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REVIEW ARTICLE

A REVIEW ON LIQUISOLID SYSTEMS

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ABSTRACT

Solubility & dissolution rate enhancement from solid oral dosage form is a key issue for current formulation and development. This review discusses, out of several techniques available, liquisolid system to improve dissolution rate of water insoluble drugs and to enhance dissolution rate of water soluble drugs. Different carriers and coating materials like Fujicalin®, Neusilin®, Avicel®, and Aerosil® can be used as carrier materials to prepare liquisolid system. Various non-volatile solvents like propylene glycol, liquid polyethylene glycols, polysorbates, glycerine, N,N-dimethylacetamide and fixed oils can be used to dissolve water insoluble molecules. Liquid drugs can be mixed directly with carriers to produce liquisolid systems. Liquisolid systems can be used to either enhance or retard drug release.

Keywords: Solubility enhancement, Liquidsolid systems, Liquid vehicles

INTRODUCTION

Liquisolid technology, as described by Spireas[1] may be used to transform a liquid into a free flowing, easily compressible and apparently dry powder by simple physical mixing with selected excipients named the carrier and coating material. The liquid portion can be a liquid drug, a drug suspension or a drug solution in suitable non-volatile liquid vehicles. This liquid is incorporated into the porous carrier material (Fig. 1). Organic solvent systems which are inert and preferably water-miscible with high boiling point, such as propylene glycol, liquid polyethylene glycols, or glycerine are best suitable as liquid vehicles. Upon saturation of the carrier with liquid, a liquid layer is formed on the particle surface which is readily adsorbed by the fine coating particles [2]. Hence, a dry, free flowing, and compressible powder is obtained.

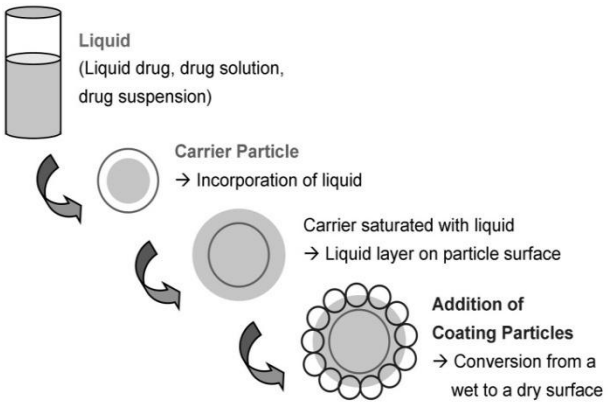

Fig. 1: Schematic representation of liquisolid systems[2]

Different excipients such as lubricants and disintegrants (immediate release) or matrix forming materials (sustained release) may be added to the liquisolid system to produce liquisolid compacts (Fig. 2).

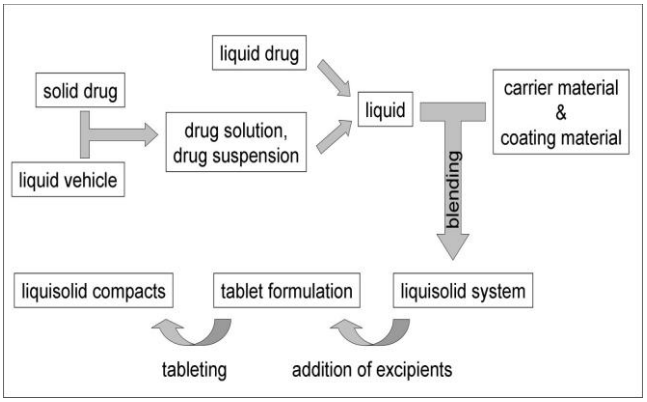

Fig. 2: Schematic outline of the steps involved in the preparation of liquisolid compacts [1]

Liquisolid compacts of poorly soluble drugs containing a drug solution or drug suspension in a solubilising vehicle show enhanced drug release due to one or more of the following reasons, an increased surface area of drug available for release, an increased aqueous solubility of the drug, and an improved wettability of the drug particles [3-6]. Subsequently, this improved drug release may result in a higher drug absorption from the gastrointestinal tract and thus, an improvement in oral bioavailability[7, 8].

As shown in Fig. 3, drug release from liquisolid compacts is significantly faster than that from their directly compressed systems. Here, liquisolid compacts with hydrocortisone containing a 5 % [w/w] drug solution in polyethylene glycol 400 were investigated

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using microcrystalline cellulose and colloidal silica as carrier and coating materials, respectively [9].

The liquisolid technology may also be used to prolong dissolution rate [1, 10-12]. Sustained release oral dosage forms are beneficial with regard to patient compliance because of the reduced dosing frequency. Ideally, a sustained release dosage form leads to therapeutic plasma levels, which are maintained throughout the dosing interval. It has been shown that with hydrophobic carriers such as Eudragit® RL and RS instead of hydrophilic carriers, sustained release systems may be obtained [13]. Sustained release from liquisolid compacts with the conventional carrier and coating materials may also be observed after addition of a matrix forming material such as hydroxypropyl methylcellulose [1].

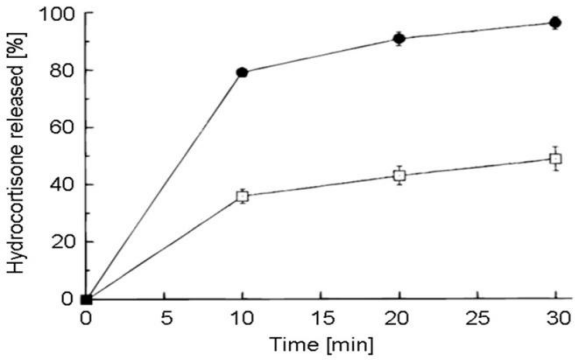

Fig. 3: Hydrocortisone release profiles from liquisolid compacts containing a 5 % [w/w] drug solution in polyethylene glycol 400 (●) and from directly compressed tablets (□) with the same drug dose of 10 mg [9]

Liquisolid technology may be used to prepare sustained release tablets with a zero order drug release pattern (Fig. 4). Here, liquisolid compacts with nifedipine containing a 30 % [w/w] drug suspension in polyethylene glycol 400 were prepared using microcrystalline cellulose and colloidal silica as carrier and coating materials, respectively [1]. In addition, 22 % [w/w] of the matrix former hydroxypropyl methylcellulose with a viscosity grade of 15 mPa·s was added to obtain sustained drug release.

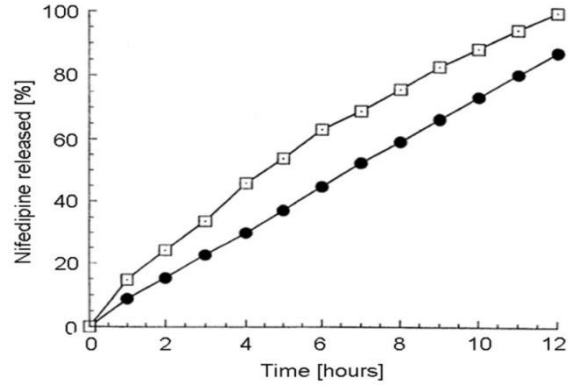

Fig. 4: Nifedipine release profiles from sustained release liquisolid compacts containing a 30 % [w/w] drug suspension in polyethylene glycol 400 (□) and from commercial tablets (●) (Procardia XL) with the same drug dose of 30 mg [1]

LIQUISOLID SYSTEMS THEORY

A powder can retain only certain amount of liquid while maintaining acceptable flow and compression properties. To calculate the required amounts of powder excipients (carrier and coating materials), a mathematical approach for the formulation of liquisolid systems has been developed by Spireas [1, 13]. This approach is based on the flowable (Φ-value) and compressible (Ψ-number) liquid retention potential introducing constants for each powder/liquid combination.

The Φ-value of a powder represents the maximum amount of a given non-volatile liquid that can be retained inside its bulk [w/w] while maintaining an acceptable flowability. The flowability may be determined from the powder flow, by measurement of the angle of repose or by measurement of angle of slide[1].

The Ψ-number of a powder is defined as the maximum amount of liquid the powder can retain inside its bulk [w/w] while maintaining acceptable compactability resulting in compacts of sufficient hardness with no liquid leaking out during compression. The compactability may be determined by pactisity measurement[1] which describes the maximum (plateau) crushing strength of a one-gram tablet compacted at sufficiently high compression forces.

The terms “acceptable flow and compression properties” imply the desired and thus preselected flow and compaction properties which must be met by the final liquisolid formulation.

Depending on the excipient ratio (R) of the powder substrate an acceptably flowing and compressible liquisolid system can be obtained only if a maximum liquid load on the carrier material is not exceeded. This liquid/carrier ratio is termed “liquid load factor L_f“ [w/w] and is defined as the weight ratio of the liquid formulation (W) and the carrier material (Q) in the system:

$$L_f = W / Q \qquad \text{Eq. (1)}$$

R represents the ratio between the weights of the carrier (Q) and the coating (q) material present in the formulation:

$$R = Q / q \qquad \text{Eq. (2)}$$

The liquid load factor that ensures acceptable flowability ($^{\Phi}L_f$) can be determined by:

$$^{\Phi}L_f = \Phi + \varphi \cdot (1/R) \qquad \text{Eq. (3)}$$

where Φ and φ are the Φ-values of the carrier and coating material, respectively. Similarly, the liquid load factor for production of liquisolid systems with acceptable compactability ($^{\Psi}L_f$) can be determined by:

$$^{\Psi}L_f = \Psi + \psi \cdot (1/R) \qquad \text{Eq. (4)}$$

where Ψ and ψ are the Ψ-numbers of the carrier and coating material, respectively.

Therefore, the optimum liquid load factor (L_o) required to obtain acceptably flowing and compressible liquisolid systems is equal to either $^{\Phi}L_f$ or $^{\Psi}L_f$, whichever represents the lower value.

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As soon as the optimum liquid load factor is determined, the appropriate quantities of carrier (Q_o) and coating (q_o) material required to convert a given amount of liquid formulation (W) into an acceptably flowing and compressible liquisolid system may be calculated as follows:

$$Q_o = W / L_o \quad \text{Eq. (5)}$$

and

$$q_o = Q_o / R \quad \text{Eq. (6)}$$

The validity and applicability of the above mentioned principles have been tested and verified by producing liquisolid compacts possessing acceptable flow [2] and compaction properties [1].

Liquisolid formulations for enhanced drug release

Table 1: Formulations of liquisolid systems with enhanced/sustained drug release

Polymer/ Variations	Drug / Molecule	Comments	Reference
Lactose + Cremophor® EL	Griseofulvin	Enhanced Dissolution was achieved	14
Cremophor® EL, Synperonic® PE/L61, PEG400 + Avicel® PH102	Naproxen	Better shelf life	15
Tween 80 + Microcrystalline Cellulose	Piroxicam	Enhanced Dissolution was achieved	6
Avicel® PH102	Famotidine	Enhanced Dissolution was achieved	16
Neusilin®	Griseofulvin	Enhanced release was achieved	17
Avicel®PH 200	Prednisolone	Enhanced Dissolution was achieved	13
Avicel PH 102, and Aerosil 200	Carbamazepine	Enhanced Dissolution was achieved	18
Silica–Eudragit RL or RS	Theophylline	Liquisolid compacts has a potential to produce zero-order release kinetics for less water soluble drugs	19
Eudragit RL or RS as the carrier and silica as the coating material	Propranolol hydrochloride	Sustained release was achieved	5
Capryol™ 90,Solutol® HS-15 and Kollicoat® SR 30 D as non-volatile liquid vehicles	Spironolactone	Enhanced Dissolution was achieved	20
Propylene glycol as solvent, Avicel PH102 as carrier, and Aerosil 200 as the coating material	Valsartan	Enhanced Dissolution was achieved	21

PEG: polyethylene glycol

Many poorly soluble drugs have been formulated as liquisolid systems showing enhanced drug release. Different liquid vehicles, carrier and coating materials were used to formulate these drug delivery systems (Table 1).

MECHANISMS OF ENHANCED DRUG RELEASE FROM LIQUISOLID SYSTEMS

Several mechanisms of enhanced drug release have been proposed in literature for liquisolid systems. The three main suggested mechanisms include an increased surface area of drug available for release, an increased aqueous solubility of the drug, and an improved wettability of the drug particles. Formation of a complex between the drug and excipients or any changes in crystallinity of the drug could be ruled out using DSC and XRPD measurements [4, 6].

a. Increased drug surface area

When the drug within the liquisolid system is completely dissolved in the liquid vehicle, it is located in the powder substrate still in a solubilized, molecularly dispersed state. Hence, the available surface area for drug release is much higher than that of drug particles within directly compressed tablets.

Similarly, when drug content exceeds the solubility limit, fraction of undissolved drug in the liquid vehicle increases and the release rate decreases. With various drugs it could be observed that the release rates are directly proportional to the fraction of the drug molecularly dispersed (F_M) in the liquid formulation [3, 5, 11, 14]. F_M is defined by Spireas as the ratio between the drug's solubility (S_d) in the liquid vehicle and the actual drug concentration (C_d) in this vehicle carried by each system [9].

Therefore:

$$F_M = S_d / C_d \quad \text{Eq. (7)}$$

where $F_M = 1$ if $S_d \geq Cd$.

Fig. 5 shows the effect of the fraction of the molecularly dispersed drug (F_M) on the release rate of hydrocortisone formulated as liquisolid compacts containing various drug concentrations in varying amounts of propylene glycol as liquid vehicle. The drug release rate increases linearly with increasing F_M. However, this linear increase may be observed only above a certain F_M-limit.

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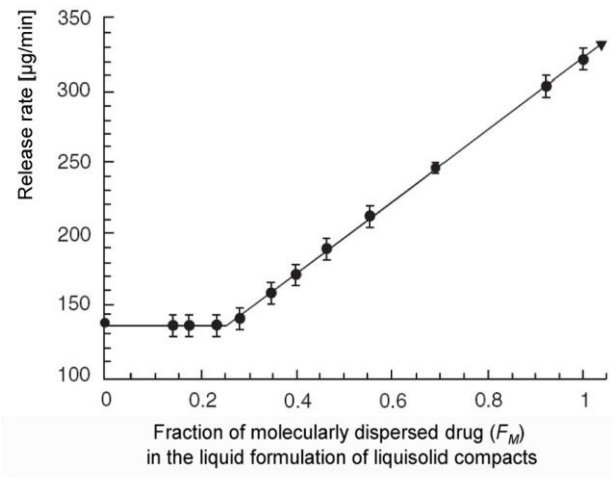

Fig. 5: Effect of the fraction of molecularly dispersed drug (F_M) on the hydrocortisone release rate at 30 min of liquisolid compacts (means ± SD , n = 3) [9]

b. Increased aqueous solubility of the drug

In addition to the first mechanism of drug release enhancement it is expected that Cs, the solubility of the drug, might be increased with liquisolid systems. In fact, the relatively small amount of liquid vehicle in a liquisolid compact is not sufficient to increase the overall solubility of the drug in the aqueous dissolution medium. However, at the solid/liquid interface between an individual liquisolid primary particle and the release medium it is possible that in this microenvironment the amount of liquid vehicle diffusing out of a single liquisolid particle together with the drug molecules might be sufficient to increase the aqueous solubility of the drug if the liquid vehicle acts as a cosolvent. The overall increase in the solubility of drugs caused by liquisolid systems was confirmed by Yadav et al.[22].

c. Improved wetting properties

Due to the fact that the liquid vehicle can either act as surface active agent or has a low surface tension, wetting of the liquisolid primary particles is improved. Improved wettability in-turn results into improved dissolution of drug. Wettability of these systems has been demonstrated by measurement of contact angles [6] and water rising times[22].

OPTIMIZATION OF LIQUISOLID FORMULATIONS WITH ENHANCED DRUG RELEASE

The liquisolid technology has been successfully applied to low dose, poorly water soluble drugs. The formulation of a high dose, poorly soluble drug is one of the limitations of the liquisolid technology. As the release rates are directly proportional to the fraction of molecularly dispersed drug (F_M) in the liquid formulation, a higher drug dose requires higher liquid amounts for a desired release profile. Also, to obtain liquisolid systems with acceptable flowability and compactability high levels of carrier and coating materials are needed. However, this results in an increase in tablet weight ultimately leading to tablet sizes which are difficult to swallow. Therefore, to overcome this and various other problems of the liquisolid technology several formulation parameters may be optimized (Table 2).

In various studies the effect of different types of non-volatile liquid vehicles has been investigated. The results suggest that the selection of a liquid vehicle with a high solubilizing capacity for the drug and thus, an increased FM, leads to enhanced release profiles [23]. That means that by selection of a liquid vehicle with optimum solubilizing properties the amount of liquid and thus, the weight and size of the liquisolid compacts can be reduced. However, in addition to the drug solubility in the liquid vehicle other physicochemical characteristics of the liquid vehicles such as polarity, viscosity, molecular weight, chemical structure, and lipophilicity may also have an effect on drug release [24].

A further approach to minimize tablet weight is to increase the liquid load factor by using carrier and coating materials with a high specific surface area or by adding PVP to the liquid formulation. It was found that the higher the specific surface area of an excipient the higher the liquid load factor [2]. For instance, the liquid adsorption capacity of microcrystalline cellulose (1.18 m²/g) is higher than that of lactose (0.35 m²/g), starch (0.6 m²/g), and sorbitol (0.37 m²/g) [4]. Fujicalin® (30 m²/g), a spherically granulated dicalcium phosphate anhydrous, and Neusilin® US2 (300 m²/g), a magnesium aluminometasilicate, turned out to be very effective excipients for liquid adsorption while maintaining acceptable flow and compaction properties [25].

Table 2: Optimization of formulation parameters for liquisolid systems with immediate drug release

Formulation parameter	Optimization	Effect
liquid vehicle	high drug solubility in the vehicle	increased fraction of the molecularlydispersed drug (FM)
carrier and coating materials	high specific surfacearea	increased liquid load factor (Lf)
addition of excipients	Polyvinylpyrrolidone(PVP)	increased liquid load factor (Lf), increased viscosity of liquid vehicle,inhibition of precipitation
	Superdisintegrant	fast disintegration
excipient ratio (R)	high R-value	fast disintegration, inhibition of precipitation

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Khaled [8] noticed precipitation and consequently retention of the drug in the cavities of porous excipients upon contact of the liquid formulation with the release medium. This retention could be minimized by using either a diluted drug solution or PVP as crystallization inhibitor. Moreover, PVP may also act as binder during compaction leading to an increase of the liquid load factor [1].

The release rate of a drug from a dosage form is dependent on its disintegration and the dissolution rate of the drug. Therefore, it is very important for liquisolid systems with enhanced drug release to ensure that disintegration is not the rate-limiting step and drug dissolution is not hindered by a slow disintegration of the dosage form. It was found that the release rate increases by addition of superdisintegrants such as sodium starch glycolate or croscarmellose sodium to the liquisolid formulation[22].

Another formulation parameter that may be optimized is the ratio of carrier to coating material (R). An increase in the R-value results in an enhanced release rate if microcrystalline cellulose and colloidal silica are used as carrier and coating materials, respectively. Liquisolid compacts with high R-values contain high amounts of microcrystalline cellulose, low quantities of colloidal silica, and low liquid/powder ratios. This is associated with enhanced wicking, disintegration and thus, enhanced drug release. In contrast, if high amounts of colloidal silica are used, which means that the R-value is low, the liquisolid compact is overloaded with liquid formulation due to a high liquid load factor. In such cases, even though drug diffusion out of the primary particles may be rapid, oversaturation might occur resulting in local precipitation/ recrystallization of the drug and thus decreased release rates. Moreover, as colloidal silica is a hydrophobic material high amounts of it can cause retardation of drug release. Therefore, Spireas et al. recommend a minimum R-value of 20[13]. In the case of liquisolid sustained release compacts lower R-values may be used.

Stability of liquisolid systems with enhanced drug release

To obtain information on the stability of liquisolid systems, the effects of storage on the release profile and the crushing strength of liquisolid compacts were investigated. Stability studies of liquisolid systems containing polythiazide (40 °C/ 42 and 75 % R.H., 12 weeks), hydrocortisone (ambient conditions, 10 months) [1], carbamazepine (25 °C/ 75 % R.H., 6 months), indomethacin (25 °C/ 75 % R.H., 12 months), piroxicam (25 °C/ 75 % R.H., 6 and 9 months, respectively), or naproxen (20 °C/ 76 % R.H., 4 weeks) showed that storage at different conditions neither had an effect on the hardness nor on the release profiles of liquisolid compacts. This indicates that the technology is a promising technique to enhance the release rate without having any physical stability issues.

LIQUISOLID FORMULATIONS FOR SUSTAINED DRUG RELEASE

Numerous methods have been described to produce sustained release formulations, among which the liquisolid technology is a quite new and promising technology resulting in a sustained release pattern with zero order kinetics [8, 12]. So far, only few drugs have been formulated as liquisolid systems with prolonged drug release. In Table 3 the formulations of these drugs with the respective liquid vehicle, carrier and coating material as well as the additional retarding agent (matrix forming material) are listed.

Table 3: Formulations of liquisolid systems with sustained drug release

Drug	Liquid vehicle	Carrier & coating material	Additional retardant agent	Ref.
Nifedipine	PEG 400	MCC & ColloidalSilica	HPMC(15 mPa·s)	1, 26
Propranolol HCl	Polysorbate 80	Eudragit® RS or RL &Colloidal Silica	HPMC (4000 mPa·s)	5, 27
Theophylline	Polysorbate 80	Eudragit® RS or RL &Colloidal Silica	HPMC (4000 mPa·s)	28
Tramadol HCl	PG	MCC & ColloidalSilica	HPMC(4000 mPa·s)	29

PEG: polyethylene glycol, PG: propylene glycol, MCC: microcrystalline cellulose, HCl: hydrochloride, HPMC: hydroxypropyl methylcellulose

Mechanisms of sustained drug release from liquisolid systems

With X-ray crystallography and DSC measurements it could be confirmed, that sustained drug release from these liquisolid compacts is not caused by a change in crystallinity or by complex formation of the drug during the manufacturing process of the sustained release liquisolid formulations [27]. Liquisolid formulations with sustained drug release may contain hydrophobic carriers such as Eudragit® RL or RS instead of hydrophilic carriers, the latter being used for fast release liquisolid formulations [5]. Hydrophobic carriers may lead to poor wetting properties of the compacts resulting in slow disintegration and thus, prolonged drug release.

Accordingly, the liquid vehicle may affect drug release. A comparison of drug release from conventional matrix tablets (direct compression) and liquisolid compacts, both containing Eudragit® RS or RL as matrix forming material, showed that the retardation effect of liquisolid compacts with polysorbate 80 as liquid vehicle is much more higher than that of conventional matrix tablets [5]. This confirms the important role of the liquid vehicle in sustaining drug release from liquisolid matrix systems. It was shown that the liquid vehicle polysorbate 80 may act as a plasticizer [30] and thus, decreases the glass transition temperature of the polymer Eudragit® RS. Similarly, with liquisolid compacts the coalescence of the polymer particles occurs at lower temperatures than with

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conventional matrix tablets. This more pronounced coalescence of polymer particles of liquisolid compacts leads to a matrix with lower porosity and higher tortuosity. Consequently, the drug is surrounded by a fine network of the hydrophobic polymer resulting in a sustained release of the drug [31].

Moreover, it has been shown that the addition of hydroxypropyl methylcellulose (HPMC) increases the retardation effect of liquisolid compacts[1]. HPMC is commonly used for the preparation of hydrophilic matrix systems. Depending on its molecular weight the polymer either swells in contact with water and forms a hydrated matrix layer through which the drug has to diffuse or erodes resulting in a zero order drug release kinetic [43]. In the case of HPMC it was also found that a stronger retardation effect was observed with liquisolid compacts as compared to directly compressed tablets (conventional formulation) [38].

Optimization of liquisolid formulations with sustained drug release

In contrast to liquisolid compacts with immediate drug release liquisolid sustained release formulations may be optimized by selection of low R-values, suspensions with a high percentage of undissolved drug and by avoidance of disintegrants.

If the R-value is low, which means that the applied amount of silica is high, the liquisolid compacts are overloaded with liquid formulation due to a high liquid load factor. In such cases oversaturation might occur resulting in local precipitation of the drug and thus, decreased release rates [18, 29]. Moreover, the higher the percentages of undissolved drug in the liquid formulation the slower the release rate. This is especially important for poorly soluble drugs, as the dissolution rate of these drugs is low. In addition, as drug release from a tablet is dependent on the disintegration of the tablet and the subsequent dissolution of the drug, the absence of disintegrants, which prevents disintegration, will slow down drug release.

Furthermore, it was shown with liquisolid compacts that the higher the HPMC concentration and the higher the amount of Eudragit® RS / RL, respectively, the more pronounced the decrease in drug release [31].

CONCLUSION

Various methods are known to improve water solubility and drug release, among which the liquisolid technology is one of the most promising approaches. With this technology liquids such as solutions or suspensions of poorly soluble drugs in a non-volatile liquid vehicle are converted into acceptably flowing and compressible powders by simple physical blending with selected excipients named the carrier and the coating material. As highest drug release rates are observed with liquisolid compacts containing a drug solution as liquid portion, liquisolid compacts may be optimized by selection of the liquid vehicle and the carrier and coating materials. The addition of disintegrants may further accelerate drug release from liquisolid compacts. The liquisolid technology may also be used for the preparation of sustained release formulations with zero order release pattern. Thus, a constant plasma level will be reached, which is maintained throughout the dosing interval. For sustained release liquisolid compacts, the selection and the concentration of the excipients such as liquid vehicle, retarding agent (matrix forming material) as well as carrier and coating material play an important role. The liquisolid approach is a promising technology because of the simple manufacturing process, low production costs and the possibility of industrial manufacture due to the good flow and compaction properties of liquisolid formulations.

REFERENCES

1. Spiridon Spireas, E.F.R.N.P.A., *Liquisolid systems and methods of preparing same*. 2002: US.
2. Spireas S.S., C.I. Jarowski, and B.D. Rohera, *Powdered solution technology: principles and mechanism.* Pharmaceutical research, 1992. **9**(10): p. 1351-1358.
3. Javadzadeh Y., et al., *Evaluating retardation and physicochemical properties of co-ground mixture of Na-diclofenac with magnesium stearate.* Powder Technology, 2012. **218**(0): p. 51-56.
4. Javadzadeh Y., B. Jafari-Navimipour, and A. Nokhodchi, *Liquisolid technique for dissolution rate enhancement of a high dose water-insoluble drug (carbamazepine).* Int J Pharm, 2007. **341**(1-2): p. 26-34.
5. Javadzadeh Y., L. Musaalrezaei, and A. Nokhodchi, *Liquisolid technique as a new approach to sustain propranolol hydrochloride release from tablet matrices.* Int J Pharm, 2008. **362**(1-2): p. 102-8.
6. Javadzadeh Y., et al., *Enhancement of dissolution rate of piroxicam using liquisolid compacts.* Farmaco, 2005. **60**(4): p. 361-5.
7. El-Houssieny B.M., L. Wahman, and N. Arafa, *Bioavailability and biological activity of liquisolid compact formula of repaglinide and its effect on glucose tolerance in rabbits.* Bioscience trends, 2010. **4**(1).
8. Khaled K.A., Y.A. Asiri, and Y.M. El-Sayed, *In vivo evaluation of hydrochlorothiazide liquisolid tablets in beagle dogs.* International journal of pharmaceutics, 2001. **222**(1): p. 1-6.
9. Spireas S., S. Sadu, and R. Grover, *In vitro release evaluation of hydrocortisone liquisolid tablets.* Journal of pharmaceutical sciences, 1998. **87**(7): p. 867-872.
10. Nokhodchi A., C.M. Hentzschel, and C.S. Leopold, *Drug release from liquisolid systems: speed it up, slow it down.* Expert opinion on drug delivery, 2011. **8**(2): p. 191-205.
11. Karmarkar A.B., I.D. Gonjari, and A.H. Hosmani, *Liquisolid technology for dissolution rate enhancement or sustained release.* Expert opinion on drug delivery, 2010. **7**(10): p. 1227-1234.
12. Spireas S. and S. Bolton. *Sustained-release liquisolid compacts*. in *Proc Int Symp Control Rel Bioact Mater*. 1998.
13. Spireas, S., *Enhancement of prednisolone dissolution properties using liquisolid compacts.* International Journal of Pharmaceutics, 1998. **166**(2): p. 177-188.
14. Elkordy A.A., et al., *Combination of lactose (as a carrier) with Cremophor® EL (as a liquid vehicle) to enhance dissolution of griseofulvin.* Powder Technology, 2013. **246**(0): p. 182-186.
15. Tiong, N. and A.A. Elkordy, *Effects of liquisolid formulations on dissolution of naproxen.* Eur J Pharm Biopharm, 2009. **73**(3): p. 373-84.
16. Fahmy R.H. and M.A. Kassem, *Enhancement of famotidine dissolution rate through liquisolid tablets formulation: in vitro and in vivo evaluation.* Eur J Pharm Biopharm, 2008. **69**(3): p. 993-1003.
17. Hentzschel C.M., et al., *Enhancement of griseofulvin release from liquisolid compacts.* Eur J Pharm Biopharm, 2012. **80**(1): p. 130-5.

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18. Tayel S.A., Soliman, II, and D. Louis, *Improvement of dissolution properties of Carbamazepine through application of the liquisolid tablet technique.* Eur J Pharm Biopharm, 2008. **69**(1): p. 342-7.
19. Nokhodchi A., et al., *Liquisolid compacts: the effect of cosolvent and HPMC on theophylline release.* Colloids Surf B Biointerfaces, 2010. **79**(1): p. 262-9.
20. Elkordy A.A., X.N. Tan, and E.A. Essa, *Spironolactone release from liquisolid formulations prepared with Capryol 90, Solutol(R) HS-15 and Kollicoat(R) SR 30 D as non-volatile liquid vehicles.* Eur J Pharm Biopharm, 2012. **83**(2): p. 203-223.
21. Chella N., N. Shastri, and R.R. Tadikonda, *Use of the liquisolid compact technique for improvement of the dissolution rate of valsartan.* Acta Pharmaceutica Sinica B, 2012. **2**(5): p. 502-508.
22. Yadav V. and A. Yadav, *Improvement of Solubility and Dissolution of Indomethacin by Liquisolid and Compaction Granulation Technique.* Journal of Pharmaceutical Sciences & Research, 2009. **1**(3).
23. Nokhodchi A., et al., *The effect of type and concentration of vehicles on the dissolution rate of a poorly soluble drug (indomethacin) from liquisolid compacts.* J Pharm Pharm Sci, 2005. **8**(1): p. 18-25.
24. Grover R., S. Spireas, and C. Lau-Cam, *Development of a simple spectrophotometric method for propylene glycol detection in tablets.* J Pharm Biomed Anal, 1998. **16**(6): p. 931-8.
25. Hentzschel C.M., A. Sakmann, and C.S. Leopold, *Suitability of various excipients as carrier and coating materials for liquisolid compacts.* Drug development and industrial pharmacy, 2011. **37**(10): p. 1200-1207.
26. Gubbi S. and R. Jarag, *Liquisolid technique for enhancement of dissolution properties of Bromhexine Hydrochloride.* Research Journal of Pharmacy and Technology, 2009. **2**(2): p. 382-386.
27. Nokhodchi A., Y. Javadzadeh, and L. Mosaalrezaei, *Liquisolid technique for sustaining the drug release from compacts.* Journal of Pharmacy and Pharmacology, 2007. **59**: p. 49.
28. Nokhodchi A., et al., *Liquisolid compacts: The effect of cosolvent and HPMC on theophylline release.* Colloids and Surfaces B: Biointerfaces, 2010. **79**(1): p. 262-269.
29. Gonjari I.D., A.B. Karmarkar, and A.H. Hosmani, *Evaluation of in vitro dissolution profile comparison methods of sustained release tramadol hydrochloride liquisolid compact formulations with marketed sustained release tablets*. Digest Journal of Nanomaterials & Biostructures (DJNB), 2009. **4**(4).
30. Gruetzmann R. and K.G. Wagner, *Quantification of the leaching of triethyl citrate/polysorbate 80 mixtures from Eudragit® RS films by differential scanning calorimetry*. European journal of pharmaceutics and biopharmaceutics, 2005. **60**(1): p. 159-162.
31. Azarmi S., W. Roa, and R. Lobenberg, *Current perspectives in dissolution testing of conventional and novel dosage forms.* Int J Pharm, 2007. **328**(1): p. 12-21.

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