



LIQUISOLID TECHNIQUE: A NOVEL APPROACH TO ENHANCE SOLUBILITY AND BIOAVAILABILITY OF BCS-II DRUGS

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ABSTRACT

Liquisolid technique is new and promising method that can enhance the dissolution rate of poorly water soluble drugs. At present 56% of the drugs coming directly from synthesis are poorly water soluble drugs. The enhancement of oral bioavailability of poorly water soluble drugs is one of the challenging aspects of drug development. Liquisolid technique is based upon the dissolving the drug in a suitable non-volatile solvent and admixture of drug loaded solutions with appropriate carrier and coating materials to convert into acceptable flowing and compressible powders. By applying the mathematical models the carrier and coating materials optimized. In this case the drug is almost solubilised in the solvent or molecularly dispersed state which contributes the enhanced drug dissolution.

Keywords: Liquisolid technique, poorly water soluble drugs, dissolution rate enhancement, oral bioavailability

INTRODUCTION

Therapeutic effectiveness of a drug depends upon the bioavailability which is dependent on the solubility of drug molecules. Solubility is one of the important parameter to achieve desired concentration of drug in systemic circulation for pharmacological action. Poorly water soluble drugs will be inherently released at a slow rate owing to their limited solubility. The dissolution rate is often the rate determining step in the drug absorption. The challenge for poorly water soluble drugs is to enhance the rate of dissolution. This in turn subsequently improves absorption and bioavailability. Formulation methods targeted at dissolution enhancement of poorly soluble substances by various techniques have been employed to formulate oral drug delivery system that would enhance the dissolution profile and in turn, the absorption efficiency of water insoluble drug. Solid dispersion, micronisation, lyophilisation, use of complexing agents, solubilization by surfactants, solid solutions, inclusion of the drug solution or liquid drug into soft gelatin capsules are some of the methods which have been used to enhance dissolution characteristics of water insoluble drugs.

METHODS TO ENHANCE THE DISSOLUTION OF POORLY WATER SOLUBLE DRUGS

The effort to improve the dissolution and solubility of a poorly and practically water insoluble drugs remain one of the most challenging tasks in drug development. Several methods such as salt formation¹, solubilization², cosolvency³, complexation⁴ and particle size reduction⁵, steam-aided granulation⁶ have been introduced to increase dissolution rate and thereby oral absorption and bioavailability of such drugs. There are some practical limitations of the above mentioned techniques. Salt formation may increase hygroscopicity leading to stability problems⁷. Palatability is also needs to be addressed for salts of strong acids and bases. Drugs dissolved using cosolvents may precipitate on dilution. Solubilization of drugs in organic solvents or in aqueous media by the use of surfactants and cosolvents leads to liquid formulations that are usually undesirable from patient acceptability and

commercialization. By particle size reduction the resultant fine particles may not produce expected faster dissolution and absorption. This primarily results from the possible aggregation and agglomeration of the fine particles due to their increased surface energy and subsequent stronger vanderwaals attraction between nonpolar molecules⁸. In case of complexation, if the complexing agent is of high molecular size then, the size of dosage form may increase. If the ratio of drug and complexing agent increase there is a chance of toxicity. The release of drug from complexing agent is also sometimes a problem. In case of miscellar solubilization if the concentration of surfactant is more it may have palatability problems and toxic effects. There is a chance for interactions between surfactant and preservatives⁹.

Solid dispersion has shown promising results in improving solubility, wettability, dissolution rate of drug, subsequently its bioavailability. However, only a few solid dispersion products are commercially available. This is due to their poor physical characteristics for dosage form formulation. Solid dispersions prepared using water soluble carrier such as PEG and PVP are soft and tacky mass, which is difficult to handle especially in capsule filling and tablet making process. Solid dispersions prepared by melting technique may give rise to stability problems. Similarly use of large quantity of organic solvent in preparation of solid dispersion may pose environmental and safety concerns. The liquisolid technique was hence introduced in order to overcome these problems.

“Liquisolid technology” or “Powdered solution technology” is one of the most promising and more recent techniques which promotes dissolution rate of poorly water soluble drugs. Powdered solutions are designed to formulate liquid medications in powdered form. The concept of powdered solutions enables one to convert a liquid drug or poorly water-soluble solid drug dissolved in a suitable non-volatile solvent into a dry, non-adherent, free flowing and readily compressible powder by its simple admixture with selected carrier and coating materials. In spite of formulating the drug

in a tableted or an encapsulated dosage form, it is held in solution thus enhancing its release¹⁰.

ADVANTAGES OF LIQUISOLID COMPACT

- A great number of slightly and very slightly water-soluble and practically water-insoluble liquid and solid drugs such as Digitoxin, Prednisolone¹¹ and Hydrocortisone¹² etc. can be formulated into lquisolid systems using the new formulation-mathematical model.
- Better availability of an orally administered water-insoluble drug is achieved when the drug is in solution form.
- Though the drug is in a tableted or encapsulated dosage form it is held in a solubilized liquid state, which consequently contributes to increased drug wetting properties, thereby enhancing drug dissolution.
- Production cost of lquisolid systems is lower than that of soft gelatin capsules.
- Advantage of lquisolid systems, particularly for powdered liquid drugs, during dissolution of a lquisolid tablet, after the disintegration process is completed, the drug solution or liquid drug, carried on the suspended and thoroughly agitated primary particles, is dispersed throughout the volume of the dissolution medium; such a phenomenon does not extensively occur during the dissolution process of soft gelatin capsule preparations. Therefore, since more drug surface is exposed to the dissolving medium, lquisolid systems exhibit enhanced drug release.
- Optimized rapid-release lquisolid tablets or capsules of water-insoluble drugs exhibit enhanced in-vitro and in-vivo drug release as compared to their commercial counterparts.
- Optimized sustained-release lquisolid tablets or capsules of water-insoluble drugs exhibit surprisingly constant dissolution rates (zero-order release) comparable only to expensive commercial preparations that combine osmotic pump technology and laser-drilled tablets¹³.

DISADVANTAGES OF LIQUISOLID SYSTEM

- The lquisolid systems have low drug loading capacities and they require high solubility of drug in non-volatile liquid vehicles¹⁴.
- It requires more efficient excipients which have higher adsorption capacities which provide faster drug release with a smaller tablet size to improve lquisolid formulations¹⁵.
- To maintain acceptable flowability and compatibility for lquisolid powder formulation high levels of carrier and coating materials are require and that in turn will increases the weight of each tablet above 1 gm which is very difficult to swallow¹⁴.

LIMITATIONS

- Acceptable compression properties may not be achieved since during compression liquid drug may be squeezed out of the lquisolid tablet resulting in tablets of unsatisfactory hardness¹⁰.
- Introduction of this method on industrial scale and to overcome the problems of mixing small quantities of viscous liquid solutions onto large amounts of carrier material may not be feasible.
- Not applicable for formulation of high dose insoluble drugs¹⁶.

CLASSIFICATION OF LIQUISOLID SYSTEMS

Liquisolid compacts, on the other hand, are acceptably flowing and compressible powdered forms of liquid medications, and have industrial application. In addition, the term 'liquid medication' does not only imply drug solutions, as in powdered solutions, but also drug suspensions, emulsions, or liquid oily drugs.

A) Based on the formation of powdered drug in liquid vehicle these 'liquisolid compacts' are four different formulation systems namely

- Powdered drug solutions
- Powdered drug suspensions
- Powdered drug emulsions
- Powdered liquid drugs

Since the non volatile solvents are used to provide the drug solution or suspension, the liquid vehicle does not evaporate and thus, the drug is carried within the liquid system which in turn is dispersed throughout the final product¹⁷.

B) Based on the formulation technique used, liquisolid systems may be classified into two categories which include

- Liquisolid compacts
- Liquisolid microsystems.

The term "liquisolid compacts" refers to immediate or sustained release tablets or capsules prepared, combined with the inclusion of appropriate adjuvant required for tableting or encapsulation, such as lubricants, and for rapid or sustained release action, such as disintegrants or binders, respectively.

The term "liquisolid Microsystems" refers to capsules prepared by combining the drug with carrier and coating materials, combined with inclusion of an additive e.g., PVP in the liquid medication wherein the resulting unit size may be as much as five times that of liquisolid compacts¹⁰.

DEFINITIONS

- Liquid medication includes liquid lipophilic drugs and drug suspensions or solutions of solid water insoluble drugs in suitable non-volatile solvent systems.
- Carrier material refers to a preferably porous material possessing sufficient absorption properties, such as microcrystalline and amorphous cellulose, which contributes in liquid absorption¹⁰.
- Liquisolid systems 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, non-adherent, free-flowing and readily compressible powder admixtures by blending with selected carrier and coating materials.
- 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 liquid¹⁶.

NEED OF LIQUISOLID SYSTEM

The oral route remains the preferred route of drug administration due to its convenience, good patient compliance and low medicine production costs. In order for a drug to be absorbed into the systemic circulation following oral administration, the drug must be dissolved in the gastric fluids. Thus, one of the major challenges to drug development today is poor solubility, as an estimated 37% of all newly developed drugs are poorly soluble or insoluble in

water. In addition, up to 47% of orally administered drug compounds suffer from formulation problems related to their low solubility and high lipophilicity⁸⁻⁹. Bioavailability of poorly water soluble hydrophobic drugs (class II in biopharmaceutics classification system) is limited by their solubility and dissolution rate. The dissolution rate of these drugs can be improved by decreasing particle size, decreasing crystallinity, and/or increasing the surface area. Several studies have been carried out to increase the dissolution rate of drugs by decreasing the particle size, by creating nanoparticles and microparticles¹⁷.

However, the fine drug particles have high tendency to agglomerate due to van der Waals attraction or hydrophobicity, which both result in a decrease in surface area over time. Another way of increasing the dissolution rate is adsorption of the drug onto a high-surface area carrier. In this technique, the drug is dissolved in an organic solvent followed by soaking of the solution by a high-surface-area carrier such as silica. Here, agglomeration of the drug particles is prevented due to the binding of drug to the carrier. However, due to the presence of the residual solvent in the drug formulation, it is disadvantageous to use toxic solvents¹⁸⁻¹⁹.

To overcome the problem, the technique of 'liquisolid compacts' is a new and promising approach towards dissolution enhancement. Liquisolid compacts possess acceptable flowability and compressibility properties. They are prepared by simple blending with selected powder excipients referred to as the carriers and the coating materials. Many grades of cellulose, starch, lactose, etc. can be used as carriers, where as silicas of very fine particle size can be used as coating materials. In such systems, the drug existed in a molecular state of subdivision and systems were free flowing, on-adherent, dry looking powders²⁰⁻²¹. This technique was successfully applied for low dose water-insoluble drugs. Due to significantly increased wetting properties and surface area of drug available for dissolution, liquisolid compacts of water insoluble substances may be expected to display enhanced drug release characteristics and, consequently, improved oral bioavailability. Since dissolution of a non polar drug is often the rate limiting step in gastrointestinal absorption, better bioavailability of an orally administered water-insoluble drug is achieved when the drug is already in solution, thereby displaying enhanced dissolution rates. The technique of liquisolid compacts has been successfully employed to improve the in vitro release of poorly water soluble drugs such as Prednisolone¹¹, Hydrocortisone¹², Carbamazepine¹⁴, Piroxicam²⁰, Indomethacin²¹, Famotidine²² and Naproxen²³.

MECHANISMS OF ENHANCED DRUG RELEASE FROM LIQUISOLID SYSTEMS

Several mechanisms of enhanced drug release have been postulated 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 measurements²⁴.

a. Increased drug surface area

If 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.

Therefore, the surface area of drug available for release is much greater than that of drug particles within directly compressed tablets²⁵.

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 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 cosolvent²⁵.

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. Wettability of these systems has been demonstrated by measurement of contact angles and water rising times²⁶.

COMPONENTS

The major components of liquisolid compacts include Drug, Non volatile solvent, Carrier materials, Coating materials, Disintegrants and Lubricants.

Drug

The drug must be poorly water soluble and having biopharmaceutical classification system II and IV.

Non volatile solvent

It should be inert, high boiling point, preferably water-miscible and less viscous organic solvent systems. Examples include propylene glycol, liquid polyethylene glycols, polysorbates, glycerin, N, N-dimethyl acetamide, fixed oils, PEG 560 and 370, Tween80 and 19, Span80 and 19, Glycerin.

Carrier material

It should be of materials with porous surface, closely matted fibers in their interior, sufficient absorption properties and high surface area. Examples includes microcrystalline and amorphous cellulose, Starch, Lactose, MCC (Avicel PH 102), DCP (dibasic calcium phosphate), Eudragit RL and RS

Coating materials

Fine and highly adsorptive particles contributes in covering the wet carrier particles and displaying a dry-looking powder. Particle size range of about 10 nm to 4560 nm in diameter. Examples includes amorphous silicon dioxide (silica 2), silica (Cab-O-Sil M5), Syloid.

Disintegrants

Most commonly used Sodium starch glycolate, Cross carmellose sodium, Cross povidone, Explotab, Pregelatinized Starch etc.

OPTIMIZATION OF LIQUISOLID FORMULATIONS

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 (FM) in the liquid formulation a higher drug dose requires higher liquid amounts for a desired release profile. Moreover, to obtain liquisolid systems with acceptable flowability and compatibility 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 shown in Table 1²⁷⁻²⁸.

PREPARATION OF LIQUISOLID COMPACTS

The technology involved in preparation of liquisolid compacts is simple but novel. Drug is dissolved in non-volatile solvent to form a solution or a suspension. It is absorbed onto a suitable carrier material. The wet particles are formed and converted into dry particles by the addition of coating material. The liquisolid systems are made into compacts by the addition of other tablet 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 as shown in Fig 1 and Fig 2¹⁶.

LIQUISOLID SYSTEM FOR CONTROLLED DRUG DELIVERY

Development of sustained release oral dosage forms is beneficial for optimal therapy in terms of efficacy, safety and patient compliance. There are several techniques for preparation of sustained release formulations, among which control of drug dissolution is one of the best and most successful methods due to its viability. Several methods have been developed to this end or to achieve this aim. It is suggested that liquisolid technique has the potential to be optimized for the reduction of drug dissolution rate and thereby production of sustained release systems. If hydrophobic carriers such as Eudragit RL and RS are used instead of hydrophilic carriers in liquisolid systems, sustained release systems can be obtained¹⁹.

The mechanism of release prolongation is likely to be a more efficient encapsulation of drug particles by the hydrophobic polymers. The presence of nonvolatile solvent reduces the glass transition temperature (T_g) of polymers and imparts flexibility. Therefore, reduction of T_g of the polymer might be the reason for the release prolongation of liquisolid tablets. In the temperature above the T_g , a better coalescence of the polymer particles occurs that forms a fine network and a matrix with lower porosity and higher tortuosity. In this way, the drug is surrounded and entangled by the polymer network, resulting in the restricted leaching of the drug thus, sustaining the release of drug from liquisolid matrices²⁹.

APPLICATION OF MATHEMATICAL MODEL FOR DESIGNING LIQUISOLID SYSTEMS

The flowability and compressibility of liquisolid compacts are addressed simultaneously in the 'new formulation mathematical model of liquisolid systems', which was used to calculate the appropriate quantities of the carrier and coating materials required to produce acceptably flowing and compressible powders based on new fundamental powder properties called the flowable liquid retention potential (Φ - value) and compressible liquid retention potential (Ψ - number) of the constituent powders¹⁰. The flowable liquid retention potential of a powder is defined as the maximum amount of a given non-volatile liquid that can be retained inside its bulk (w/w) while maintaining acceptable flowability¹⁷.

The compressible liquid retention potential (Ψ) of a powder is the maximum amount of liquid, the powder can retain inside its bulk (w/w) while maintaining acceptable compactability, to produce compacts of suitable hardness and

friability, with no liquid squeezing out phenomenon during the compression process. The Φ value of powders may be determined using a new procedure, the liquisolid flowability (LSF) test. The Ψ number of powders may be determined using a new method termed the liquisolid compressibility (LSC) test which employs the 'pactisity theories' to evaluate the compaction properties of liquid/ powder admixtures¹⁰. According to the new theories, the carrier and coating powder materials can retain only certain amounts of liquid while maintaining acceptable flow and compression properties. Depending on the excipients ratio (R) or the carrier: coating ratio of the powder system used,

Where,

$$R = Q/q \dots\dots\dots (1)$$

As R represents the ratio between the weights of carrier (Q) and coating (q) materials present in the formulation. An acceptably flowing and compressible liquisolid system can be prepared only if a maximum liquid on the carrier material is not exceeded; such a characteristic amount of liquid is termed the liquid load factor (Lf) and defined as the ratio of the weight of liquid medication (W) over the weight of the carrier powder (Q) in the system, which should be possessed by an acceptably flowing and compressible liquisolid system. i.e.

$$Lf = W/Q \dots\dots\dots (2)$$

The powder excipients ratios R and liquid load factors

Lf of the formulations is related as follows:

$$\Phi Lf = \Phi + \Phi (1/R) \dots\dots\dots (3)$$

In order to calculate the required ingredient quantities, the flowable liquid retention potentials (Φ -values) of powder excipients were utilized. So to calculate the required weights of the excipients used, first, from Eq. (3), Φ and Φ and are constants, therefore, according to the ratio of the carrier/ coat materials (R), Lf was calculated from the linear relationship of Lf versus $1/R$. Next, according to the used liquid vehicle concentration, different weights of the liquid drug solution (W) will be used. So, by knowing both Lf and W, the appropriate quantities of carrier (Q) and coating (q) powder materials required to convert a given amount of liquid medication (W) into an acceptably flowing and compressible liquisolid system could be calculated from equations (1) and (2).

EVALUATION OF LIQUISOLID COMPACTS

Flow behavior

Flow properties are the important concern in the formulation and industrial production of tablet dosage form. Angle of repose is characteristic to the flow rate of powder³⁰. Flow properties of the drug and prepared melt granules were studied by determining the bulk density (s_b), tap density (s_t), Carr's Index and Hausner ratio. A weighed quantity of samples was taken to determine the bulk and tap density. The parameters selected to study flow properties were determined using following equations³¹.

$$\text{Bulk density } (s_b) = \text{Mass} / \text{Poured volume} \dots\dots\dots 1$$

$$\text{Tap density } (s_t) = \text{Mass} / \text{Tapped volume} \dots\dots\dots 2$$

$$\text{Carr's Index} = [(s_t - s_b) / s_t] \times 100 \dots\dots\dots 3$$

$$\text{Hausner ratio} = (s_t / s_b) \dots\dots\dots 4$$

Angle of repose (Fixed funnel and free standing cone method): A funnel with the end of the stem cut perpendicular to the axis of symmetry is secured with its tip 2.5 cm height (h) above graph paper placed on a flat horizontal surface. The powder sample to be analyzed is carefully poured through the funnel until the apex of the conical pile so formed just

reached the tip of the funnel (h). The mean diameter (d) of the powder cone is determined and the tangent of the angle of repose is given by the equation:

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

$$\theta = \tan^{-1} (h/r),$$

$$\tan \theta = h/0.5d, (5)$$

Where

θ = Angle of repose,

h = height of the tip of funnel from horizontal plane,

r = radius of the pile made by powder,

d = diameter of cone.

Values for angle of repose = 29° usually indicate free flowing material and angle = 37° suggested a poor flowing material.

Solubility studies

Solubility studies are carried out by preparing saturated solutions of drug by adding excess of drug to non volatile solvent and shaking them for 24 hrs on orbital shaker under constant shaking. After this, the solutions are filtered and analyzed spectrophotometrically.

Dissolution studies of lquisolid tablet

Generally Dissolution studies of Lquisolid tablet are carried out using dissolution apparatus USP II at $36^\circ\text{C} \pm 0.5^\circ\text{C}$. Many researchers revealed that at low drug concentrations in liquid medication, more rapid release rates are observed. The consistent and higher dissolution rate displayed by lquisolid compacts will improve the absorption of drug from gastrointestinal tract.

CHARACTERIZATION OF LIQUISOLIDS

Differential Scanning Calorimetry (DSC)

Thermal properties of the untreated drug and prepared samples are analyzed by DSC. It is necessary to determine any possible interaction between excipients used in the formulation. This will also indicate success of stability studies. If the characteristic peak for the drug is absent in the DSC thermogram, there is an indication that the drug is in the form of solution in lquisolid formulation and hence it is molecularly dispersed within the system³⁶.

Fourier Transform Infrared spectroscopy (FTIR)

FTIR studies are performed to determine the chemical interaction between the drug and excipients used in the formulation. The presence of drug peaks in the formulation and absence of extra peaks indicates there is no chemical interaction.

Powder X-ray diffraction (PXRD)

Generally, disappearance of characteristic peaks of drug in the lquisolid formulation and retaining peaks of carrier material is observed³². This indicates that drug gets converted to amorphous form or to solubilized form in the lquisolid formulation.

STABILITY STUDIES

To obtain information on the stability of lquisolid systems, the effects of storage on the release profile and the crushing strength of lquisolid compacts were investigated. Stability studies of lquisolid systems containing polythiazide ($37^\circ\text{C}/38$ and 75% R.H., 12 weeks)³³, hydrocortisone (ambient conditions, 10 months)¹⁰, carbamazepine ($24^\circ\text{C}/75\%$ R.H., 6 months)³⁴, indomethacin ($24^\circ\text{C}/75\%$ R.H., 12 months)³⁵, piroxicam ($24^\circ\text{C}/75\%$ R.H., 6 and 9 months, respectively)³⁶⁻³⁷, or naproxen ($19^\circ\text{C}/76\%$ R.H., 4 weeks)³⁹ showed that storage at different conditions neither had an effect on the hardness nor on the release profiles of lquisolid compacts. This indicates that the technology is a promising technique to

enhance the release rate without having any physical stability issues.

IN-VIVO STUDIES

The lquisolid technology is a promising approach for the enhancement of drug release of poorly soluble drugs. However, the improved bioavailability to be expected from lquisolid systems has not been investigated in detail. Khaled *et al.*, studied the absorption characteristics of hydrochlorothiazide lquisolid compacts in comparison with commercial tablets in beagle dogs³⁸. Significant differences in the area under the plasma concentration-time curve, the peak plasma concentration, and the absolute bioavailability of the lquisolid 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 lquisolid compacts was 14 % higher than that from the commercial formulation. Fahmy *et al.* investigated the in vitro and in vivo performance of famotidine lquisolid compacts in comparison with directly compressed tablets and commercial famotidine tablets, respectively⁴¹. The dissolution rate of famotidine in 0.1 N HCl was shown to be enhanced with the lquisolid compacts compared to directly compressed tablets.

The in-vivo evaluation of famotidine lquisolid compacts was compared to that of commercial famotidine tablets using six healthy male volunteers aged between 19 and 37. It was found that there were no significant differences between the mean peak plasma concentrations ($c_{\max}$), the mean times of peak plasma concentrations ($t_{\max}$), or the mean area under the plasma concentration-time curve (AUC). Unfortunately, the in vivo evaluation of the directly compressed tablets was not determined in this study and thus, an improved bioavailability of lquisolid compacts compared to directly compressed tablets could not be shown. Tayel *et al.*, measured drug release of the poorly soluble antiepileptic drug carbamazepine from lquisolid compacts and commercial tablets³⁹. It was observed that drug release from lquisolid compacts and that from commercial tablets is comparable. Furthermore, an oral dose of carbamazepine administered to mice led to lquisolid technology⁴⁰ less protection against an electroshock-induced convulsion with lquisolid compacts compared to the commercial product. This lower pharmacological activity of lquisolid compacts is probably due to the high drug concentration in the liquid vehicle and thus a precipitation of carbamazepine in the silica pores. El-Houssieny *et al.* investigated the bioavailability and biological activity (glucose tolerance in rabbits) of repaglinide formulated as lquisolid compacts and commercial tablets, respectively⁴¹. It was found that the relative bioavailability of repaglinide from the lquisolid compacts was significantly higher than that from the commercial tablets. The increase in insulin blood level was more pronounced with the lquisolid compacts than with the commercial tablets indicating a higher bioavailability from the lquisolid compacts. Moreover, lquisolid compacts of repaglinide decreased blood glucose levels significantly more than the commercial tablets. Studies carried out using lquisolid technique were mentioned in the Table 2.

CONCLUSION

Nowadays, new chemical entities often possess a high molecular weight and a high lipophilicity. Especially poorly soluble and highly permeable active pharmaceutical

ingredients represent a technological challenge, as their poor bioavailability is solely caused by poor water solubility, which may result in low drug absorption. Numerous methods have been described to improve water solubility and drug release, respectively, 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. Moreover, the addition of disintegrants may further accelerate drug release from liquisolid compacts. 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.

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Table 1: Optimization of liquisolid formulations²⁷⁻²⁸

Formulation parameter	Optimization	Effect
liquid vehicle	high drug solubility in the vehicle	increased fraction of the molecularly dispersed drug (FM)
carrier and coating materials	high specific surface area	increased liquid load factor (Lf)
addition of excipients	Polyvinyl pyrrolidone (PVP)	increased liquid load factor (Lf), increased viscosity of liquid vehicle, inhibition of precipitation
excipient ratio (R)	high R-value	fast disintegration, inhibition of precipitation

Table 2: Studies carried out on liquisolid technique

Drug	Liquid vehicle	Carrier & Coating material	References
Gemfibrozil	Tween80	Avicel PH 190 & Cab-o-sil M5	S.Spireas ¹⁰
Nifedipine	PEG 370	Avicel PH 190 & Cab-o-sil M5	S.Spireas ¹⁰
Prednisolone	PG	MCC & Colloidal Silica	Spireas S, Sadu S ¹¹
Prednisolone	Propylene glycol	Avicel PH101, lactose & Cab-o-sil	Spireas S, Sadu S and Grover R ¹²
Hydrocortisone	PG	MCC & Colloidal Silica	Spireas S, Sadu S and Grover R ¹²
Piroxicam	Polysorbate 80	MCC & Colloidal Silica	Javadzadeh Y, Siahi MR, Barzegar Jalali M and Nokhodchi A ²⁰
Indomethacin	PG	MCC & Colloidal Silica	Nokhodchi A, Javadzadeh Y, Siahi MR and Barzegar-Jalali.M ²¹
Indomethacin	PEG 370	MCC & HPMC	Nokhodchi A, Javadzadeh Y, Siahi MR and Barzegar-Jalali.M ²¹
Prednisolone	N,N-dimethylacetamide/PEG370 (7:3 v/v)	Various Silicas	Spireas S, Sadu S ²⁵
Aceclofenac	PEG 370	MCC & HPMC	Yadav VB, Nighute AB, Yadav AV, Bhise SB ²⁶
Polythiazide	PEG 370	MCC & Colloidal Silica	Sheth A, Jarowski CI ³³
Hydrochlorothiazide	PEG 190	MCC, Magnesium carbonate & Colloidal Silica	Khaled KA, Asiri YA, El-Sayed YM ³⁸
Carbamazepine	PEG 190	MCC & Colloidal Silica	Tayel SA, Soliman II, Louis ³⁹
Naproxen	Cremophor® EL	MCC & Colloidal Silica	Tiong, N, Elkordy ³⁹
Fenofibrate	PEG 370	MCC & Colloidal Silica	Karmarkar AB, Gonjari ID, Hosmani AH, Dhabale PN, Bhise SB ⁴⁰
Fenofibrate	PG	MCC & Colloidal Silica	Karmarkar AB, Gonjari ID, Hosmani AH, Dhabale PN, Bhise SB ⁴⁰
Famotidine	PG	MCC & Colloidal Silica	Fahmy RH, Kassem MA ⁴¹
Furosemide	Synperonic® PE/L 81	MCC & Colloidal Silica	Akinlade B, Elkordy AA, Essa EA, Elhagar S ⁴²
Indomethacin	PEG 370	MCC & HPMC	Azarmi S, Farid J, Nokhodchi A, Bahari-Saravi SM, Valizadeh H ⁴³
Glibenclamide	PEG 370	MCC & Colloidal Silica	Darwish, IAE, El-Kamel AH ⁴⁴
Ibuprofen	PEG 290	MCC & Colloidal Silica	Hentzschel CM, Alnaief M, Smirnova I, Sakmann A, Leopold CS ⁴⁶
Lamotrigine	PEG 370	MCC & Colloidal Silica	Yadav VB, Yadav AV ⁴⁷
Methyclothiazide	PEG 370	MCC & Colloidal Silica	Spireas S, Wang T, Grover R ⁴⁸
Repaglinide	Polysorbate 80	MCC & Calcium Silicate	Sheth A, Jarowski CI ⁴⁹
Prednisone	PG	MCC & Colloidal Silica	Liao CC, Jarowski CI ⁵⁰
Glibenclamide	PEG 370	Avicel PH 190 & aerocil	Darwish, I.A.E, El-Kameel ⁵¹
Indomethacin	Propylene glycol	MCC & Silica	Ali Nokhodchi, Y Javadzadeh, Mohammad Reza Siahi-Shadbad ⁵²
Indomethacin	2-Pyrrolidone	Kollidon CLM & Aerosil 290	Ali Nokhodchi, Y.Javadzadeh, Mohammad Reza Siahi-Shadbad ⁵²
Methyclothiazide	PEG 370	MCC & Silica	S Spireas, T Wang, R Grover ⁵³
Piroxicam	Tween 80	MCC & Silica	Y Javadzadeh ⁵⁴

Griseofulvin	PEG 370	MCC & Colloidal Silica	Spiro Spireas, S.Sadu and Rakesh Grover ⁵⁵
Hydrocortisone	Propylene glycol	Avicel PH190 & Cab-o-sil	Spiro Spireas, S Sadu and Rakesh Grover ⁵⁵
Hydrochlorthiazide	PEG 190	Avicel PH101/102 & Aerosil	KA Khaled, YA Asiri, YMEI-Sayed ⁵⁶
Famotidine	PG	MCC & Colloidal Silica	KA.Khaled, Y.A.Asiri, YMEI-Sayed ⁵⁶

Fig. 1: Schematic representation of liquisolid systems

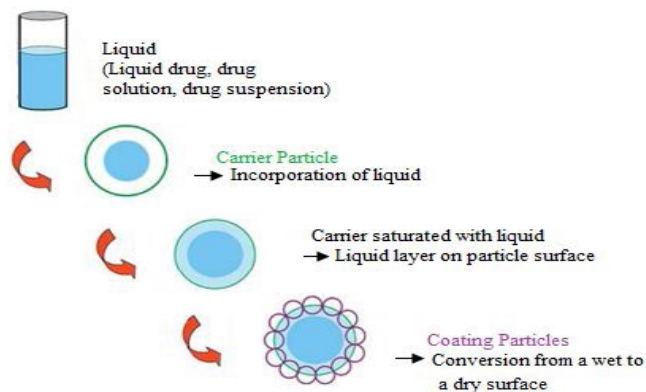


Fig2: Steps involved in preparation of liquisolid compacts

