

REVIEW ARTICLE

SOLUBILITY ENHANCEMENT AND DISSOLUTION IMPROVEMENT- LIQUISOLID TECHNIQUE

*Kapoor D¹, Sharma S², Patel M¹, Vyas RB¹, Chaitali Lad¹¹Dr. Dayaram Patel Pharmacy College, Sardarbaug, Station Road, Bardoli, Dist – Surat, Gujarat, India, Pin-394601²Department of Pharmacy, Banasthali Vidyapith, Rajasthan, India, Pin-304022*Corresponding Author's E-mail id – dev7200@gmail.com, Contact Info - +91-7874223242**ABSTRACT:**

This technique is based upon the admixture of drug loaded solutions with appropriate carrier and coating materials. The use of non-volatile solvent causes improved wettability and ensures molecular dispersion of drug in the formulation and leads to enhance solubility. By using hydrophobic carriers (non-volatile solvents) one can modify release (sustained release) of drugs by this technique. Liquisolid system is characterized by flow behavior, wettability, powder bed hydrophilicity, saturation solubility, drug content, differential scanning calorimetry, Fourier transform infra red spectroscopy, powder X-ray diffraction, scanning electron microscopy, in-vitro release and in-vivo evaluation. The increased bioavailability is due to either increased surface area of drug available for release, an increased aqueous solubility of the drug, or improved wettability of the drug particles. According to the new formulation method of liquid-solid compacts, liquid medications such as solutions or suspensions of water insoluble drugs in suitable non-volatile liquid vehicles can be converted into acceptably flowing and compressible powders by blending with selected powder excipients. It has been speculated that such systems exhibit enhanced release profiles. In this case, even though the drug is in a solid dosage form, it is held within the powder substrate in solution or, in a solubilized, almost molecularly dispersed state, which contributes to the enhanced drug dissolution properties. According to the new formulation method of liquid-solid compacts, liquid medications such as solutions or suspensions of water insoluble drugs in suitable non-volatile liquid vehicles can be converted into acceptably flowing and compressible powders by blending with selected powder excipients. Large scale production of fabricated drug on commercial level successful liquid-solid tablet is a determination of optimal flowable liquid retention.

Keywords: Poorly soluble drugs, coating material, carrier, hydrophilic solvent, liquid-solid compacts

INTRODUCTION:

The poorly soluble drug having dissolution rate too slow therefore uptake cannot be completed within the time at absorption site. If it remains in GIT for longer period may lead to decomposition of drug. There are two parameters useful for identifying poorly soluble drugs. One is its aqueous solubility should be less than 100 µg/ml and another is dose: solubility ratio. Dose: solubility ratio can be defined as volume of gastrointestinal fluids necessary to dissolve the administered dose.¹

The liquid-solid technique as described by Spireas is a novel concept, where a liquid may be transformed into a free flowing, readily compressible and apparently dry powder by simple physical blending with selected carrier and coating material. The liquid portion, which can be a liquid drug, a drug suspension or a drug solution in suitable non-volatile liquid vehicles, is included into the porous carrier material. Inert, preferably water-miscible organic solvent systems with high boiling point such as liquid polyethylene glycols, propylene glycol, or glycerine are most excellent fitting as liquid vehicles. As the carrier is saturated with liquid, a liquid layer is formed on the particle surface which is instantly adsorbed by the fine coating particles.²

Solid dispersions consist of one or more active ingredients dispersed in a readily soluble solid hydrophilic matrix prepared by a melting (fusion) or solvent method³. With the melting method the drug is added to the molten carrier and the mixture is stirred until a homogenous melt is obtained. With the solvent method drug and carrier are dissolved in small amounts of solvent with final solvent

evaporation. The higher release rates of solid dispersions may be ascribed to a number of factors which include formation of the amorphous form of the drug, reduction of particle size to nearly the molecular level, improved wetting properties and solubilisation of the drug by the carrier. The advantages of this methodology are the molecular dispersion of the drug within the hydrophilic carrier and the comparably high drug stability. However, for the preparation of solid dispersions usually special equipment is needed such as a spray dryer or a fluid bed apparatus.^{4,9}

Liquid-solid compact:

Liquid-solid technique is a new and promising method that can change the dissolution rate of drugs. It has been used to enhance dissolution rate of poorly water-soluble drugs. For poorly soluble (Class II) drugs and class (Class IV) the rate of oral absorption is often controlled by the dissolution rate in the gastrointestinal tract. The new 'liquid-solid' technique may be applied to formulate liquid medications (i.e., oily liquid drugs and solutions, suspensions or emulsions of water-insoluble solid drugs carried in non-volatile liquid vehicles) into powders suitable for tableting or encapsulation. Since, the liquid-solid tablets contain a solution of the drug in suitable solvent; the drug surface available for dissolution is tremendously increased. Due to significantly increased wetting properties and surface area of drug available for dissolution, liquid-solid compacts of water-insoluble substances may be expected to display enhanced drug release characteristics and, consequently, improved oral bioavailability.

Drugs that can be incorporated into liquisolid systems:

Antihistaminic: chlorpheniramine

Antiarrhythmic: digoxin, digitoxin

Antihypertensive: nifedipine

Antilipidemics: clofibrate, gemfibrozil

Antiepileptic: Carbamazepine, valproic acid.

Chemotherapeutic agent: etoposide.

Diuretics: Hydrochlorothiazide, methylchlorothiazide, polythiazide, spironolactone.

Glucocorticoids: prednisolone, hydrocortisone, prednisone.

NSAIDs: piroxicam, indomethacin, ibuprofen.

Water-insoluble vitamins: vitamin A, D, E, and K

Advantages:

- Huge number of Bio-Pharmaceutical classification class II drugs with high permeability, slightly or very slightly water soluble and practically insoluble liquids and solid drugs can be formulated into liquisolid systems.
- Improvement of bioavailability of an orally administered water insoluble drugs is achieved.
- This principle governs or administers the mechanism of drug delivery from liquisolid systems of powdered drug solutions and it is mainly responsible for the improved dissolution profiles exhibited by these preparations.
- In this technique, production cost is low compared to soft gelatin capsules.
- Drug is formulated in a tablet form or encapsulated dosage form and is held in solubilized liquid state, which confers developed or improved drug wetting properties thereby improving drug dissolution profiles.
- Greater drug surface area is exposed to the dissolution medium. This liquisolid system is specifically for powdered liquid medications.
- Capability of industrial production is also possible.
- Enhanced bioavailability can be obtained as compared to conventional tablets.
- Differentiate the dosage form by admixture of color into liquid vehicle.

Limitations¹⁰:

- Formulation of high dose lipophilic drugs the liquisolid tablet is one of the limitations of this technique.
- This technique is not applicable for high dose insoluble drug.
- Mathematical calculations require.

Advantages of liquisolid tablets over convention tablets:

- ✓ Liquisolid systems are low cost formulations than soft gelatin capsules.
- ✓ Production of them is similar to that of conventional tablets.
- ✓ Drug release can be modified using suitable formulation ingredients.

- ✓ Drug can be molecularly dispersed in the formulation.
- ✓ Capability of industrial production is also possible.
- ✓ Enhanced bioavailability can be obtained as compared to conventional tablets.
- ✓ Omit the process approaches like nanonisation, micronization techniques.
- ✓ Differentiate the dosage form by admixture of colour into liquid vehicle.
- ✓ To minimize excipients in formulation compare with other formulations like solid dispersions.

Theory of liquid solid systems:

A powder can retain only limited amounts 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 liquid-solid systems has been developed by Spirea. 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 or by measurement of the angle of repose. 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.^{11, 12}

Depending on the excipient ratio (R) of the powder substrate an acceptably flowing and compressible liquid-solid 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:

$$L_f = W/Q \text{----- (1)}$$

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

$$R = Q/q \text{----- (2)}$$

The liquid load factor that ensures acceptable flowability (L_f) can be determined by:

$$L_f = \Phi + \phi \cdot (1/R) \text{----- (3)}$$

Where Φ and ϕ are the Φ -values of the carrier and coating material, respectively. Similarly, the liquid load factor for production of liquid-solid systems with acceptable compactability (ΨL_f) can be determined by:

$$\Psi L_f = \Psi + \psi \cdot (1/R) \text{----- (4)}$$

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

Classification:

- Based on the type of liquid medication contained therein, liquid systems may be classified into three subgroups:
 - Powdered drug solutions
 - Powdered drug suspensions
 - Powdered liquid drugs

The first two may be produced from the conversion of drug solutions or (e.g. prednisolone solution in propylene glycol) or drug suspensions (e.g. gemfibrozil suspension in Polysorbate 80), and the latter from the formulation of liquid drugs (e.g. clofibrate, valproic acid, liquid vitamins, etc.), into liquid systems.

- Based on the formulation technique used, liquid systems may be classified into two categories, namely,
 - Liquid compacts
 - Liquid microsystems

Liquid compacts are prepared using the previously outlined method to produce tablets or capsules, whereas the liquid microsystems are based on a new concept which to produce an acceptably flowing admixture for encapsulations.¹³

Mechanism of enhanced drug release:

From liquid solid systems:

Several mechanisms of enhanced drug release have been postulated for liquid-solid 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.

a. Increased Drug Surface Area

If the drug within the liquid-solid system is completely dissolved in the liquid vehicle it is located in the powder substrate still in a solubilized, molecularly dispersed state. Therefore, the surface area of drug available for release is much greater than that of drug particles within directly compressed tablets¹².

b. Increased Aqueous Solubility of the Drug

In addition to the first mechanism of drug release enhancement it is expected that C_s , the solubility of the drug, might be increased with liquid-solid systems. In fact, the relatively small amount of liquid vehicle in a liquid-solid 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 liquid-solid primary particle and the release medium it is possible that in this microenvironment the amount of liquid vehicle diffusing out of a single liquid-solid particle together with the drug molecules might be sufficient to increase the aqueous solubility of the drug if the liquid vehicle acts as a cosolvent¹².

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 liquid-solid primary particles is improved. Wettability

of these systems has been demonstrated by measurement of contact angles and water rising times.¹⁴

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

Principle of Liquid Compacts:

Important terminologies in Principle:

Liquid medication includes liquid lipophilic drugs and drug suspensions or solutions of solid water insoluble drugs in suitable non-volatile solvent systems.

Liquid system refers to powdered forms of liquid medications formulated by converting liquid lipophilic drugs, or drug suspensions or solutions of water insoluble solid drugs in suitable non-volatile solvent systems, into dry, nonadherent, free-flowing and readily compressible powder admixtures by blending with selected carrier and coating materials.

Carrier material refers to a preferably porous material possessing sufficient absorption properties, such as microcrystalline and amorphous cellulose, which contributes in liquid absorption.

Coating material refers to a material possessing fine and highly adsorptive particles, such as various types of silica, which contributes in covering the wet carrier particles and displaying a dry looking powder by adsorbing any excess liquid.¹⁵

With the liquid technology, a liquid may be transformed into a free flowing, readily compressible and apparently dry powder by simple physical blending with selected excipients named the carrier and coating material. The liquid portion, which can be a liquid drug, a drug suspension or a drug solution in suitable non-volatile liquid vehicles, is incorporated into the porous carrier material (Fig. 1).

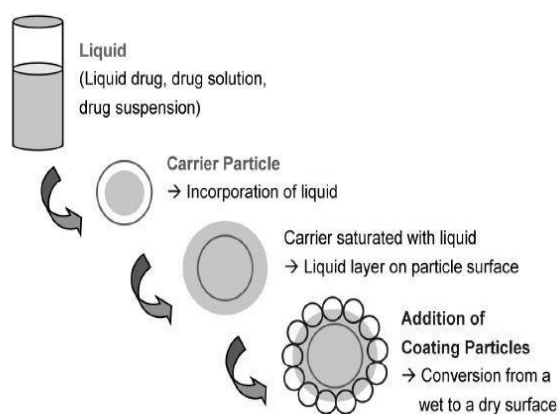


Figure 1: Schematic representation of liquid solid systems.

Inert, preferably water-miscible organic solvent systems with high boiling point such as propylene glycol, liquid polyethylene glycols, or glycerine are best suitable as liquid vehicles. Once the carrier is saturated with liquid, a liquid layer is formed on the particle surface which is instantly adsorbed by the fine coating particles. Thus, an apparently dry, free flowing, and compressible powder is obtained. Usually, microcrystalline cellulose is used as

carrier material and amorphous silicon dioxide (colloidal silica) as coating material.

Preparation of liquid solid compacts:

As shown in figure, a liquid lipophilic drug (e.g. Chlorpheniramine, Clofibrate, etc.) can be converted into a liquid-solid system without being further modified. On the other hand, if a solid water-insoluble drug (e.g. Hydrochlorothiazide, Prednisone, etc.) is formulated, it should be initially dissolved or suspended in a suitable nonvolatile solvent system to produce a drug solution or drug suspension of desired concentration. Next, a certain amount of the prepared drug solution or suspension, or the liquid drug itself, is incorporated into a specific quantity of carrier material which should be preferably of a porous nature and possessing sufficient absorption properties, such as powder and granular grades of microcrystalline and amorphous cellulose are most preferred as carriers. The resulting wet mixture is then converted into a dry-looking, non-adherent, free-flowing and readily compressible powder by the simple addition and mixing of a calculated amount of coating material. Excipients possessing fine and highly adsorptive particles, such as various types of amorphous silicon dioxide (silica), are most suitable for this step. Before compression or encapsulation, various adjuvants such as lubricants and disintegrates (immediate) or binders (sustained-release) may be mixed with the finished liquid-solid systems to produce liquid-solid compacts i.e. tablets or capsules.^{16, 17, 18}

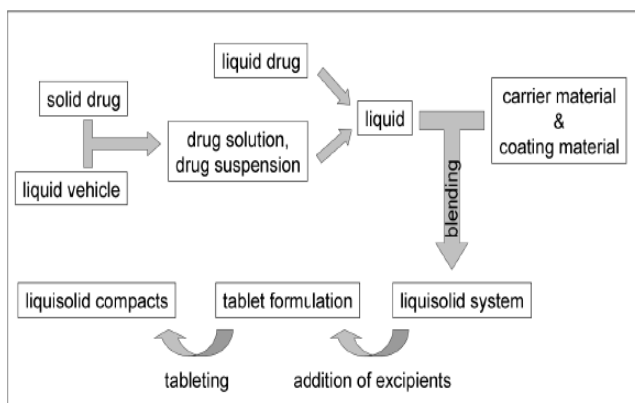


Figure 2: Schematic outline of the steps involved in the preparation of liquid solid compacts

Pre-compression evaluation parameters of liquid solid systems:

Flow Properties of the Liqui-Solid System:^{19, 20}

The flow properties of the liquid-solid systems were estimated by determining the angle of repose, Carr's index, and Hausner's ratio. The angle of repose was measured by the fixed funnel and freestanding cone method. The Bulk density and Tap densities were determined for the calculation of Hausner's ratio and Carr's Index.

Angle of repose:

The angle of repose physical mixtures of liquid-solid compacts were determined by fixed funnel method. The accurately weighed physical mixtures of liquid-solid compacts were taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touches the apex of the heap of the powder. The

powder was allowed to flow through the funnel freely into the surface. The height and diameter of the powder cone was measured and angle of repose was calculated.

$$\tan \theta = h/r$$

Where, θ is the angle of repose, h is the height in cms, r is the radius in cms

Values for angle of repose $\leq 30^\circ$ usually indicate a free flowing material and angles $\geq 40^\circ$ suggest a poorly flowing material. 25-30 showing excellent flow properties, 31-35 showing good flow properties, 36-40 showing fair flow properties, 41-45 showing passable flow properties.

Bulk Density:

The loose bulk density and tapped density were determined by using bulk density apparatus. Apparent bulk density was determined by pouring the blend into a graduated cylinder. The bulk volume (V_b) and weight of the powder (M) was determined. The bulk density was calculated using the formula:

$$D_b = M/V_b$$

where, M is the mass of powder, V_b is bulk volume of powder

Tapped Density:

The measuring cylinder containing a known mass of blend was tapped for a fixed time. The minimum volume (V_t) occupied in the cylinder and the weight (M) of the blend was measured. The tapped density was calculated using the formula:

$$D_t = M/V_t$$

Where, M is the mass of powder, V_t is tapped volume of powder

Carr's Index (%):

The compressibility index has been proposed as an indirect measure of bulk density, size and shape, surface area, moisture content and cohesiveness of material because all of these can influence the observed compressibility index. The simplest way for measurement of free flow of powder is Carr's Index, a indication of the ease with which a material can be induced to flow is given by Carr's index (CI) which is calculated as follows:

$$CI (\%) = \left[\frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \right] \times 100$$

The value below 15% indicates a powder with usually gives rise to good flow characteristics, whereas above 25% indicates poor flowability. 1-10 showing excellent flow properties, 11-25 showing good flow properties 16-20 showing fair to passable, 21-25 showing passable.

Hausner's Ratio:

Hausner's ratio is an indirect index of ease of powder flow. It is calculated by the following formula.

$$\text{Hausner's Ratio} = \frac{\text{Tapped density } (\rho_t)}{\text{Bulk density } (\rho_b)}$$

Where ρ_t is tapped density and ρ_b is bulk density. Lower Hausner's ratio (<1.25) indicates better flow

properties than higher ones, between 1.25 to 1.5 showing moderate flow properties and more than 1.5 poor flow.

Fourier Transform Infra Red Spectroscopy (FT-IR):

FT-IR spectra of prepared melt granules are recorded on FTIR-8400 spectrophotometer. Potassium bromide (KBr) pellet method is employed and background spectrum is collected under identical situation. Each spectrum is derived from single average scans collected in the region 400 - 4000 cm^{-1} at spectral resolution of 2 cm^{-2} and ratio against background interferogram. Spectra are analyzed by software.²¹

Differential scanning calorimetry (DSC):

Differential scanning calorimetry (DSC) is performed in order to assess the thermotropic properties and the thermal behaviors of the drug, excipients used in the formulation of the liquisolid system. Complete disappearance of characteristic peaks of drug indicates the formation of drug solution in the liquisolid powdered system, i.e., the drug is molecularly dispersed within the liquisolid matrix.^{21, 22, 23}

X-ray diffraction (XRD):

For the characterization of crystalline state, X-ray diffraction (XRD) patterns are determined for physical mixture of drug and excipients used in formulation and for the prepared liquisolid compacts.²⁴ Absence of constructive specific peaks of the drug in the liquisolid compacts in X-ray diffractogram specify that drug has almost entirely converted from crystalline to amorphous or solubilized form. Such lack of crystallinity in the liquisolid system was understood to be as a result of drug solubilization in the liquid vehicle i.e., the drug has formed a solid solution within the carrier matrix. This amorphization or solubilization of drug in the liquisolid compacts it may contribute to the consequent improvement in the apparent solubility and enhancement of dissolution rate of the drug.²⁵

Post compression evaluation parameter of liquid solid compacts:

Weight Variation:

Twenty tablets were randomly selected from each batch and individually weighed. The average weight and standard deviation three batches were calculated. It passes the test for weight variation test if not more than two of the individual tablet weights deviate from the average weight by more than the allowed percentage deviation and none deviate by more than twice the percentage shown. It was calculated on an electronic weighing balance.

Thickness:

The thickness of liquid-solid tablets was determined by using Digital micrometer. Ten individual tablets from each batch were used and the results averaged.

Hardness:

The hardness of the tablets was determined by using Monsanto hardness tester. Five individual tablets from each batch were used and results averaged.

Friability:

The friability values of the tablets were determined using a Roche-type friabilator. Accurately weighed six tablets were placed in Roche friabilator and rotated at 25 rpm for 4 min. Percentage friability was calculated using the following equation.

$$\text{Friability} = \frac{[\text{WO} - \text{W}]}{\text{WO}} \times 100$$

Where,

WO = Weight of the tablet at time zero before revolution,
W = Weight of the tablet after 100 revolutions.

Disintegration Test

Six tablets were taken randomly from each batch and placed in USP disintegration apparatus baskets. Apparatus was run for 10 minutes and the basket was lifted from the fluid, observe whether all of the tablets have disintegrated.

Contact angle measurement:

For assessment of wettability, contact angle of liquisolid tablets is measured according to the imaging method. The commonly used method is to measure contact angle directly for a drop of liquid resting on a plane surface of the solid, the so-called imaging method. A saturated solution of the drug in dissolution media is prepared and a drop of this solution is put on the surface of tablets. The contact angles are calculated by measuring the height and diameter of sphere drop on the tablet.²⁴

Scanning electron microscopy (SEM):

Scanning electron microscopy (SEM) is utilized to assess the morphological characteristics of the raw materials and the drug-carrier systems.²⁵

In-vitro dissolution studies:

Works of many researchers revealed that technique of liquisolid compacts could be a promising alternative for formulation of water-insoluble drugs. This technique of liquisolid compacts has been successfully employed to improve the *in-vitro* release of poorly water soluble drugs as hydrocortisone,²⁶ Prednisolone²⁷ Carbamazepine²⁸ Piroxicam^{24, 29} Also several water insoluble drugs nifedipine, gemfibrozil, and ibuprofen, have shown higher bioavailability in rats as compared to their commercial counterparts.

9. In-vivo evaluation of liquisolid systems:

This liquisolid technology is a promising tool for the enhancement of drug release of poorly soluble drugs. The absorption characteristics of Hydrochlorothiazide liquisolid compacts in comparison with commercial tablets were studied in beagle dogs. Significant differences in the area under the plasma concentration-time curve, the peak plasma concentration and the absolute bioavailability of the liquisolid and the commercial tablets were observed. However, for the mean residence time, the mean absorption time, and the rate of absorption no significant differences were found. The absolute bioavailability of the drug from liquisolid compacts was 15% higher than that from the commercial formulation.³⁰

Stability studies:

Drug content was determined after the crystals were charged for accelerated stability studies according to ICH

guidelines. Samples were taken and analysed for specified intervals.

Bioavailability assessment for different active pharmaceutical ingredients:

Bioavailability assessment is required for liquisolid technique. Because it was proved that enhancing the drug releases from the dosage form by determination of *in-vitro* release studies. So, this parameter should establish for determination of the efficacy of the formulation.³⁰

Atorvastatin calcium (ATR) is a BCS class II drug used as a lipid lowering agent by acting as HMGCoA reductase inhibitor. The prepared liquisolid compacts of ATR showed higher release rates compared to the directly compressed tablets. The pharmacokinetic parameters of liquisolid compacts of ATR, such as the AUC, t_{max} and C_{max} showed the better bioavailability compared with the conventional formulation.³¹

Liquisolid Compacts of Aceclofenac oral dispersible tablets were formulated and evaluated. The study is based on the effect of combined mixture of super disintegrants disintegrating action on drug release. Propylene glycol, PEG 400, Tween 80, microcrystalline cellulose were used as carrier. The liquisolid compacts with Sodium starch glycolate added intra granularly and Crosspovidone extra granularly showed highest dissolution rate. Oral dispersible liquisolid compacts prepared with Tween 80 enhance the dissolution rate of aceclofenac to a larger extent.³²

Approaches to augment dissolution of active pharmaceutical ingredient release from its immediate release tablets:

Liquisolid compacts confirmed significantly higher drug release rates, in different dissolution media, compared to tablets prepared by the direct compression method. It was also observed that the drug dissolution rate from liquisolid tablets were independent of the volume of dissolution medium, in difference to the plain tablets which exposed declining drug release patterns with decreasing dissolution volumes.²⁷

Cyclosporine (CS) Self Micro-Emulsifying Tablet (SME), the tablets were prepared by the liquisolid compaction technique. Formulation consists of oil, surfactant and cosurfactant which were selected on the basis of solubility and emulsification ability for the SME

formulation. In this study, the mixture of Lauroglycol FCC: Maisine 35-1 (1: 1w/w) was selected as the oil phase, PEG-35 Castor Oil was selected as the surfactant and PEG-400 was selected as the co-surfactant. 1 to 6 was selected as the ratio between the drug and the mixture. An emulsion could not be formed in several oils, such as Carprylol 90, Lauroglycol 90 and Lauroglycol FCC even in which the CS has good solubility. Due to the cyclic structure of CS-A, some excipients absorbed the drug and could not be selected as carrier material and coating material, e.g., silica powders. The liquisolid tablets were effective in enhancing dissolution of CS-A, a poorly water-soluble drug. The tablets exhibited good flowability and compactability. The results showed that the liquisolid compaction technique is a promising alternative technique to improve the solubility and the dissolution rate, for poorly water-soluble drugs CS-A.³³

Naproxen is a non-steroidal anti-inflammatory drug (NSAID) commonly used for the reduction of fever, pain and inflammation. Liquisolid compacts change the properties of naproxen particles by simply dispersing the drug particles in a non-volatile hydrophilic liquid vehicle, which increase the wetting properties of drug particles, and enhances the dissolution rate and shows improved bioavailability of the drug. At present, naproxen is available commercially in high

dose tablets between 250 and 500 mg; the liquisolid formulations may help in reduction of the dose also.³⁴

CONCLUSION:

This technique is a potential substitute for formulation of water-insoluble/soluble drugs. The improved rate of drug dissolution from liquisolid tablets is almost certainly due to an amplification in wetting properties and surface area of drug particles obtainable for dissolution. Rapid disintegration rates are experimentally compared to conventional tablets. Hence they show improved release rates and greater bioavailability. By this technique, sustained drug delivery systems were also developed for the water soluble drugs in which hydrophobic non-volatile solvents are used as vehicles. Alteration of formulation by use of definite agent's source it control the release of drugs from the liquisolid tablets.

REFERNECES:

- Spireas S. Lquisolid System and method of preparing same. U.S Patent 6423339B1, 2002.
- Merisko E. Liversidgenanocrystals: resolving pharmaceutical formulation issues associated with poorly soluble compounds in: J.J matty (Ed), Particles, Marcel Dekker, Orlando, 2002.
- Jarowski CI, Rohera BD, Spireas S. Powdered solution technology: principles and mechanism. Pharm Res. 1992; 9: 1351-1358.
- Barzegar JM, Javadzadeh Y, Nokhodchi A, Siahi-Shadbad MR. Enhancement of dissolution rate of piroxicam using liquisolid compacts. II Farmaco. 2005; 60: 361-365.
- Nokhodchi A, Hentzschel CM, Leopord CS. Drug release from liquisolid system: speed it up, slow it down. Expert Opin Drug Del. 2011; 8: 191-205.
- El-Houssieny BM, Wahman LF, Arafa NMS. Bioavailability and biological activity of liquisolid compact formula of repaglinide and its effect on glucose tolerance in rabbits. Bio Sci Trends.2010; 4: 17-24.
- Khaled KA, Asiri YA, El-Sayed YM. *In-vivo* evaluation of hydrochlorothiazide liquisolid tablet in beagles dogs. Int J Pharm. 2001; 222: 1-6.
- Naseem A, Olliff CJ, Martini LG, Lloyd AW. Effects of plasma irradiation on the wettability and dissolution of compacts of griseofulvin. Int J Pharm.2004; 269, 443-450.
- Craig DQM. The mechanisms of drug release from solid dispersions in water-soluble polymers. Int. J. Pharm., 2002, 231: 131-144.
- Javadzadeh Y and Nokhodchi A. Liquisolid technique for dissolution rate enhancement of a high dose water-insoluble drug (carbamazepine). Int J Pharm. 341:26-34.
- Spireas, S. Liqui-solid systems and methods of preparing same. U.S. Patent 6423339B1 2002.
- Spireas, S., Sadu, S.Enhancement of prednisolone dissolution properties using liqui- Solid compacts.Int. J.Pharm. 1998, 166: 177-188.
- Nokhodchi A. The effect of type and concentration of vehicles on the dissolution rate of a poorly soluble drug (indomethacin) from liquisolid compacts. J pharm Sci. 8(1):18-25.
- Yadav, V.B., Nighute, A.B., Yadav, A.V., Bhise, S.B. Aceclofenac size enlargement by non aqueous granulation with improved solubility and dissolution. Arch. Pharm. Sci.and Res. 2009, 1: 115-122.
- Rajesh V, Areefulla S, Mallikarjun V, Solubility and Dissolution Enhancement: An overview. Journal of Pharmacy Research.2010,3,141- 145.
- Barzegar-Jalali M, Dastmalchi S. Kinetic analysis of chlorpropamide dissolution from solid dispersions. Drug Dev. Ind. Pharm.,2007, 33: 63-70.
- Valizadeh H, Zakeri-Milani P, Barzegar-Jalali M, Mohammadi G, Danesh- Bahreini MA, Adibkia K, Nokhodchi A. Preparation and characterization of solid dispersions of piroxicam with hydrophilic carriers. Drug Dev. Ind. Pharm., 2007, 33: 45-56.
- Valizadeh H, Nokhodchi A, Qarakhani N, Zakeri-Milani P, Azarmi S, Hassanzadeh D, LoebenbergR.Physicochemical characterization of solid dispersions of indomethacin with PEG 6000, Myrj 52, lactose, sorbitol, dextrin and Eudragit® E100. Drug Dev. Ind. Pharm.,2004,30: 303-317.
- Bhise SB, Nighute AB, Yadav AV, Yadav VB, Aceclofenac size enlargement by non aqueous granulation with improved solubility and dissolution. Arch Pharm Sci& Res. 2009; 1:115-122.
- Craig DQM. Pharmaceutical applications of DSC. In: Craig DQM, Reading M (eds). Thermal analysis of pharmaceuticals. Boca Raton, USA, CRC Press, 2007, pp. 53-99.
- Grover R, Spireas S, Wang T. Effect of powder substrate on the dissolution properties of Methcrothiazideliquisolid compacts. Drug DevInd Pharm. 1999; 25: 163-168.
- Asnaashari S, Javadzadeh Y, Siahi MR., A. Nokhodchi, An investigation of physicochemical properties of piroxicamlquisolid compacts. Pharm Develop Tech. 2007; 12: 337-343.
- Rakshit P, Ridhish P, Moinuddin S. Formulation and evaluation of liquisolid compacts of piroxicam. Ind drugs.2007; 44: 967-972.
- Martindale, The Complete Drug Reference, 6 Edn, The Pharmaceutical Press, London, 1999, pp. 937.
- Naseem A, Olliff CJ, Martini LG, Lloyd AW. Effects of plasma irradiation on the wettability and dissolution of compacts of griseofulvin.Int J Pharm.2004; 269, 443-450.
- Sadu S, Spireas S, Grover R. In vitro release evaluation of hydrocortisone liquisolid tablets.J Pharm Sci. 1998; 87:867-872.
- Spiro S, Srinivas S. Enhancement of Prednisolone dissolution properties using liquisolid compacts. Int J Pharm. 1998; 166:177-188.
- Rakshit P, Ridhish P, Moinuddin S. Formulation and evaluation of liquisolid compacts of piroxicam. Ind drugs.2007; 44: 967-972.
- Tayel SA, Louis D, Soliman V. Improvement of dissolution properties of carbamazepine through application of the liquisolid tablet technique. Eur J Pharm Bio pharm. 2008; 69: 342-347
- Khaled KA, Asiri YA, El-Sayed YM. *In-vivo* evaluation of hydrochlorothiazide liquisolid tablet in beagles dogs. Int J Pharm. 2001; 222: 1-6.
- Gubbi SR, Jarag R. Formulation and characterization of Atorvastatin calcium liquisolid Compacts. Asian J Pharm Sci. 2010; 2:50-60.
- El-say KM, Samy AH, Fetouh MI. Formulation and Evaluation of oral dispersible Liquisolid Compacts of Aceclofenac. Int J Pharm Sci Rev Res 2010; 3:135-142.
- Zhao YQ, Zhou S, Potharaju H, Lou HM, Brunson E, Almoazen H, Johnson J. Development of a self micro-emulsifying tablet of Cyclosporine- A by the liquisolid compact technique. IJPSR, 2011; 2(9): 2299-2308.
- Tiong N, Amal AE. Effects of liquisolid formulations on dissolution of Naproxen.Euro Journal of Pharm &Biopharm.2009; 73: 373-384.