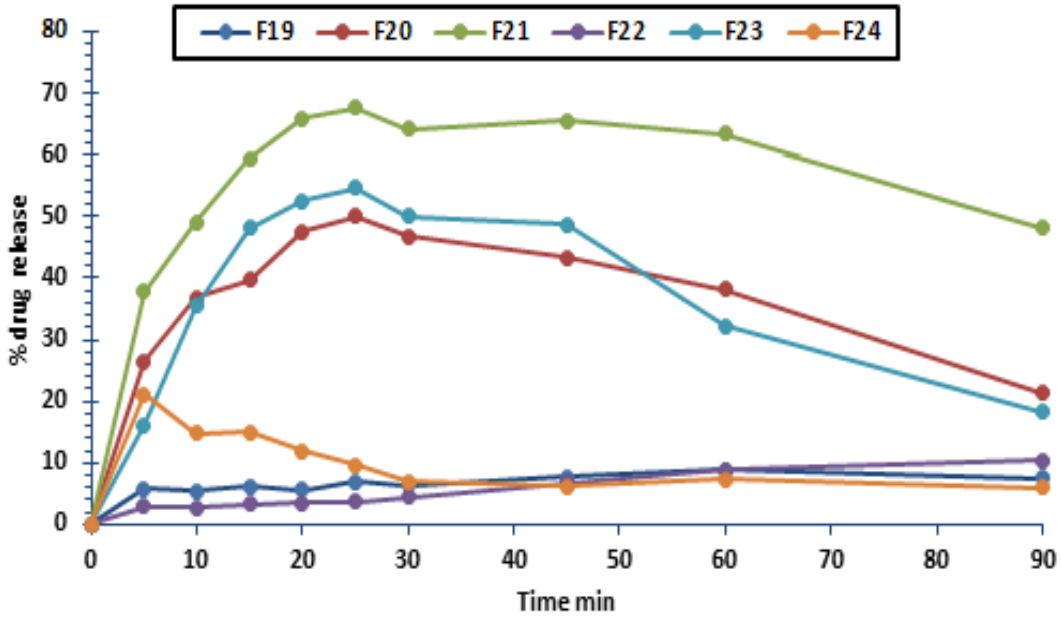


Figure 6-7: Dissolution profiles for Cremophor® RH40 liquid medication at 120 mg, 200 mg and 400 mg; Cremophor® RH40 with 10 mg PVP and Brji® S 100 liquisolid formulation in distilled water at pH = 6.1 (See Table 2-5).

Moreover, the addition of PVP into the liquid vehicle in formulation F23 with 200 mg Cremophor® RH40 shows no significant differences with the formulation that does not have the PVP (F20) (see Figure 6-7). The similarity factor between them is about 61.19%.

However, adding solid powder (carrier and coating) to convert the liquid medication to liquisolid admixture in formulation F24 leads to record a significant decrease in the percentage of drug release. The similarity factor between F20 and F24 is 26.03%, limiting the rule of the heat in the dissolution behaviour.

Finally, using Brji® S100 as a liquid vehicle with cinnarizine does not improve the dissolution of the drug because it leads to only 10% of drug release after 90 minutes, sharing the same results with the liquid vehicles mentioned in Figure 6-4.

To sum up, the cremophor® RH40 could be a good selection as liquid vehicle to dissolve cinnarizine but it needs to be used in higher quantities with heating. However, it is still better than Solutol® HS 15 as it is less sensitive to the temperature change in term of dissolution behaviour in neutral dissolution media, whether using distilled water at pH 6.1 or phosphate buffer solution at pH 7.2. Also, the combination between Cremophor® RH40 and the surfactants that show higher degree of solubility could give mixtures with higher dissolution results.

6.4. Dissolution results for self-emulsifying drug delivery systems (SEDDS):

A Self –emulsifying drug delivery system (SEDDS) could be defined as a system which emulsifies hydrophobic drugs in the aqueous solutions under gentle conditions of agitation to cause dispersion in a manner of colloidal dimensions [49]. The principle mixture of SEDDS consists usually of oils, which are medium chain fatty acids (triglycerides, diglycerides, monoglycerides or mixtures of them). Moreover, it contains surfactants usually with HLB values > 11 as well as hydrophilic co-solvents in different percentages. These systems showed a successful enhancement of dissolution of the hydrophobic drugs in the aqueous media in the previous studies and decreased the particle size of the emulsion to micrometre levels and even to nanometre level [93] . As a consequence, the application of this technique could show an improvement in the case of cinnarizine. However, several considerations should be noticed in term of using SEDDS. For example, the type of the oil, surfactant and co-solvent, the optimum percentages of these components and the overall concentration of the system that suits the volume of the dissolution medium from one side and the minimum liquid medication that could be applied to convert to liquisolid tablet later from another

side. The strategy that was followed in this research for selecting the type of the oil, surfactant and co-solvent depends mainly on the solubility of the drug in each one of them (refer to Figure 6-3). As a consequence of this, two SEDDS were selected; the first one contains Capryol™ 90 as a medium chain fatty acid, Kolliphor® RH40 as a surfactant and Transcutol® P as a co-solvent, whereas the second one consists of isopropyl myrestate (IPM) as an oil, Kolliphor® RH40 and Transcutol® P as a surfactant and co-solvent, respectively.

The screening dissolution tests for the first SEDDS in the aqueous medium (distilled water pH = 6.1) were selected according to ternary phase mixture design with 10 different percentages at specific quantity (refer to fromulation F25 to F34 Table 2-5), and the dissolution profiles were summarized in Figure 6-8.

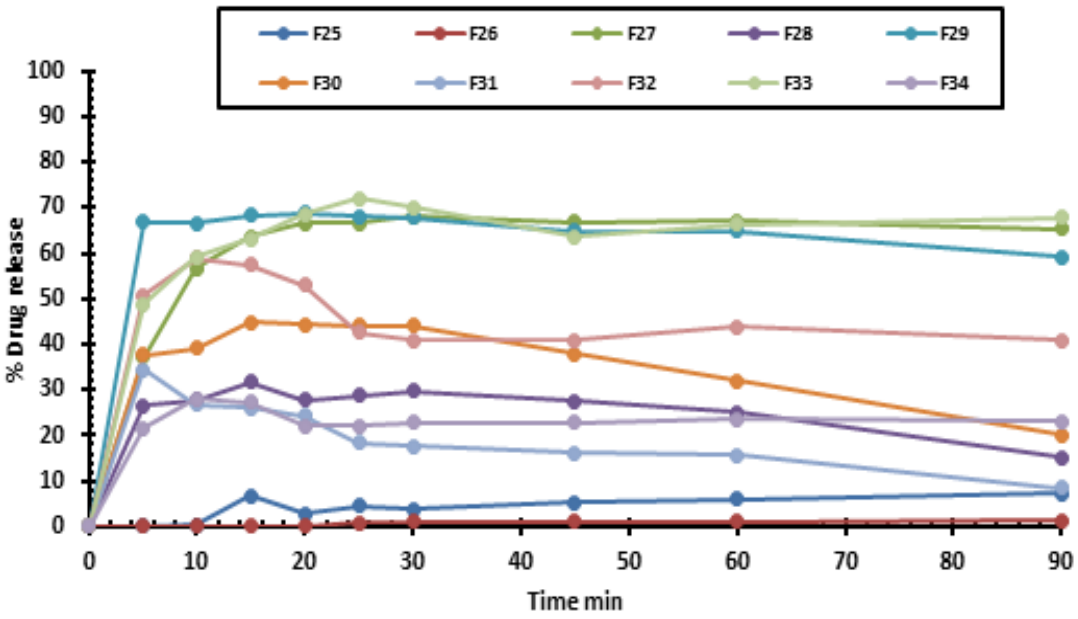


Figure 6-8: Dissolution profiles in distilled water (pH=6.1) for liquid medications of cinnarizine with the SEDDS consist of different percentages of Capryol™ 90, Kolliphor® RH40and Transcutol® P (see Table 2-5).

The investigation of the dissolution profiles assigns that there are three formulations recorded the highest percentages of the drug release (formulations

F27, F29 and F33 in Figure 6-8). While the formulations F27 contains 100% Kolliphor® RH40, the formulations F29 and F33 contain the surfactant in 50% sharing with Capryol™ 90 only in F29, and it is at 66.66% sharing equal percentages (i.e. 16.66%) with the oil and co-solvent in F33. The expected reason for the recorded higher percentages in these formulations could be referred to the unique chemical structure of Kolliphor® RH40. It includes a hydrogenated castor oil, which acts as an organic solvent to the cinnarizine particles, as well as it has a 40 parts of polyethylene glycole (PEG), which acts as a hydropilic co-surfactant, which can dissolve quickly in water. Furthermore, the presence of PEG in the structure of Kolliphor® RH40 and the connection of it with the hydrophobic part decreases the interfacial tension that could form between the hydrogenated caster oil and cinnarizine particles from one side and the aqueous dissolution medium from another side. As a consequence of this, the stability of the emulsion particles records improvement results when this surfactant is the predominant in the formulations.

On the other hand, the successful dissolution profiles that can be seen in the presence of the Kolliphor® RH40 cannot present when this surfactant is absent. The lowest percentages of the drug release were recorded in the case of formulation F25, which include Capryol™ 90 alone and F26, which contains Capryol™ 90 and Transcutol® P (50:50). Thus, the combination between the diethylene glycol monoethyl ether (Transcutol® P) with propylene glycol monocaprylate (Capryol™ 90) does not seem to be a successful combination for dispersing the cinnarizine in the aqueous medium, even though the applied heat and the quantity that used during the preparation are similar to those used in the Kolliphor® RH40 formulations. This is probably due to that the affinity of the

hydrophobic drug to dissolve in monocaprylate in the precence of propylene glycol is very small (the solubility is only 1.57 mg/ml at 37 ^{o}C (Figure 6-3) so that the propylene glycol does not work as PEG that is found in Kolliphor® RH40. Thus, the lowering of the interfacial tension in the case of Kolliphor® RH40 cannot attain in the case of Capryol™ 90 alone and even in the presence of Transcutol® P.

To sum up, as long as Kolliphor® RH40 presents in the formulation, there are a significant enhancement in the cinnarizine dissolution profiles in the aqueous medium.

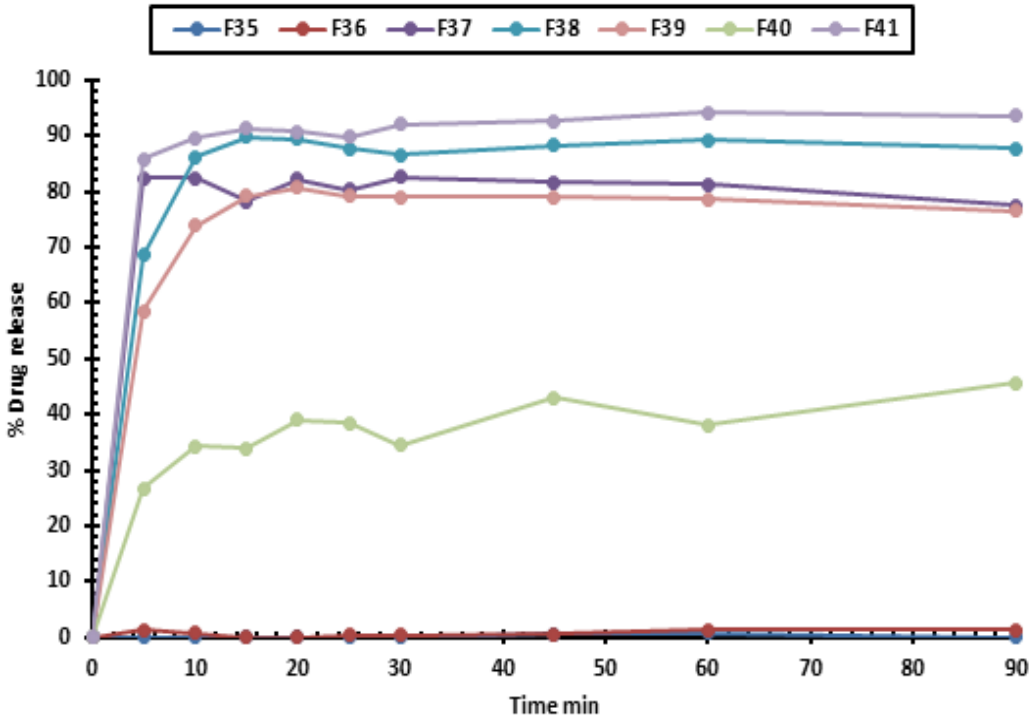


Figure 6-9: Dissolution profiles in distilled water medium (pH=6.1) for liquid medications of cinnarizine with the SEDDS consist of different percentages of IPM, Kolliphor® RH40 and Transcutol® P (see Table 2-5).

Regarding the second SEDDS (Figure 6-9); there is significant indication that substitution of Capryol™ 90 with IPM enhances the percentage of cinnarizine release in the aqueous dissolution medium. The highest recorded percentage reaches to 94.04% after 60 minutes in formulation F41, which contains the oil, the surfactant and the co-solvent in equal percentages (see Table 2-5). Moreover,

there is a significant enhancement in the percentage of the drug release in formulations F37 and F38, where the percentage of the IPM in the SEDDS is high. However, the enhancement of the dissolution profiles is not recorded without presence of Kolliphor® RH40. For example, formulations F35 and F36, which contain 100% IPM and 50% IPM with Transcutol® P, respectively, have practically no drug release. This means that the combination between IPM and Kolliphor® RH40 shows good enhancement in the dissolution profiles due to its ability to provide a stable dispersed mixture in the aqueous medium. This stability could come from the affinity of cinnarizine to dissolve more in IPM, especially when it mixes with Kolliphor® RH40 with heating. As a result, the crystal particles of cinnarizine will become smaller and occupy in a smaller size of emulsion droplets so that they become more stable in the aqueous dissolution medium. Finally, the presence of Transcutol® P in the mixture of IPM and Kolliphor® RH40 in optimum percentage supports the dispersion of the emulsion particles inside the dissolution medium. As a consequence, Transcutol® P works as a better co-solvent when IPM presents in the SEDDS mixture.

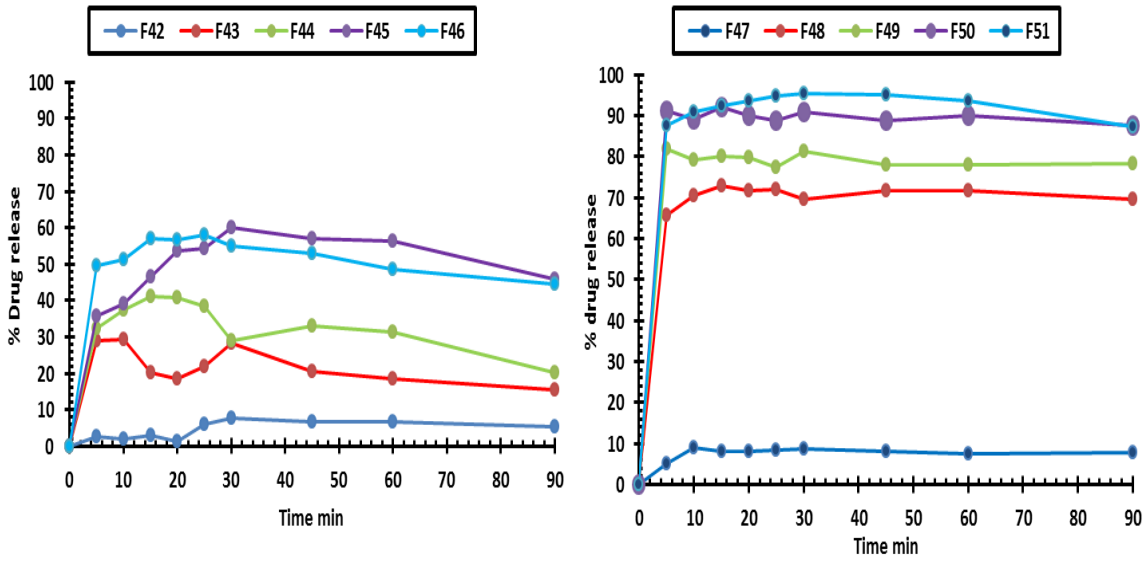


Figure 6-10: Comparison between dissolution profiles of formulations from F42 to F51 (see Table 2-5).

After determining the optimum percentages for the two types of the SEDDS mixtures, it is worth to specify the maximum liquid medication concentration that can be used for 15 mg cinnarizine and achieve the similar enhancement in the dissolution profile that the assigned from ternary phase design screening tests as shown below. Figure 6-10 compares between Capryol™ 90/ Kolliphor® RH40/ Transcutol® P (70:15:15) SEDDS mixtures (Figure 6-10 left) and IPM/ Kolliphor® RH40/ Transcutol® P (35:35:30) SEDDS mixtures (Figure 6-10 right) at 15% w/w, 7.5% w/w, 5% w/w, 3.75% w/w and 3% w/w for 15 mg drug, respectively.(refer to Table 2-5 for full compositions).

For both SEDDS, the percentage of the drug release decreases when the liquid medication concentration increases, although both of them records no significant differences when increases the concentration of liquid medication from 3% w/w to 3.75% w/w (the similarity factors in the case of Capryol™ 90 mixture are 54.5% and 69.6% in the case of IPM mixture). However, the SEDDS containing IPM shows more stability with high percentages of the drug release comparing with the SEDDS containing Capryol™ 90 when increases the concentration of the liquid medication from 3.75% to 5% w/w. The similarity factor in the case of IPM between formulations F49 and F50 is 48.6% and between formulations F44 and F45 is only 35.9%.

In the case of dissolution tests of the Capryol™ 90 SEDDS, another phenomenon could be noticed which a partial decrease in the dissolution profile is assigned after a period of time. It becomes more obvious when the concentration of the liquid medication increases, such as in the case of formulations F43 and F44 (see Table 2-51). Further investigations by using FTIR analysis (see section 2.4.3) determine that there is a formation of drug crystals gradually with time. Figure 6-11

represents a comparison between the FTIR spectra before starting the dissolution test (left) and after one hour period time (right) applied on dried precipitant after one hour dissolution run. It is obvious that the FTIR spectrum of the SEDDS containing the cinnarizine particles before the starting of the dissolution test is compatible with the FTIR spectrum of the SEDDS without addition of cinnarizine, indicating that the drug particles completely dissolve in the SEDDS mixture. However, after one hour of the dissolution experiment, the FTIR spectrum of the collected white crystals is identical to the spectrum of the pure cinnarizine. This means that there is a gradual accumulation of the drug particles with time due to the rotation of the puddle of the dissolution device. The agitation power of the dissolution medium may change the value of the surface free energy of the emulsion system so that it increases and destabilizes the thermodynamic state of the system. This change allows the crystals of the drug to reconstitute inside the dissolution medium and then float on the surface of the vessel as noticed. This could explain the gradual decrease in the dissolution profile after reaching to the maximum level not only when increasing the concentration of the liquid medication, but also in the case when the SEDDS contains Transcutol® P in 100% (F30, see Table 2-5) or in the case of mixing Transcutol® P with Kolliphor® RH40 in equal percentage (F31, see Table 2-5), where its emulsion system make droplets sensitive and fragile to the force of agitation (see Figure 6-11).

In conclusion, the IPM SEDDS mixtures not only provide more enhancement dissolution profiles comparing with the Capryol™ 90 ones, but also it shows ability to accept higher concentrations of liquid medications.

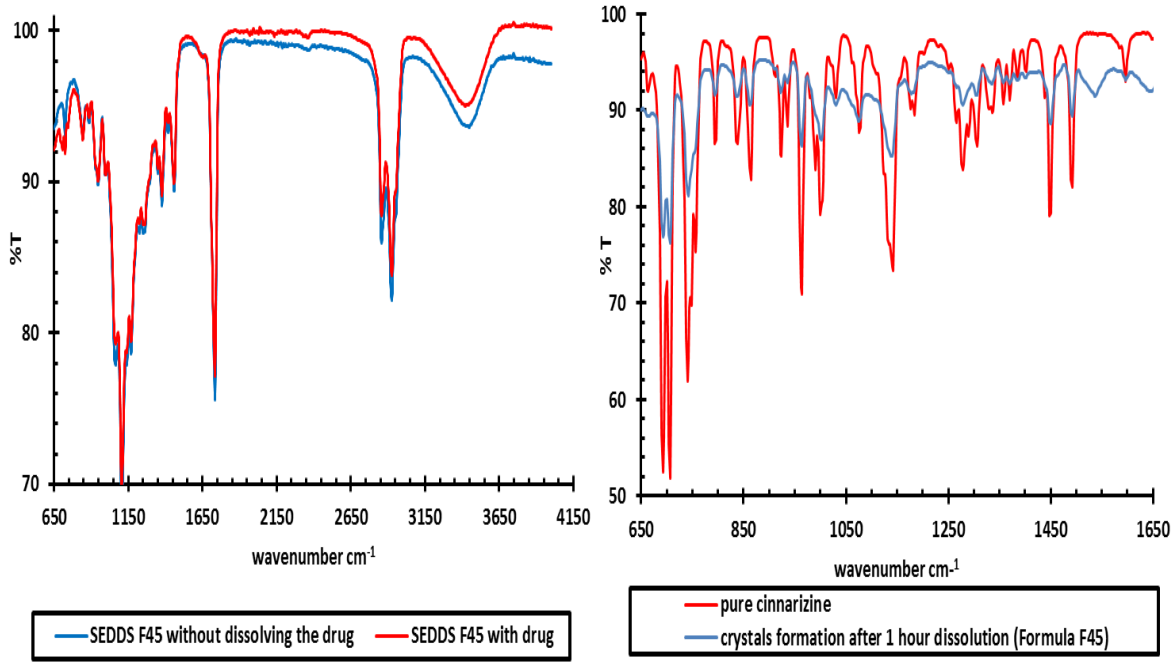


Figure 6-11: Compare between FTIR spectra of formulation F45 (see Table 2-5) with its blank (left), and compare between the spectra of pure cinnarizine with the crystal sample that is collected after one hour run of dissolution test for formulation F45 (right).

6.5. Emulsion droplet size analysis and the relation with the percentage of cinnarizine release in the aqueous dissolution medium:

The study of the droplet size of SEDDS mixtures (Capryol™ 90 and IPM) was determined by dynamic light scattering technique. The effective diameter (nm) from each formulation was grouped according to the type of the SEDDS and plotted as Pseudo-colour ternary phase diagram (Figure 6-12) in order to obtain an easier comparison with the trapezoidal area under the curve for the relative dissolution profiles (Figure 6-13).

Regarding the Capryol™ 90 SEDDS, the larger particle sizes take place in two distinct areas; the first one is around the formulations including Kolliphor® RH40 and Capryol™ 90 in equal percentage and the second one is around Kolliphor® RH40 and Transcutol® P in (50:50) percentage ratio. However, the general examination of the ternary phase diagram determines that the dark blue colour

covers smaller area (Figure 6-12, left). This means that the range of the particle size in most of the formulations of the Capryol™ 90 SEDDS is larger than 1 µm. The relative higher particle sizes reflect directly on the AUC of the dissolution profiles (Figure 6-12 and Figure 6-13, left sides), where the range of the AUC values do not exceed 3500 % drug release* minute. In other words, most of the dissolution profiles do not record stable high percentages of drug release during the dissolution test.

Thermodynamically, the larger droplet sizes mean a larger probability of collision to happen. This leads to increase the surface free energy (W), which directly proportional to interfacial tension (γ_{SL}) between the solid particles and the liquid of the dissolution medium and the change of the interfacial area (ΔA) according to the following equation ($W = \gamma_{SL} \times \Delta A$) [94].

However, the larger droplet sizes mean also larger quantity of surfactant that makes the surface tension low. Thus, the SEDDS in the situation that contains high amount of surfactant will keep at a stable state. This explains why there is a large AUC values in the same area of the large effective diameter (Figure 6-12 and Figure 6-13, left side), which is at high percentage of Kolliphor® RH40 in the formulations.

On the other hand, when Capryol™ 90 is predominant in the SEDDS formulations, the decrease in the change of the interfacial area attains but the decrease in the interfacial tension does not achieve unless there is a presence of Kolliphor® RH40. Therefore, there is a blue area at the higher amount of Capryol™ 90 in the particle size triangle plot, and there is a sharp increase in the AUC tringle from dark blue to dark red when the surfactant starts including in the SEDDS formulations.

In the case of the formulation where the Transcutol® P is the predominant, the particle size is on a middle average size and it increases when the amount of the surfactant increases. Although the presence of the surfactant plays an important role in decreasing the interfacial tension in order to stabilize the state of the system, the capability of the formulations in this region does not resist the force of coalesce of the emulsion droplets, which comes from the spontaneous collision of the droplets that are rotating inside the dissolution medium. Thus, the small positive value of the interfacial tension that usually insoluble solid particles possess will grow up gradually, leading to form light fluffy conglomerates, which are held together by weak Van der Waals forces and float on the surface of the dissolution medium [94]. This reflects on the relative AUC plot with values between 2500 and 3500 % drug release *minutes due to the gradual decrease of the dissolution profiles.

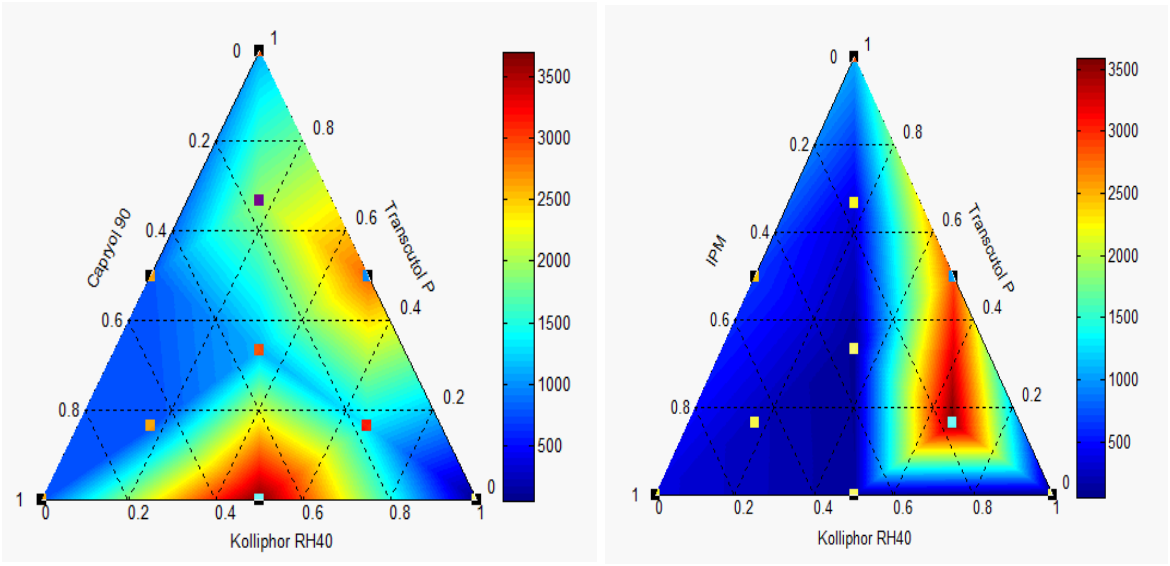


Figure 6-12: Pseudo-colour ternary phase plots show effective diameters (nm) of the particle size for SEDDS formulations from F25 to F34 (left) and from F35 to F41 including F27, F30 and F31 (right) (see Table 2-5). Each triangle represents the percentage ratios of the SEDDS components.

Finally, due to the higher solubility of the cinnarizine in IPM, the effective diameter of the IPM SEDDS formulations show smaller size and the dark blue area covers more than the half of the plotted ternary phase diagram (Figure 6-12, right). This reflects as higher AUC values where the dark red area is larger (Figure 6-13, right). It seems that the presence of IPM instead of Capryol™ 90 helps to resist the force of the droplet collision and keeps the system stable at low interfacial tension as well. Thus, high percentage of the drug release with larger AUC values can be achieved.

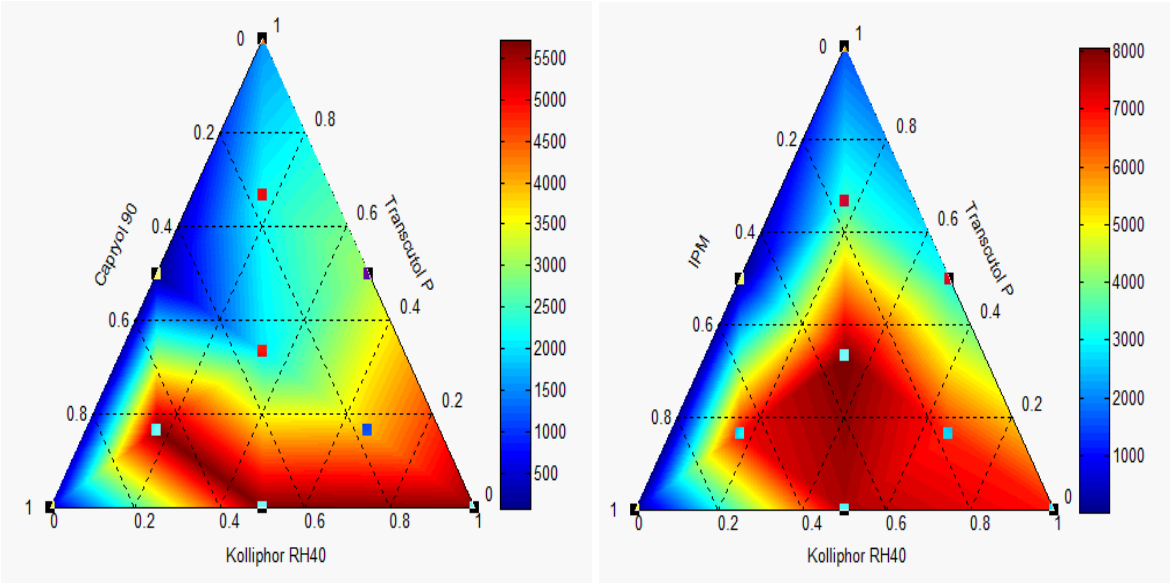


Figure 6-13: Pseudo-colour ternary phase plots show trapezoidal area under the curves (AUC) of the dissolution profiles (% drug release x min) for SEDDS formulations from F25 to F34 (left) and from F35 to F41 including F27, F30 and F31 (right) (see Table 2-5). Each triangle represents the percentage ratios of the SEDDS components.

6.6. Conclusion:

The aim of this study is to determine the best liquid medication that shows higher percentages of the cinnarizine release in the aqueous media. The solubility studies show that the hydrophobic drug has a larger affinity to dissolve in medium chain lipids. It also shows that cinnarizine is sensitive to the raising temperature,

although some surfactants, such as Cremophor® RH40 and PEG400 show no significant differences between the room temperature (21 ^{o}C) and the body temperature. The study continued with testing different formulations in the aqueous dissolution medium. It interacted with the solubility studies in terms of selecting Cremophor® RH40 as a good surfactant after applying heating until the drug particles completely dissolve. It shows that the quantity of the surfactant has a significant effect on the dissolution profiles. After that, the study examined two SEDDS mixtures. The one that contains IPM, Kolliphor® RH40 and Transcutol® P at (35:35:30) percentage ratios show the highest percentage of drug release, reaching over 90% after 15 minutes with no recorded of re-crystallization during the 90 minutes. It also shows that it is possible to increase the concentration of the liquid medication to 4.285 %w/w for 15 mg cinnarizine without significant change on the dissolution profile, suggesting that this mixture could apply in the pharmaceutical industries by filling into hard gelation capsule as SEDDS.

Chapter Seven: Combination between SEDDS, wet granulation and liquisolid technique in order to prepare cinnarizine tablets

7.1. Introduction:

After preparation of the optimum SEDDS mixture that showed the highest percentage of the cinnarizine release in the aqueous medium during the dissolution test, the next step was to convert this mixture to liquisolid tablets. The plan was to use the advantage of wet granulation process to enhance the value of the compressibility load factor in order to maximize the amount of liquid medication with small amount of solid particles (carrier and coating materials) so that meet the acceptable limit of the compressibility. The central composite design was selected to develop a mathematical model that finds the predicted response (log pactisity) using the solid ratio (R = weight of carrier/ weight of coating), liquid/solid ratio (CW) and the percentage of water to the solid amount in the unit dose (Water w/w) as the main factors. However, during the scoping study to determine the best level for these factors, there were problems with the components of the optimum SEDDS mixture (i.e. IPM, Kolliphor® RH40 and Transcutol® P). The SEDDS mixture was evaporating during the drying process so that the concentration of the drug increased in one tablet more than 50% from the selected dose.

Moreover, the dissolution tests in the aqueous medium show that the prepared liquisolid tablets gave approximately no drug release. The investigation for this phenomenon resulted in the presence of the silica powder (coating material) in the formulation caused this problem. This led to change the composition of the SEDDS in order to avoid these problems, and the selection was based on Capmul® MCM EP, Kolliphor® RH40 and PEG400.

Therefore, the aims of this chapter are to optimize the percentages of the newly selected SEDDS components regarding the dissolution test in the aqueous medium, to obtain formula with the lowest amount of the liquid vehicle that gives the highest percentage of the drug release; to determine the optimal amount of the carrier without presence of the coating material, using the benefit of the incorporating the wet granulation process in the liquisolid preparation and, finally, to evaluate the prepared formulations in terms of dissolution, quality control tests, DSC, FTIR and stability studies.

7.2. Studying the Dissolution profiles and Emulsion droplet sizes for self-emulsifying drug delivery systems (SEDDSs) including Capmul® MCM EP, Kolliphor® RH40 and PEG400:

The challenges of construction SEDDSs do not stop at their capability to enhance the percentage of a hydrophobic drug release in the aqueous distilled water only, but also they extend to include their suitability to be stable during this test. This stability could be resulted in decreasing the particle size of the system, using materials that do not show high sensitivity towards the changing in the temperature, and preparing SEDDSs easily and be fast disperse inside the aqueous liquid medium.

The interpretation of these points obliges to expand the selection criteria of the components of SEDDSs to examine the chemical structure of the oil, surfactant and co-solvent in addition to investigate the drug solubility as well as temperature sensitivity of each of them. This could be attained from selecting an oil and a co-solvent that integrate with the chemical structure of the surfactant (Kolliphor® RH40) from one side and the chemical structure of cinnarizine from another side. Consequently, the substitution of Transcutol® P (refer to chapter 6) with PEG400

could help to achieve this point because Kolliphor® RH40 has 40 polyethylene glycol parts in its structure, which are workable for PEG400. Furthermore, replacing Capryol™ 90 with Capmul® MCM EP will improve the role of the oil because of removing the propylene glycol, which seems to be less soluble with cinnarizine, from the structure of the oil, and keeping the medium chain fatty acids alone, such as 8-Caprylic acid and 10-Capric acid.

The strategy of screening dissolution tests examines the SEDDS, consisting of Capmul® MCM EP, Kolliphor® RH40 and PEG400, in the aqueous medium (distilled water pH = 6.1). It is applied according to the ternary phase mixture design with 10 different percentages at a specific quantity (refer to formulations F1 to F10 in Table 2-6). These dissolution profiles were summarized in Figure 7-1.

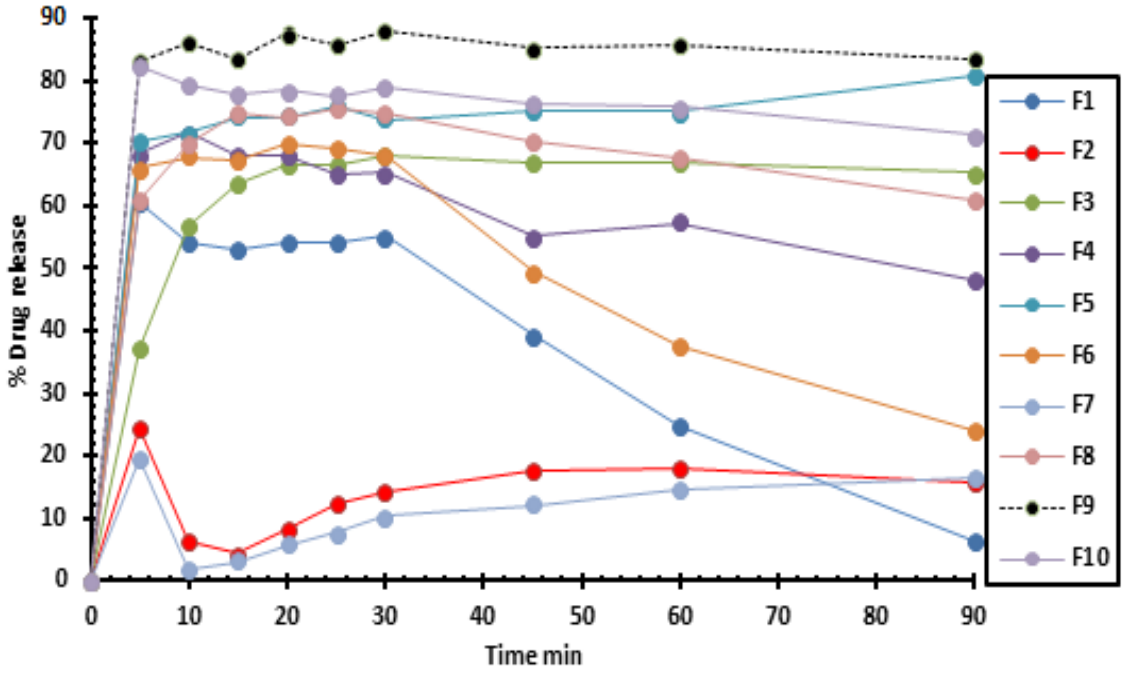


Figure 7-1: Dissolution profiles for liquid medications of cinnarizine with the SEDDS consist of different percentages of Capmul® MCM EP, Kolliphor® RH40 and PEG400 (see Table 2-6).

The screening dissolution tests show that the highest percentage of cinnarizine release is 88.18 % after 30 minutes. It is recorded at formulation F9 where the

percentages of the oil, surfactant and co-solvent are (66.67:16.66: 16.66), respectively (Figure 7-1).

Other formulations in these tests could be classified into three groups; the first one includes four formulations (F3, F5, F8 and F10). The order of the quantities of the components is as follows; Kolliphor® RH40, Capmul® MCM EP and PEG400, respectively. Also, in these formulations, there is a certain level of stability during the dissolution test and no significant evidence to recrystallization.

On the contrary, the second group, which includes formulations F1, F4 and F6, has a significant decrease in the percentage of the drug release, especially after the first 30 minutes from starting the tests. The highest percentage of recrystallization recorded at formulation F1 where Capmul® MCM EP is 100%, whereas the lowest recrystallization in this group is when there is a minimum level of sharing between the three components.

The last group consists of two formulations; F2 and F7, where there is no surfactant, indicating that using co-solvent alone or a mixture between the co-solvent and the oil alone is not good approach to enhance the dissolution of cinnarizine in aqueous dissolution medium.

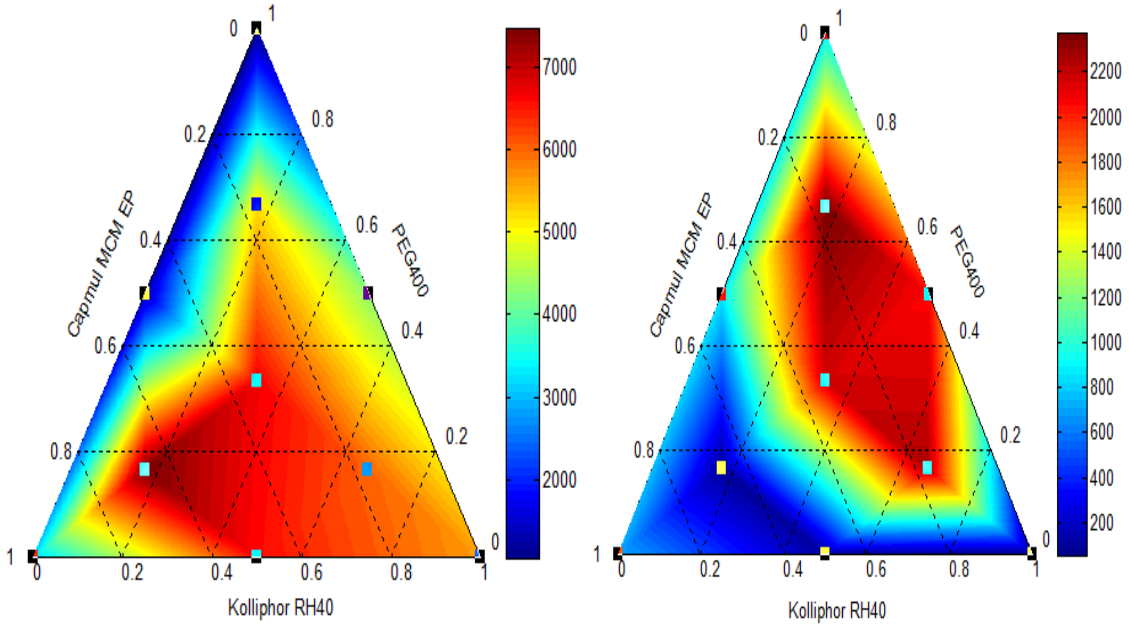


Figure 7-2: Pseudo-colour ternary phase plots show trapezoidal area under the curves (AUC) of the dissolutions profiles (% drug release. minutes) (left) and effective diameter (nm) of the particle sizes (right) for SEDDS screening formulations of Capmul® MCM EP, Kolliphor® RH40 and PEG400 (see Table 2-6).

The comparison between the trapezoidal AUC of the dissolution profiles and the effective diameter of the particle size in the formulations from F1 to F10 shows that there is a negative correlation between them (Figure 7-2), where the area of the highest AUC value in the left triangle (dark red colour) is compatible with the area of the smallest particle sizes in the right triangle (dark blue colour). In the same manner, the area that represents the largest particle size in the right triangle (dark red colour) reflects the area in the middle range of the AUC values, which includes the formulations that represent a significant degree of recrystallization during the dissolution test. The only exception for this correlation is recorded at formulation F10 where there is a high AUC area and relatively large size of effective diameter. This could be explained according to the structure of the droplet itself rather than the formation of crystals. In other words, although the larger particle size have been recorded due to presence of the three components in equal percentages, the

large power of decreasing the interfacial tension keep high levels of stability and consequently high percentage of the drug release.

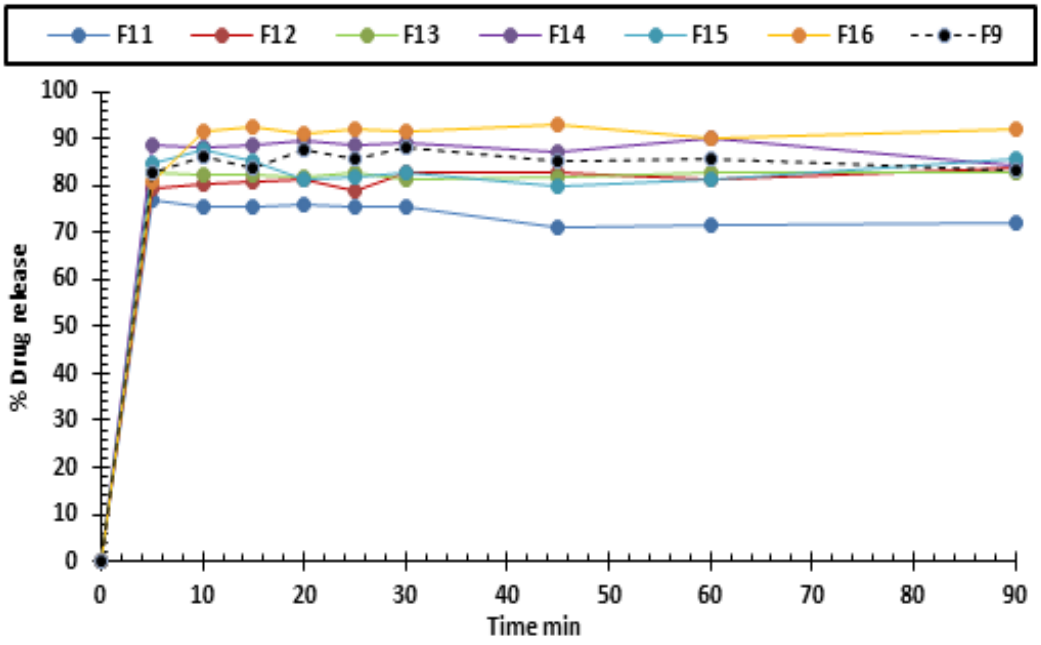


Figure 7-3: : Dissolution profiles from formulations F11 to F16 with formulation F9 show the percentage of cinnarizine release with time in order to determine the maximum concentration of the liquid medications that gives the highest drug release (see Table 2-6).

Formulation F9, which records the highest percentage of the drug release, was selected in order to investigate the effect of increasing the concentration of the liquid medication. Figure 7-3 shows the dissolution profiles of the formulations from F11 to F16, representing an increase in the concentration of the liquid medications from 3.0% w/w to 7.5% w/w for 15 mg cinnarizine. The comparisons between these formulations show that the formulation F11 is the only one show a significant decrease in its dissolution profiles from formulation F9. The similarity factor (f2) between the formulation F11 from one side and the formulations F9, F14 and F16 from other sides are always less than 50%. This means that the decreasing in the amount of the SEDDS from approximately 500 mg to approximately 250 mg does not make any significant changes on the percentage

of the drug release. As a consequence, there is a possibility to construct liquisolid tablets with acceptable weight, keeping the percentage of the drug release at its high percentage. Thus, the liquid medication at amount 250 mg for 15 mg drug (i.e. 6.0% w/w) was selected for further liquisolid applications.

7.3. Construction of the mathematical model and testing the significance of the regressions:

The generated mathematical model to determine the relative amount of solid particles that can be used to prepare liquisolid tablets with acceptable compressibility criteria depends on three variables; the log pactisity as a response variable, which is the logarithm of the average of tablet weights (g) divided on the average of their relative crushing forces (KgF), and the (w/w) of water incorporated to make the wet massing (water) and the net of the liquid/solid weight (CW) ratio are considered to be as the independent variables [6]. The initial model includes all the variables that can be used to construct a second degree of polynomial model. The multiple linear regression analysis for the response variable, log pactisity (*Y*), and the two factors, i.e. CW (*X1*) and water (*X2*), derived by the best fit method is shown in the following equation:

$$Y = 1.493 - 1.95\,X1 + 2.042\,X2 - 0.26\,X1X2 - 0.92\,X1^2 - 1.661\,X2^2 \qquad (1)$$

This model recorded a high value of the coefficient of determination R^2 = 97.07%, which describes the amount of variation in the values of the observed response (log pactisity) that is explained by the independent variables. However, the disadvantage with this value (R^2) is that it always increases when the number of factors increases [95]. Therefore, the fitted model should be considered from another term, which is called adjusted R^2, which is not affected by the number of

the factors. With this model, it records 94.97%. Furthermore, the predicted R^2, which is a static term that measures the ability of the model to predict the response values when using new observations, is relatively low (81.08%). This means that there is a significant large difference between the values of predicted R^2 and adjusted R^2. In other words, the model is overfit, which cannot predict new observations in high accuracy. Therefore, the model needs to be improved.

The analysis of variance (ANOVA) data presented in Table 7-1 are used to evaluate the significant of each factor that presented in the equation (1). It includes information about the degree of freedom (DF), adjusted sum square (Adj. SS), adjusted mean square (Adj. MS), the values of static F-test (F-values) and the relative probability values at 95% confidence interval (p-Value) for each regression coefficient mentioned in equation (1). The null hypothesis test (H_0) is used to check if there is a linear statistical relationship between the response variable (Y) and at least one of the independent variables. It can be expressed as follows:

$$H_0: \beta_1 = \beta_2 = \cdots = \beta_k = 0 \qquad (2)$$

Where $\beta_1, \beta_{2...} \beta_k$ are the regression coefficients of the variables mentioned in equation (1).

According to this null hypothesis, the F-test value can be calculated as follows:

$$F - value = \frac{Adj\ MS}{Adj\ MSE} \qquad (3)$$

Where MSE is the adjusted mean square error for the model in equation (1), which is equal to 0.002817 and can be calculated from dividing adjusted sum square error on its degree of freedom (see Table 7-1). The small p-Value for squared term

(0.037 < 0.05) indicates that there is a certain of curvature in the response surface, mainly coming from the water * water ($X2^2$). However, one quadratic term (CW *CW) has a large p-value, which means that it is significantly not important. Therefore, it should be removed from the model with the term of 2-way interaction (CW * Water %), which also have a large p-value (0.851).

Table 7-1: Analysis of Variance (ANOVA) for the initial mathematical model explained in the equation (1).

Source	DF	Adj. SS	Adj. MS	F-Value	P-Value
Model	5	0.652324	0.130465	46.31	0
Linear	2	0.621506	0.310753	110.32	0
CW	1	0.594486	0.594486	211.04	0
Water	1	0.027021	0.027021	9.59	0.017
Square	2	0.030711	0.015356	5.45	0.037
CW*CW	1	0.000591	0.000591	0.21	0.661
Water*Water	1	0.030709	0.030709	10.9	0.013
2-Way Interaction	1	0.000107	0.000107	0.04	0.851
CW*Water	1	0.000107	0.000107	0.04	0.851
Error	7	0.019718	0.002817		
Lack-of-Fit	3	0.016493	0.005498	6.82	0.047
Pure Error	4	0.003225	0.000806		
Total	12	0.672043			

Removing the non-significant variables could enhance the adequacy of the fitting of this model on the surface response so that it makes the probability of the lack-of fit error higher than 0.05.

Removing the terms from the model happened by applying backward elimination approach, where it starts with all the variables in the model, and at each step, removes one variable that has the smallest F-value. It stops removing when the probability values are less than α-level which is selected here at 0.05 [95]. Therefore, in this model, two terms are removed; CW * Water and CW * CW, respectively. Thus, the new fitted model is now as follows;

$$Y = 1.652 - 2.726\,X1 + 1.922\,X2 - 1.631\,X2^2 \qquad (4)$$

In the new reduced model, the coefficient determination decreased slightly to reach to 96.96%. However, the adjusted R^2 has improved (R^2 Adjusted = 95.95%) and the significant increase was in the value of the predicted R^2, which was recorded as 93.03. Here, the predicted R^2 become very close in its value to the adjusted R^2, indicating that the overfitting has been removed. ANOVA analysis for variable terms (see Table 7-2) shows that the all probability values are less than 0.05. This means that all included terms are significantly important and the null hypothesis can be rejected (equation 2). Moreover, the increase in the probability value of the lack-of-fit error from 0.047 to 0.092 suggests that the reduced model becomes fit to the data.

Furthermore, the negative sign of the X1 factor in equation (4) suggests that the log pactisity will decrease when the CW increased. This could be expected as the increase in the amount of the liquid vehicle inside the liquisolid system will lead to a decreased in the crushing force of the tablet. However, in the case of X2 factor, the positive sign of the coefficient regression shows that when the percentage of the liquid binder increased the hardness of the tablet will increase, but the presence of the quadratic term ($X2^2$) suggests that the direct proportional relationship between the water and the log pactisity will be true until reach to the maximum, after which the addition of the water will decrease the hardness of the prepared tablets. As a result, there is a necessity to determine the optimum amount of solid powder that can be used at the maximum level of water in order to prepare the liquisolid tablets with acceptable compressibility characteristics, which is equal to 20 KgF/g pactisity value (or 1.301 for log pactisity).

Table 7-2: Analysis of Variance (ANOVA) for the reduced mathematical model explained in the equation (2).

Source	DF	Adj. SS	Adj. MS	F-Value	P-Value
Model	3	0.651627	0.217209	95.75	0.000
Linear	2	0.621506	0.310753	136.99	0.000
CW	1	0.594486	0.594486	262.07	0.000
Water	1	0.027021	0.027021	11.91	0.007
Square	1	0.030121	0.030121	13.28	0.005
Water*Water	1	0.030121	0.030121	13.28	0.005
Error	9	0.020416	0.002268		
Lack-of-Fit	5	0.017191	0.003438	4.26	0.092
Pure Error	4	0.003225	0.000806		
Total	12	0.672043			

7.4. Model Validation and optimizing the value of the liquid/solid ratio (CW):

In order to validate the reduced model (equation 4), the theoretical (predicted) values and the observed (actual) values of the log pactisity for 4 observations, presented in Table 7-3, are calculated by substituting the independent variables (i.e. X1, X2 and $X2^2$). The observations for the validation purposes are selected differently from the points constructing the central composite design, although they are still in the spherical space of the design.

Table 7-3: Theoretical (predicted) values and the observed (actual) values observed for responses Y (log pactisity).

Formulations	CW	Water	Theoretical log Pactisity	Actual Log Pactisity	Error
F30	0.25	0.4	1.4792	1.4622	-0.0170
F31	0.25	0.6	1.5361	1.5512	0.0151
F32	0.45	0.4	0.9329	0.9059	-0.0270
F33	0.30	0.6	1.4007	1.4032	-0.0025

As the error presented in Table 7-3, which comes from the difference between the actual value and the theoretical value of the response, indicated that there is a

relative high accuracy for this model. The error values do not exceed 0.03 in the value of the log pactisity, which will lead to a robust prediction to the quantity of the solid material in the liquisolid preparation.

The optimum values of the factors (CW and Water) that produce liquisolid tablets with acceptable compressibility at log pactisity equals to 1.30 can be determined by two approaches; the first one is through examining the surface response plot and the contour plot presented in Figure 7-4.

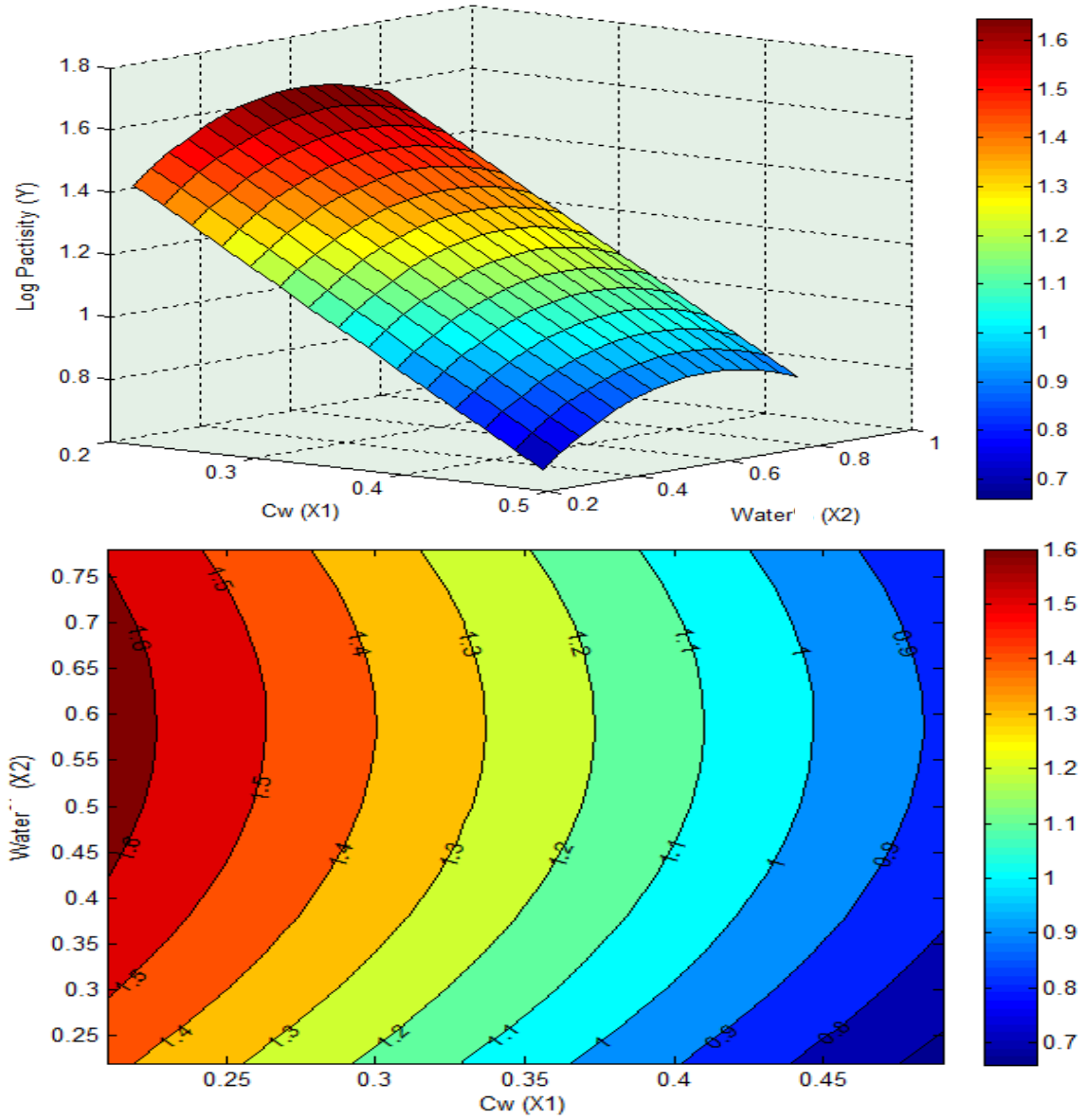


Figure 7-4: Surface response plot (top) and contour response plot (bottom) showing the effect of CW and Water on log pactisity as described in the equation (4).

Regarding the surface response plot, there is a linear increase in the value of the log pactisity with decreasing in the value of the CW. The blue colour starts very dark at a value of CW = 0.45, and increasing gradually until reaching to the area of dark red colour at CW =0.2. On the other hand, the curvature in the surface sheet reflects the effect of the squared term of the Water. At the centre of this curvature, the response value recorded the highest amount during the entire surface sheet.

In the same manner but in more informative way, the contour plot of the two factors in Figure 7-4 clarifies the distribution of the response values according to the reduced model presented in equation 4. The optimum response value (i.e. at log pactisity = 1.3) is represented by a curvature line, giving the maximum value of CW at the centre where the water is between 0.55 and 0.6.

For further accuracy in determination of the optimum value of the CW, the response optimizer plot was constructed as in Figure 7-5. At the bottom, it includes two subplots; each one represents the relationship between the factor and the response in the terms of the model (equation 4). The narrow white area represents the range of the factors' values that include the optimum target of the response, which has been identified at 1.3010. Moreover, the desirability plots (Figure 7-5, top) represents a relationship between the desirability value (between 0 and 1) on the y-axis and the response value according to each factor on the x-axis. The selected weight for the desirability functions, which determines how the desirability distributes between the upper or lower bound and the target [95], is 1.0.

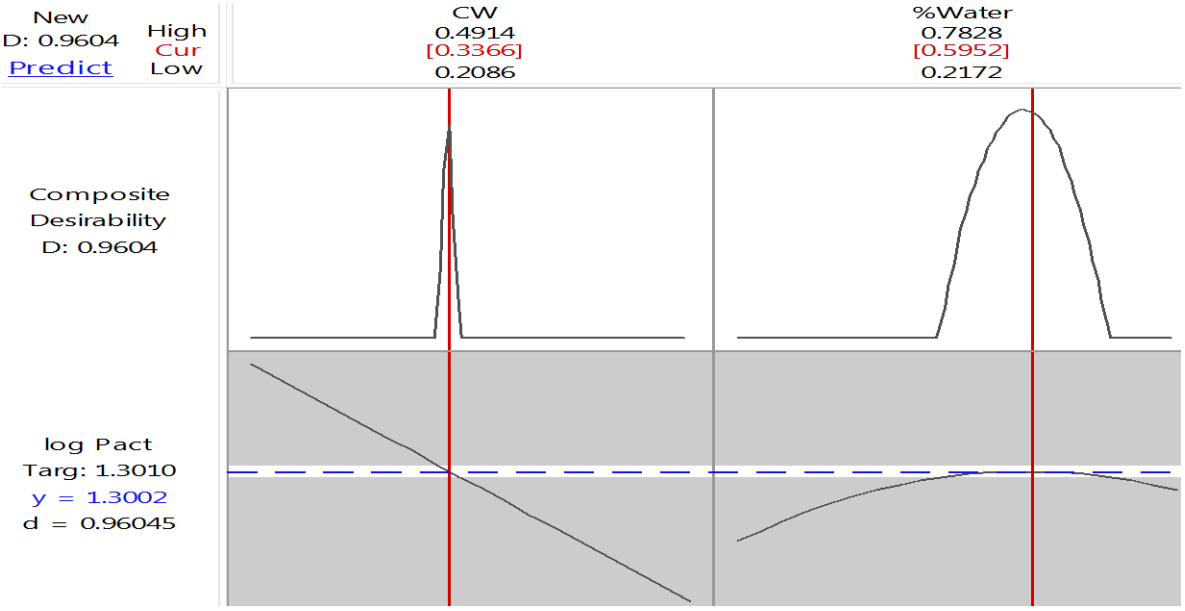


Figure 7-5: Optimization plot for CW and Water% factors (bottom) with the relative desirability functions (top).

The reason of selecting this value is that increasing over 1.0 will lead to a change in the shape of the function and suggesting two solutions in the case of the water%, which is far from the reality. On the other hand, decreasing in the value of the weight will lead to obtain a very sharp plot in the case of CW desirability function, making the optimum value at the selected target with a wide change value when moving from one point to another. As the relationship between CW and log pactisity is linear, the desirability function (top-left in Figure 7-5) shows a sharp apex, whereas the curvature in the relationship between the water% and log pactisity allows a wider apex in the desirability function. According to this, the nearest response value to the target is 1.3002 with relative high desirability value (D= 0.96045). At this value, the CW is 0.3366 and water is 0.5952.

During the formulation preparations, the selected CW was considered to be 0.336 and water was 0.60 to give log pactisity equals to 1.302 (i.e. pactisity equal 20.04).

7.5. *In vitro* dissolution studies:

After determining the optimum quantity of both the liquid medication and the solid powder, it is worth to evaluate the prepared liquisolid formulations according to their percentages of the drug release in aqueous dissolution medium. For this purpose, four formulations were prepared (from F34 to F37, Table 2-6). While F34 consists of 15 mg of the drug powder dissolved in 235 mg SEDDS, F35 and F36 consist of 10 mg and 5 mg drug powder dissolved in 156.67 mg and 73.33 mg SEDDS, respectively. The aim of this is to fix the liquid medication at 6 % w/w concentration and see how changing the quantity will affect the dissolution profiles. Moreover, formulation F37, which includes 15 mg powder drug dissolved in 185 mg SEDDS was prepared in order to investigate how the decrease in the quantity of SEDDS would affect release when converting the formulation from liquid medication to liquisolid tablets. Finally, the prepared formulations were compared with the tablets from the market containing 15 mg drug powder for their dissolution profiles in the aqueous medium (distilled water at pH =6.1) in both the aqueous and the 0.1 M HCl dissolution media. All profiles were presented in Figure 7-6 and Figure 7-7.

The investigation of the dissolution profiles shows that formulation F34 has the highest percentage of the drug release among other formulations. It reaches to about 34 % after one hour test period. Also, it shows a fast drug release from the first 5 minutes, where the percentage of the drug records 31% (Figure 7-6).

A further notice can be identified is that there is a decrease in the percentage of the drug release for formulations F35 and F36 comparing with formulation F34. The similarity factor f2 between formulations F34 and F35 and between

formulations F34 and F36 is 50.73% and 40.04%, respectively, indicating that these decreases in the dissolution profiles are significant. In other words, less drug content means less percentage of the drug release.

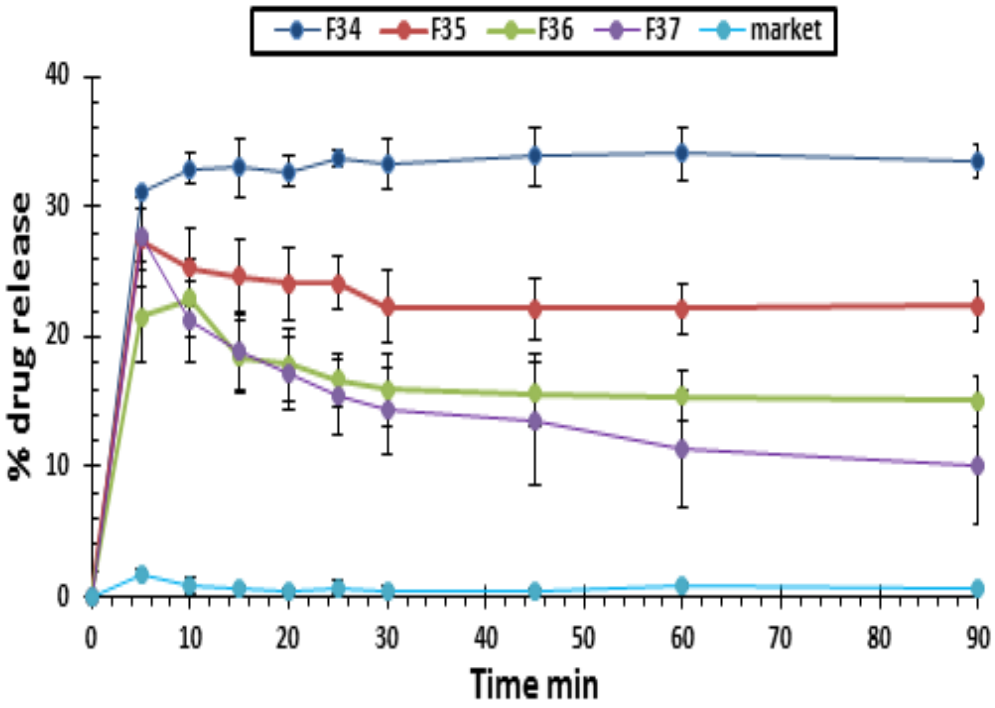


Figure 7-6: Comparison of the dissolution profiles between market tablets and prepared formulations from F34 to F37 in the aqueous dissolution medium (DW at pH=6.1) (see Table 2-6).

Regarding the two formulations F35 and F36, the dissolution profiles start relatively high after 5 minutes and then it decreases gradually with the time, whereas there is stability in the case of the dissolution profile of formulation F34. The same phenomenon can be noticed but in more obvious in the case of the dissolution profile of formulation F37, where dissolution stars at 27.7% after 5 minutes and ends at approximately 10% after 90 minutes. Nevertheless, all formulations (i.e. from F34 to F37) show a significant increase in their dissolution profiles compared to the profile of the tablets from the market, where the percentage of the drug release does not exceed 2% in aqueous dissolution medium (Figure 7-6).

The justification behind these dissolution behaviours could be as follows; at the first 5 minutes all liquisolid tablets completely disintegrate in the dissolution device, releasing the drug in the free SEDDS liquid, which does not make any bond with the carrier particles in the liquisolid tablet, into the dissolution medium(DW at pH= 6.1). When there are bonds between SEDDS and solid particles, the drug particles that dissolve in the SEDDS mixture either precipitate in the bottom of the dissolution device or make bonds with microcrystalline cellulose as part of the SEDDS mixture. In both situations, drug will not pass the filter of the dissolution device. Thus, it will not be detected by the UV spectrometer. As the result of this, formulation F34 does not exceed 33% of the drug release.

On the other hand, it seems that when decreasing the amount of the SEDDS in the liquisolid tablets, the probability to make bonds with carrier particles increases so that the percentage of the drug release decreases (e.g. F35 and F36 *vs*. F34).

Moreover, when increasing the concentration of the liquid medication from 6.0% w/w to 7.5% w/w, such as in the case of the formulations F34 and F37, the percentages of the drug release starts decreasing with the time. This could be referred to the gradual increase in the re-crystallization of the drug particles with the time. This means that the agitation power of the dissolution medium may change the value of the surface free energy by increasing the surface area of the drug particles. Thus, it leads to an increase of the energy and destabilization of the thermodynamic state of the system.

Finally, formulation F34 shows completely dissolving in acidic (0.1 M HCl) dissolution medium in the first 30 minutes, which is similar to the commercial tablets (Figure 7-7).

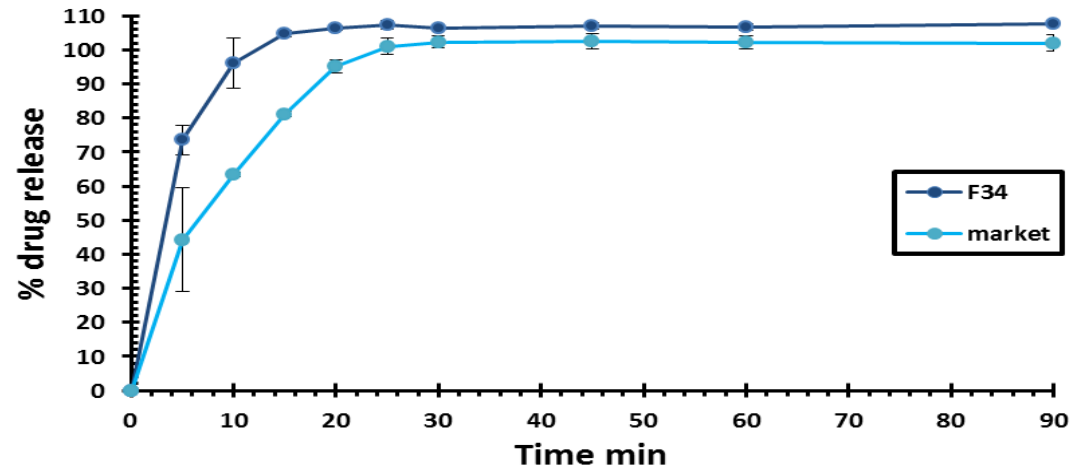


Figure 7-7: Comparison the dissolution profiles between market tablets and prepared formulation F34 in acidic (0.1 M HCl) dissolution medium.

7.6. Differential Scanning Calorimetry (DSC) analysis:

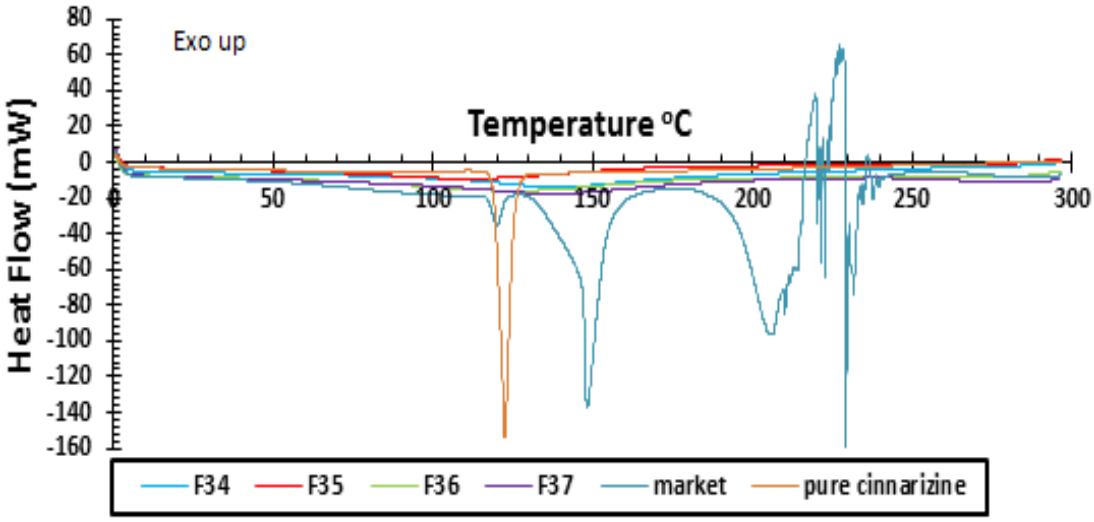


Figure 7-8: Comparison between DSC thermographs of formulations (from F34 to F37), market tablets and pure cinnarizine (see Table 2-6).

Figure 7-8 represents a comparison between the all thermograms of the SEDDS liquisolid formulations, market tablets and pure cinnarizine. It is obvious that cinnarizine pure drug has a sharp endothermic peak at melting temperature (122.29 ° C) with relatively high enthalpy value (907.6 J/g). This sharp peak indicates the crystallinity of the drug and the melting point of the sample, referring

the end of the thermogram to the decomposition of cinnarizine. Moreover, the sharp endothermic peak disappears in all SEDDS liquisolid formulations (from F34 to F37), indicating a change in the crystallinity of the drug. Furthermore, the changing in the percentage of the liquid medication, such as in the case of F37 or the size of the tablet (e.g. formulations F34, F35 and F36) seems to have no main effects on the liquisolid thermograms. This is contrary with the conclusion related with the dissolution profiles for the same formulations in the aqueous medium, where the percentage of the drug release decreases with decreasing in the size of the tablet (F35 and F36) or increase in the concentration of the liquid medication (F37). This means that the re-crystallinity that happened during the dissolution test is not direct as a result of the formulation itself. This is because the pure drug still completely dissolves in the SEDDS.

Finally, the sharp endothermic peak appears clearly in the case of the market powder, where there is no added SEDDS to the formulations. It appears at 119.3 °C with enthalpy equals to 44.34 J/g, indicating a slightly change in drug crystallinity due to the effect of the added excipients in the formulation. The rest disturbance peaks after 125 ^{o}C are probably due to the nature of the excipients in the market tablets.

7.7. Fourier transforms infra-red spectroscopy (FTIR):

The investigation of the FTIR spectra for the formulations from F34 to F37 shows that there are no effects for either changing the size of the tablet or changing the concentration of the liquid medication as the all FTIR spectra are identical (top-right Figure 7-9).

Moreover, there is no evidence for the peaks that are categorized the active ingredient (pure cinnarizine, Figure 7-10), indicating that the pure drug still completely dissolve in the SEDDS liquid medication and the addition of the carrier (Avicel® PH 101) or the disintegrant (sodium carmellose) does not lead to any change.

The supporting conclusion comes from FTIR spectra for SEDDS liquid medication alone (top-left Figure 7-9), where different concentrations of liquid medication show the identical FTIR spectra with the blank. Furthermore, when compared with the FTIR spectra that relate to the components of the SEDSS (see bottom-left Figure 7-9), they only show the interaction between them with no evidence for the distinctive functional group of the pure drug (Figure 7-10). As a result of this, the FTIR spectra of the prepared formulations support the conclusion that the solid materials do not have any direct effect on the re-crystallinity of cinnarizine particles and the lower recorded percentage of the drug release in the dissolution tests comes from the interaction between the SEDDS itself with the solid particles (carrier and disintegrant) (see top right and bottom right Figure 7-9).

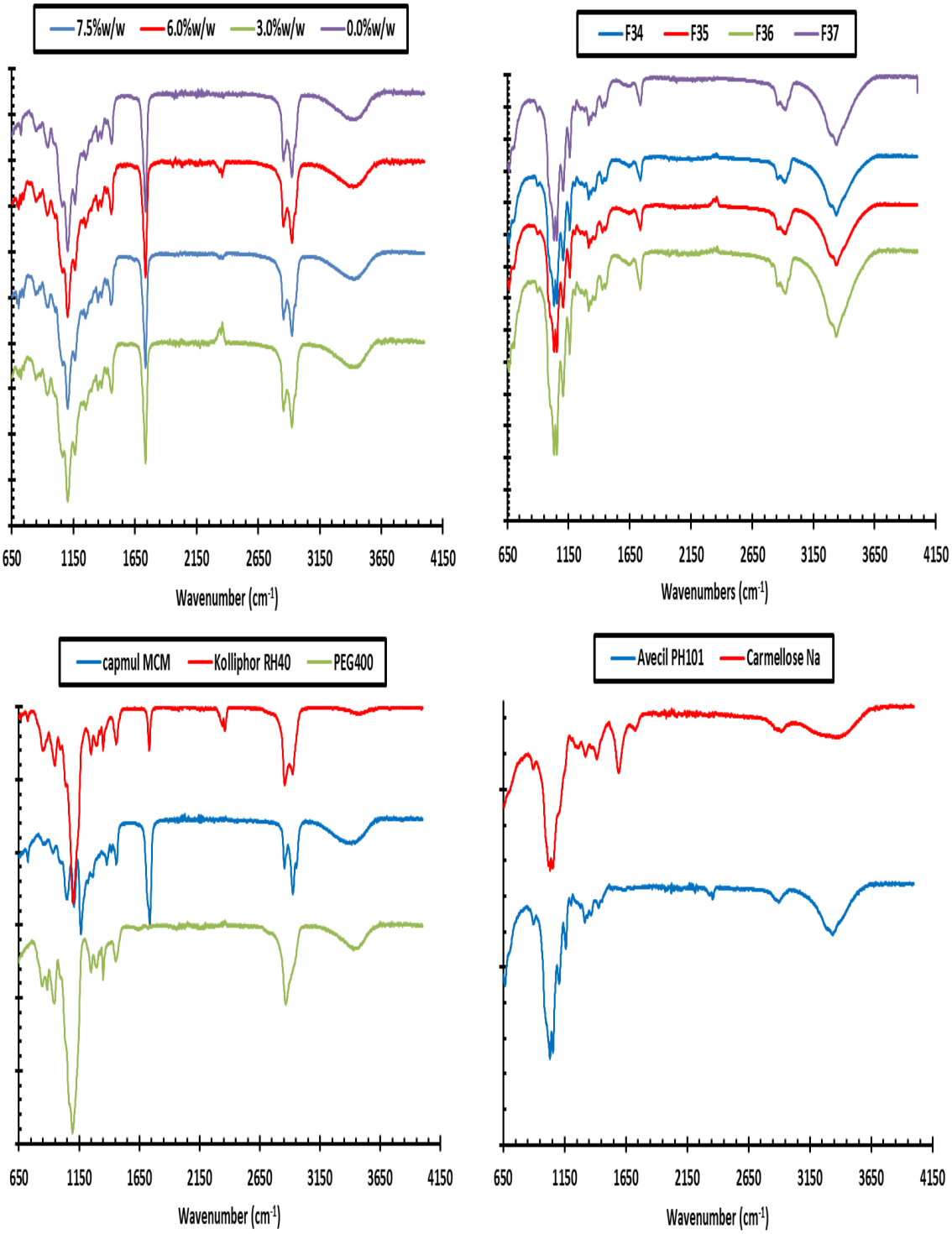


Figure 7-9: FTIR spectra (Y-axis is % Transmittance) for SEDDS liquid medications at 7.5% w/w, 6.0% w/w, 3.0% w/w and 0.0% w/w (top-left), formulations from F34 to F37 (see Table 2-6) (top-right), Capmul® MCM, Kolliphor® RH40 and PEG400 (bottom -left) and Na Carmellose and Avicel® PH 101 (bottom- right).

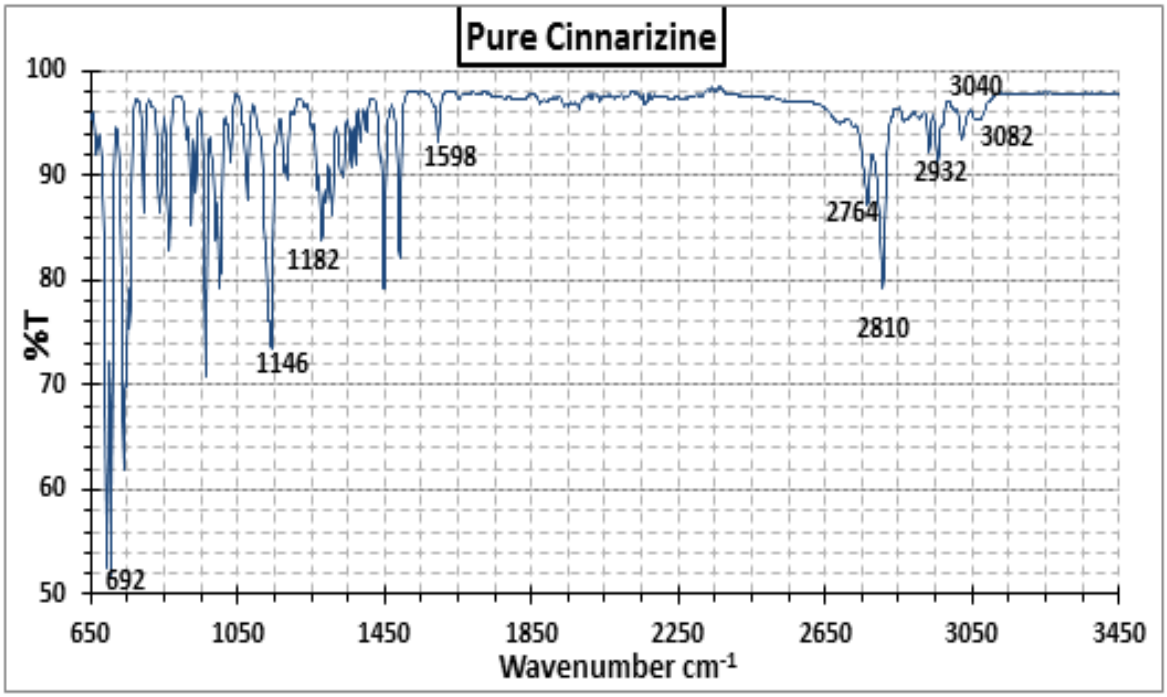


Figure 7-10: FTIR spectrum for pure cinnarizine powder

7.8. Flowability, drug content uniformity, tablet dimensions, hardness, tensile strength, friability and disintegration tests:

The investigation of the flowability behaviour results for the prepared formulations (from F34 to F37, Table 2-6) is summarised in Table 7-4. The compressibility Carr's index ranged between 20% and less than 27%, which is passable for formulations F34, F35 and F36 and poor for F37. The results for Hausner's ratio also show the same conclusion according to British Pharmacopoeia standards [56]. Thus, removing the silica as a coating material does not affect negatively on the flowability behaviour for the prepared formulations, although it decreases the amount of the liquid vehicle that could be retain inside the formulations. Finally, using water as a liquid binder in the all formulations enhances the flowability of the formulations as it decreases the Carr's compressibility index for the carrier, which is recorded as 28.89% [81] & [82].

Table 7-4: Flowability evaluations including tapped density, bulk density, Carr's compressibility index and Haussner ratio for formulations from F34 to F37 (see Table 2-6).

Formulations	Tapped density (g/cm^3)	bulk density (g/cm^3)	CI%	position	H ratio	position
F34	0.38	0.29	25.00	passable	1.33	passable
F35	0.38	0.29	22.32	passable	1.29	passable
F36	0.36	0.29	20.69	fair	1.26	passable
F37	0.40	0.30	26.45	poor	1.36	poor

Regarding the content uniformity tests, the all formulations are within the limit of the British pharmacopoeia (i.e. between 85% and 115%) [56] (see Table 7-5). Also, the percentage of the loss of the weight during friability test was less than 1% for the all formulations and all tablets stay intact after 100 rounds at 25 rpm speed. In the same way, the disintegration time is less than 15 minutes (the BP limit) for the all of the substances. In fact, they record less than 5 minutes which reflect very good time regarding the immediate release tablets. This result integrates with the percentage of the drug release in the dissolution test, where the all formulations record high percentages in the first five minutes. This is mainly due to the effect of the disintegrant, which was incorporated in 5% in the all formulations. However, the positive effect of the disintegrant on reducing the disintegration time and enhancing the percentage of the drug release of the dissolution profiles is not recognised for the hardness tests and consequently the tensile strength values. Regarding this, there is a decrease in the predicted value of the hardness for all formulations (Table 7-5), which is calibrated according to Spireas *et al.* criteria [6]. The similar result can be noticed in the case of the fast disintegrating tablets containing croscaremellose sodium and Disintequick MCC-25, which is a mixture between lactose and microcrystalline cellulose, as filler [96]. In this study, there is an indication that increasing the amount of disintegrant leads to decrease in the hardness. However, this study does not contain liquid

medication which could have a significant effect on the hardness. Also, there is no study detailed the effect of the disintegrant on the liquisolid tablet in terms of its effect on the pactisity. This could suggest a further investigation to the role of the disintegrant when it is added into the liquisolid tablet formulations.

Table 7-5: Average and standard deviations of the content uniformity test, friability test, tensile strength, hardness and disintegration tests for SEDDS liquisolid formulations (see Table 2-6).

Formula	Content Uniformity (%)			Friability (%)	Tensile strength (MPa)			Hardness (N)			Disintegration Time (sec)		
F34	106.68	+/-	4.3	0.028	0.802	+/-	0.041	31.38	**+/-**	1.462	157	+/-	5
F35	99.41	+/-	0.8	0.006	0.701	+/-	0.038	23.54	**+/-**	1.387	106	+/-	6
F36	113.49	+/-	0.6	0.032	0.680	+/-	0.031	23.44	**+/-**	1.344	132	+/-	10
F37	103.05	+/-	5.5	0.051	0.726	+/-	0.039	37.27	**+/-**	2.015	150	+/-	5

7.9. Stability studies:

Measuring the drug content uniformity inside the SEDDS formulations (from F34 to F37, Table 2-6) shows that all formulations demonstrate a reduction in their content uniformity, although they are still in the range limit of the British Pharmacopoeia (85% to 115%) [56], (Table 7-6). The investigation of the percentages, which are presented in Table 7-6, shows that this reduction ranged from 7.6% in the case of formulation F35 to 17.1% in the case of the formulation F36.

Table 7-6: Comparison the percentage of the content uniformity between fresh and 3 months stability samples for the SEDDS liquisolid samples (formulations from F34 to F37) (see Table 2-6).

	Fresh			After 3 months		
Formula	Average		Standard deviation	Average		standard deviation
F34	106.7	+/-	4.295	92.3	+/-	3.631
F35	99.4	+/-	0.844	91.8	+/-	1.534
F36	113.5	+/-	0.587	96.4	+/-	3.372
F37	103.0	+/-	5.524	92.3	+/-	1.736

In the same way, the reduction can be detected in the dissolution profiles of the stored samples (Figure 7-11). This means that the free parts of the drug particles that still dissolved in the SEDDS liquid vehicle are sensitive to the high percentage of the humidity as the all formulations demonstrate a certain degree of reduction in the amount of the active ingredients.

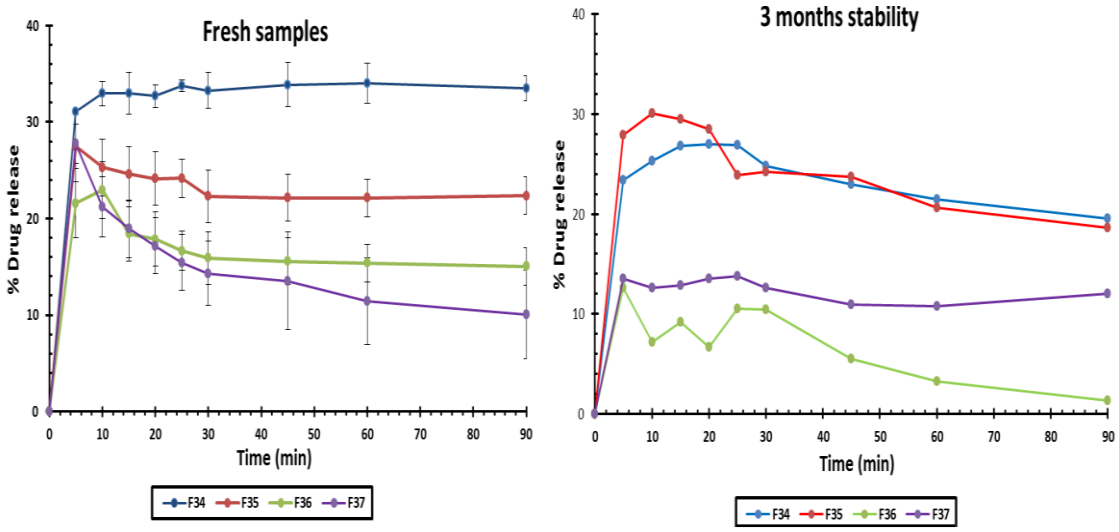


Figure 7-11: Comparison of the dissolution profiles between fresh and samples stored for 3 months on SEDDS liquisolid tablets for formulations from F34 to F37 (see Table 2-6), (the error bars were deleted for easier comparison).

The investigation to the DCS thermograms show that there is an increase in the endothermic peaks around 100 ^{o} C, indicating that all formulations adsorbed the water droplets on their powder surface. Those droplets affect negatively the particles of the active ingredient that dissolve in the SEDDS liquid (Figure 7-12).

Finally, the study of the FTIR spectra for the both fresh and stored samples (Figure 7-13) shows that there are no evidences that the drug particles have some changes due to the effect of the storage conditions. The FTIR spectra of the stored samples have the same peaks as those of the fresh samples.

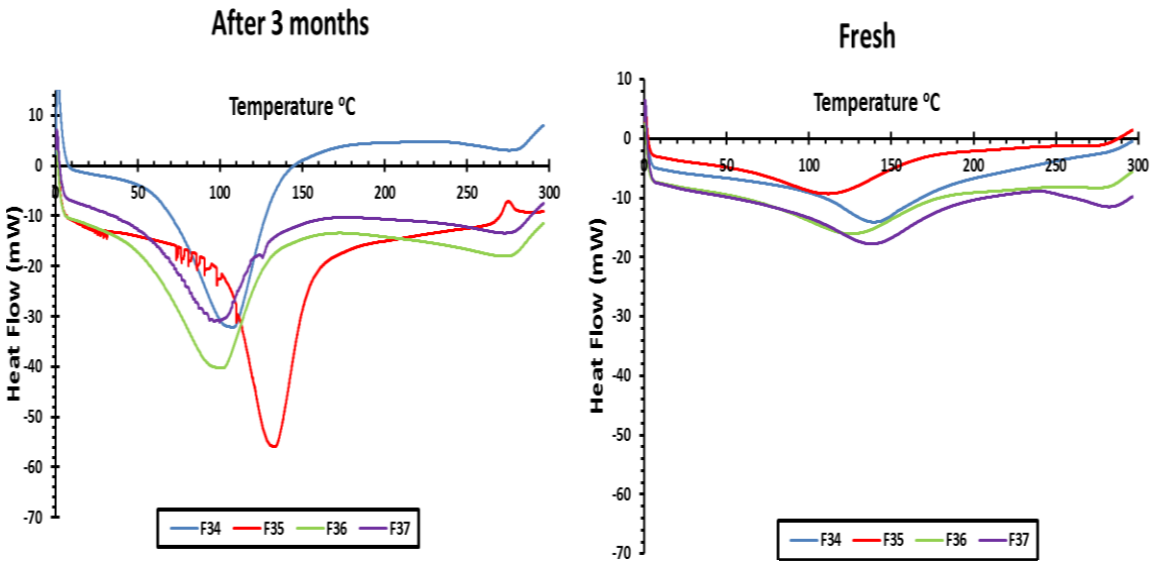


Figure 7-12: Comparison of the DSC thermograms between fresh and samples stored for 3 months in terms of SEDDS liquisolid tablets formulations from F34 to F37.

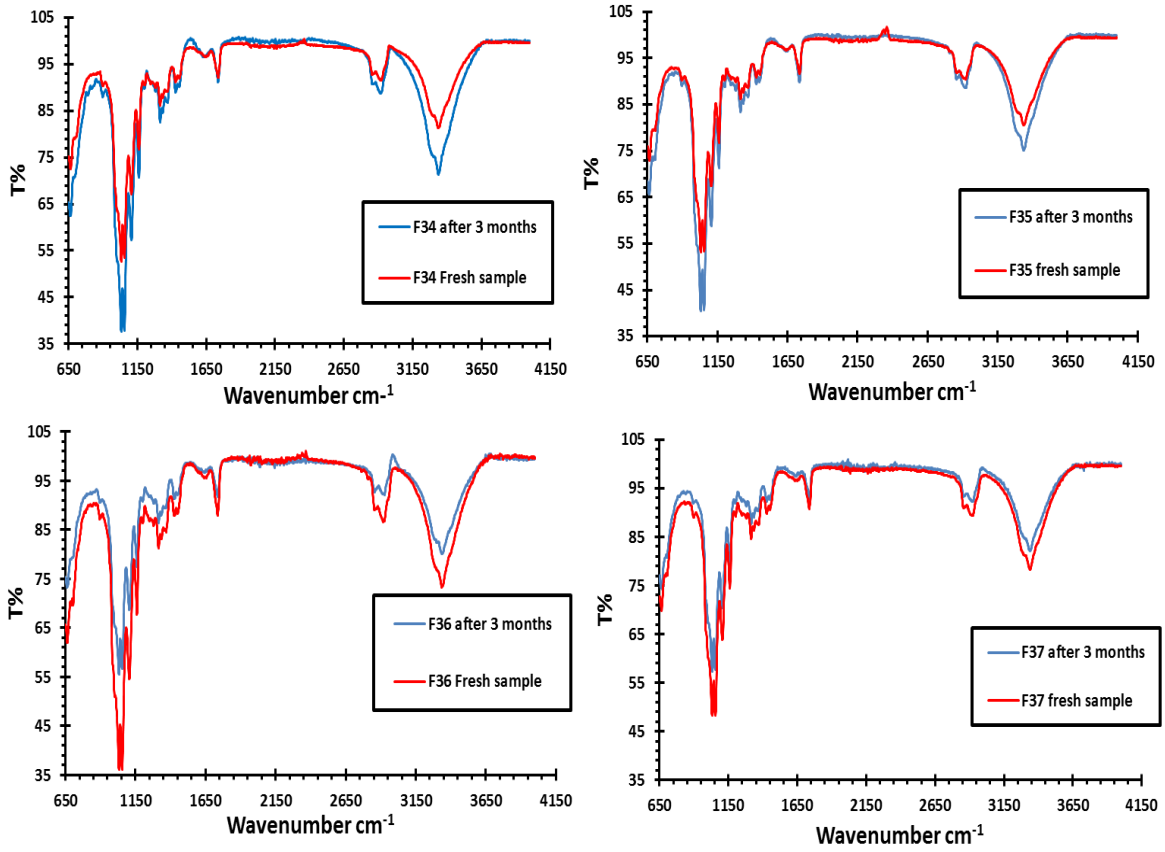


Figure 7-13: Comparison of the FTIR spectra between fresh and samples stored for 3 months in terms of SEDDS liquisolid tablet formulations from F34 to F37.

7.10. Conclusion:

The aim of this chapter is to convert the SEDDS to liquisolid tablets by using wet granulation technique. The unfavourable physicochemical characteristics , which are found in the previous chapter, consists a reasonable justification to seek altering the components of the SEDDS so that they are suitable for liquisolid process, such as they are not evaporated during the granulation process. Capmul® MCM EP, Kolliphor® RH40 and PEG400 in ratio of (16.66:66.67:16.66), respectively, are found to be acceptable due to recording a relative high percentage of the drug release in the aqueous dissolution medium during the ternary phase screening test. Moreover, the selected percentages for the SEDDS mixture show resistance to decrease in the drug release when the liquid medication increases until a concentration between 6.0 % w/w and 7.5% w/w for 15 mg cinnarizine, which means that it is possible to be prepared as liquisolid tablets with acceptable tablet weight. Furthermore, the negative effect of the role of the coating materials on the dissolution behaviour pushes toward developing a new equation that determines the optimum quantity of the carrier considering the liquid/ solid ratio (CW) and the percentage of water that can be used as a liquid binder during the preparation and simulating the principles of determination of compressibility load factor [6]. The error when validating the developed model do not exceed 0.03 of the value of the response (log pactisity), indicating a relatively accurate model. The prepared tablet formulations show a significant enhancement in the dissolution profile when they are compared with tablet from the market in the aqueous medium, reaching to 33% of the drug release compared with less than 2% for the market tablet after 90 minutes. However, the decreasing in the size of the tablet or increase the concentration of the liquid medication leads

to decrease in the percentage of the drug release. Also, the tests of the friability, disintegration, content uniformity show that the prepared formulations comply with the British Pharmacopoeia standards [56]. However, the hardness of the tablets show a slightly decrease at the optimum level due to the addition of the disintegrant in 5% to the formulations. Finally, the stability studies indicated a slightly decrease in the drug percentage after 3 months storage due to the adsorption of the water droplets on the surface of the tablet. This could suggest that this kind of preparation would be better if it is prepared as coated tablets.

Chapter Eight: Conclusion and future work

8.1. General conclusion:

The aim of this research was to enhance the solubility and dissolution of the water-insoluble drugs by using the liquisolid technique. However, the selection of norfloxacin as a model drug for applying this technique did not show an improvement in the drug dissolution as expected comparing with the conventional preparation in the aqueous medium. This is because of the unique structure of this drug as a zwitterionic one, and its interaction with selected liquid vehicles so that they form interacting layers, impairing the drug release in the dissolution test.

On the other hand, determination of the compressibility load factor of Synperonic ™ PE/L-61 provided a good opportunity to prepare tablets with acceptable compressibility characteristics, although the weight of the unit dose recorded high values. Furthermore, mixing norfloxacin with either PEG200 or Synperonic ™ EP/L-61 in order to form liquisolid formulations showed (as detected by DSC and FTIR analyses) that the crystallinity of the drug has significantly reduced. The conclusion from this initial study was suggested to use the wet granulation process with the liquisolid pharmaceutical technique in order to enhance the flowability, compressibility and the drug release in the aqueous dissolution medium.

Therefore, incorporating water as a liquid binder on the previous prepared classical liquisolid formulations provided an advantage through reducing the size of the unit dose; the large unit dose is considered a major disadvantage for the liquisolid technique. The combination between the two methods (wet granulation and liquisolid) was through re-calculating the optimum load factor, which was always the compressibility one, because granules formation provides a wider capacity to accept more liquid vehicle inside the porous structure of carrier and

coating materials. Moreover, incorporation of water as a liquid binder did not affect the entity of the liquid vehicles and application of the drying process did not lead to any evaporation of the liquid vehicle, which makes the water as a liquid binder a good candidate for the technique. The enhancement in the flowability and the compressibility was extended to the *in vitro* dissolution trends using the aqueous medium. The dissolution trends showed a significant increase in the percentage of the drug release compared to those of the classical liquisolid preparations. However, there was a question about the effect of the quantity of solid excipients on the dissolution trends. For this purpose, the water granulated liquisolid preparations were made by using the classical load factors. The results showed that the significant increase in the dissolution trends appeared only when applying the new compressibility load factor (with the granulation process) when the Synperonic ™ PE/L-61 was the liquid vehicle. However, the PEG200 formulations showed no significant differences in terms of dissolution trends when using the classical or the new calculated load factors, meaning the presence of flexibility during the preparation in large scale.

When investigating the role of PVP solution as a liquid binder in the combination between wet granulation and liquisolid techniques, it showed good flowability, compressibility and dissolution behaviours for the produced tablets. The angle of slide, which is used to evaluate the flowability, showed relative small degrees, indicating good flow characteristics. However, the pactisity studies, which is used to determine the compressibility load factor, showed that there was a decrease in their values when there was an increase in the concentration of PVP at a specific amount of excipient ratio (R values) and Synperonic ™ PE/L-61 to the solid powder (CW), whereas when using PEG200, there was no significant change ($P <$

0.05) in the pactisity values related to the PVP concentrations. On the other hand, the comparison between water and PVP formulations showed a significant decrease in the value of the compressibility load factors only when there is an increase in the solid ratio (R values). In other words, this happened when the amount of the coating materials became smaller. Finally, the dissolution trends showed a slight increase in the percentage of the drug release in the aqueous medium, compared to the water granulated liquisolid preparations in terms of using PEG200 as a liquid vehicle. In addition to content uniformity, stability and other tablets' quality control tests, using PVP solution as a liquid binder could be a good candidate with PEG200 liquid vehicle to prepare enhanced liquisolid tablets.

Regarding cinnarizine, which is practically insoluble in water, the screening dissolution tests showed no enhancement of the drug release using the liquisolid technology, in spite of using a range of surfactants with different HLB values. Due to the hydrophobicity of this drug, either the drug separated from the high HLB surfactants and floated on the surface of the aqueous medium or it makes a hydrophobic layer with low HLB surfactants and precipitated in the bottom of the dissolution apparatus. However, using non-ionic surfactants in relatively large amounts, such as Kolliphor® RH40 with its melting process, the percentage of the drug release has improved; this gives a justification to use the Self-Emulsifying Drug Delivery Systems (SEDDSs). Depending on the solubility of the drug in a range of oils, surfactants and co-surfactants, two SEDDS mixtures were selected, the one that contains IPM, Kolliphor® RH40 and Transcutol® P showed the highest percentage of the drug release at a ratio of 35:35:30, respectively. The high percentage of the drug release (over 90% after 10 minutes) permitted an increase in the concentration of the liquid medication from 3.00% w/w to 4.29% w/w for 15

mg of drug without a significant change in the dissolution trend. This could suggest that this mixture shows a promise to be used by pharmaceutical industries via filling in hard gelation capsules. After optimizing the IPM SEDDS mixture, there was a trial to upload it as the liquid vehicle to the solid admixture and then to apply the wet granulation process. However, due to the sensitivity of the components to the temperature during the drying of the liquisolid granules, the SEDDS mixture was changed to include Capmul® MCM EP, Kolliphor® RH40 and PEG400. Hence, they do not evaporate at the temperature of the drying process. The optimum ratio that gave the highest drug release was 16.66:66.67:16.66, Capmul® MCM EP: Kolliphor® RH40: PEG400, respectively, whereas the highest concentration of the liquid medication was 6.0% w/w for 15 mg of the drug. Moreover, the negative effect of the coating material on cinnarizine release in the aqueous dissolution test led to develop the new system, depending on the carrier only to prepare an acceptable flowable- compressible liquisolid tablets. A new mathematical model was developed to determine the optimum amount of the carrier and the optimum percentage of the water that should be incorporated during the granulation process. The new prepared tablets showed a significant increase in the dissolution trend compared to the commercial tablets. However, there was a decrease in the hardness due to adding 5% disintegrant, suggesting that those tablets could be manufactured as a coated one to avoid this problem.

8.2. Future work:

This project started with the investigation of applying the liquisolid technique on norfloxacin and then on cinnarizine as model hydrophobic drugs in order to enhance their solubility and dissolution trends in the aqueous media. The obtained

results with classical liquisolid preparations could be further investigated *in vivo* to check the bioavailability of the drugs.

Regarding the wet granulation technique, the selecting of the carrier and the coating materials was microcrystalline cellulose (MCC) (Avicel® PH 101) and silicon dioxide (Cab-O-Sil® M-5P), respectively. Investigating other grades of MCC with higher surface area or different types of silica could provide a higher value of the optimum loading factor so that it is possible to decrease the size of the unit dose or increase the uploaded amount of the liquid vehicle with a good capacity to increase the dose of the drug in each unit.

Additionally, using SEDDS technique helped to increase the percentage of the cinnarizine release in the aqueous dissolution medium. However, converting the optimum SEDDS mixture to liquisolid tablets faced difficulties due to the evaporation of the content of SEDDS mixture from one side and the drug precipitation from another side.

Regarding the evaporation problem, it could be solved by filling the SEDDS mixture into capsules and examining the drug release *in vitro* and *in vivo* to check the suitability.

However, for the drug precipitation, it could be referred to the drug chemical structure. Using different drugs, which they are not affected by the type of the solid materials, will allow using the advantage from the presence of coating materials (e.g. silica) in the liquisolid preparations. The results, in general, showed that using even small amount of silica as a coating material increased the compressibility loading factor. In this case, central composite design could be developed with three factors instead of two. In addition to CW and Water, the

values of R could be the third one and the developed model could include coefficients related to the third factor. This could increase the compressibility load factor so that it could increase the liquid vehicle or the drug dose per unit. The results showed that using even small amount of silica as a coating material increases the value of the compressibility loading factor. The presence of silica could reduce the negative effect of the disintegrant on the pactisity. However, this effect could be solved by using tablet coating excipients. This could be strengthening the tablets and protect them from any factor that could affect the stability of the drug.

Another solution for this problem, to be applied in the future, is to optimize the amount of the disintegrant by considering it as a main factor in the composite central design study. The response could be the AUC values from the relative dissolution trends in addition to the log pactisity. This could help to reach an optimum disintegrant percentage that gives the high dissolution trends with no significant effect on the hardness of the prepared tablets.

Finally, all successful formulations should be tested *in vivo* in order to validate its enhancement to the drug solubility and dissolution.

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