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LIQUISOLID Compacts: A Novel Approach to Enhance Bioavailability of Poorly Soluble Drugs

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Review Article

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ABSTRACT

At present 40% of the drugs in the development pipelines, and approximately 60 % of the drugs coming directly from synthesis are poorly soluble. The limited solubility of drugs is a challenging issue for industry, during the development of the ideal solid dosage form unit. Liquisolid technique is a novel and promising approach to overcome this consequence. The technique is based upon the dissolving the insoluble drug in the nonvolatile solvent and admixture of drug loaded solutions with appropriate carrier and coating materials to convert into acceptably flowing and compressible powders. The selection of non toxic hydrophilic solvent, carrier, coating materials and its ratios are independent of the individual chemical moieties. 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.

KEYWORDS: Poorly soluble drugs, coating material, carrier, hydrophilic solvent, liquisolid compacts

Introduction

Nowadays, the synthesis of poorly soluble drugs increasing steadily. Therapeutic effectiveness of a drug depends upon the bioavailability which is dependent on the solubility and dissolution rate of drug molecules. Solubility is one of the important parameter to achieve desired concentration of drug in systemic circulation for pharmacological response to be shown. The drugs which are poorly water soluble will be inherently released at a slow rate owing to their limited solubility within the GI contents. The dissolution rate is often the rate determining step in the drug absorption. The challenge for these drugs is to enhance the rate of dissolution or solubility. This in turn subsequently improves absorption and bioavailability. Formulation methods targeted at dissolution enhancement of poorly soluble substances are continuously introduced[1].

Drug substances are considered highly soluble when the largest dose of compound is soluble in < 250ml of water over a range of pH from 1.0 to 7.5. In contrast, compounds with solubilities below 0.1mg/mL face significant solubilization obstacles, and often even compounds with solubilities below 10mg/mL present difficulties related to solubilization during formulation. The Biopharmaceutical Classification System (BCS) groups poorly soluble compounds as Class II, compounds which feature poor solubility, high permeability and Class IV, compounds which feature poor

solubility and poor permeability respectively. Aqueous solubility of a drug can be a critical limitation to its oral absorption. Lipophilic molecules, especially those belonging to the biopharmaceutical classification system (BCS) class II and IV, dissolve slowly, poorly and irregularly, and hence pose serious delivery challenges, like incomplete release from the dosage form, poor bioavailability, increased food effect, and high inter-patient variability[2].

Release enhancement of poorly soluble drugs may be achieved by an increase of the drug surface area, the drug solubility, or by formulating the drug in its dissolved state. 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 such as micronization, adsorption onto high surface area carriers, lyophilization, co-grinding, formulation of inclusion complexes, solubilization by surfactants, solid dispersions, solid solutions, hydrotrophy, inclusion of the drug solution or liquid drug into soft gelatin capsules, and co solvency.[3-5] The most common method is to increase the drug surface area; there by dissolution rate is by micronization. But, in practice, the effect of micronization is often disappointing, because it alters the drug flow property, especially when the drugs are encapsulated or tableted[6-7].

Adsorption of poorly soluble drugs on hydrophilic silica aerogels was found to enhance drug dissolution[8]. This can be explained by both an increase in the specific surface area of the drug adsorbed to the aerogel and an at least partial amorphisation of the drug. However, drug adsorption is dependent on the selected drug and sometimes only low drug loads are achieved. Another disadvantage of this technique is the complex manufacturing process: Silica aerogels are loaded with drugs by adsorption from their solutions in supercritical carbon dioxide[9-10]

Co-grinding of poorly soluble drugs with different excipients may also result in an amorphisation of the drug and thus improved dissolution characteristics[11]. Crospovidone[12, 13], polyvinylpyrrolidone[13], and different types of silica[14, 15] are suitable for that purpose. Co-grinding is another straight forward procedure to achieve drug release enhancement. Complexes of a lipophilic drug with cyclodextrin, commonly known as inclusion complexes, can be easily formulated by mixing the drug with the carrier[16]. The most commonly used carrier β-cyclodextrin acts as a solubilizer and stabilizer consisting of a truncated cone type structure with an outer hydrophilic and an inner hydrophobic surface. However, the maximum possible drug load of these systems is relatively low and the inclusion complexation only works with drugs that fit into the cavities of the cyclodextrin molecule[17-20].

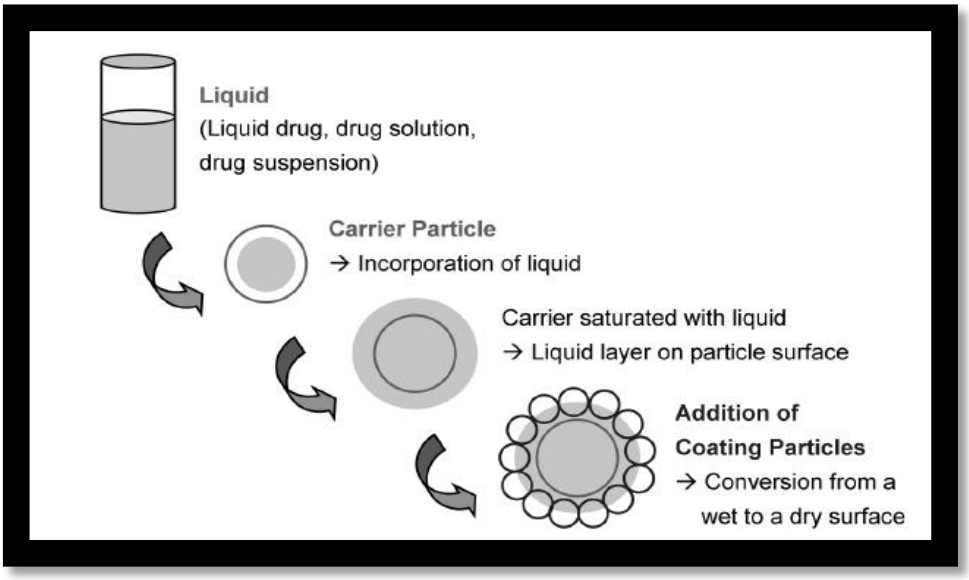
Solid dispersions consist of one or more active ingredients dispersed in a readily soluble solid hydrophilic matrix prepared by a melting (fusion) or solvent method[21]. With the melting method the drug is added to the molten carrier and the mixture is stirred until a homogenous melt is obtained. With 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[22-27].

The most promising and new technique for promoting dissolution is the formation of liquisolid tablets among the various novel techniques. Liquisolid compacts promotes dissolution rate of water insoluble drugs to a greater extent and also enhances the drug flow property[2-4].

PRINCIPLE OF LIQUISOLID COMPACTS:

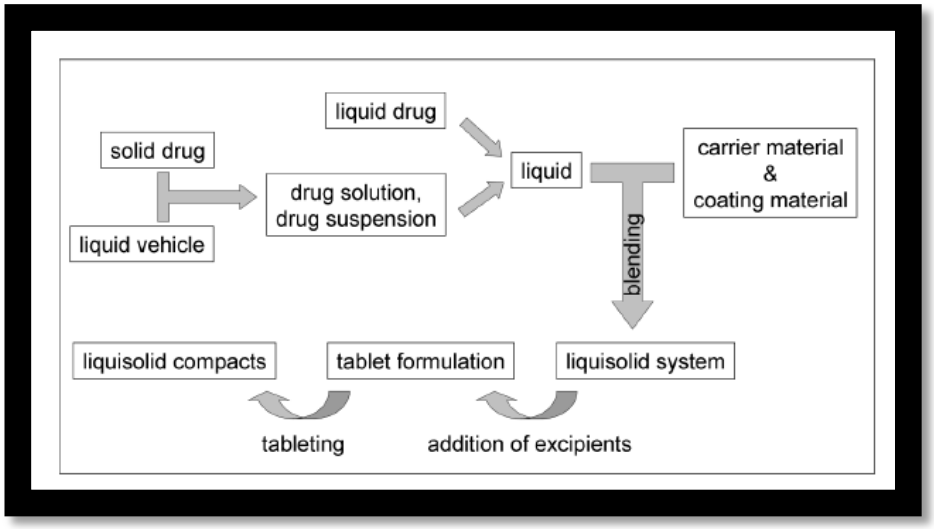
With the liquisolid technology, a liquid may be transformed into a free flowing, readily compressible and apparently dry powder by simple physical blending with selected excipients named the carrier and coating material. The liquid portion, which can be a liquid drug, a drug suspension or a drug solution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

Fig 1: Schematic representation of liquisolid 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. Various excipients such as lubricants and disintegrants 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



Liquisolid compacts of poorly soluble drugs containing a drug solution or drug suspension in a solubilising vehicle show enhanced drug release due to an increased surface area of drug available for release, an increased aqueous solubility of the drug, and an improved wettability of the drug particles[33-38]. Accordingly, this improved drug release may result in a higher drug absorption in the gastrointestinal tract and thus, an improved oral bioavailability[39, 40].

THEORY OF LIQUISOLID 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 liquisolid systems has been developed by Spireas[41, 42]. 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[43]. The compactability may be determined by the so-called "pactisity" 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:

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

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:

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

Where Φ and ϕ are the Φ-values of the carrier and coating material, respectively. Similarly, the liquid load factor for production of liquisolid 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. In **Table 1** examples of liquisolid formulation parameters of various powder excipients with commonly used liquid vehicles are listed.

Table 1: Liquisolid formulation parameters of various powder excipients with commonly used liquid vehicles

Powder excipient or syste	Φ-values		Ψ-numbers	
	Propylene glycol	PEG 400	Propylene glycol	PEG 400
Avicel PH 102	0.16	0.005	0.224	0.242
Avicel PH 200	0.26	0.02	0.209	0.232
Cab-O-Sil M5 (silica)* with Avicel PH 102	3.31	3.26	0.560	0.653
Cab-O-Sil M5 (silica)* with Avicel PH 200	2.57	2.44	0.712	0.717

***included as coating material in carrier/coating powder systems**

Therefore, the optimum liquid load factor (L_o) required to obtain acceptably flowing and compressible liquisolid systems are equal to either *ΦLf* or ΨL_f, whichever represents the lower value.

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

$$\mathbf{Q_0 = W/L_o} \text{-----(5) } \mathbf{And\ q_0 = Q_0/R} \text{-------(6)}$$

The validity and applicability of the above mentioned principles have been tested and verified by producing liquisolid compacts possessing acceptable flow and compaction properties[41].

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 measurements[34].

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 tablets[42].

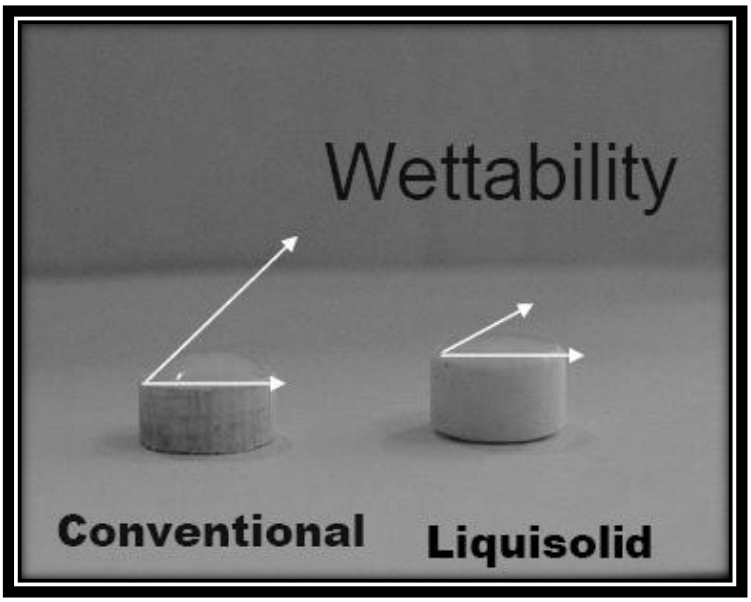
b. Increased aqueous solubility of the drug

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[42].

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 (fig 3). Wettability of these systems has been demonstrated by measurement of contact angles and water rising times[44].

Fig 3: Comparison of wettability between conventional tablet and liquisolid compacts.



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 2**).

Table 2: Formulations of liquisolid systems with enhanced drug release

Drug	Liquid vehicle	Carrier & Coating material
Aceclofenac	PEG 400	**MCC & HPMC**
Bromhexine HCl	PG	**MCC & Colloidal Silica**
Carbamazepine	PEG 200	**MCC & Colloidal Silica**
Clofibrate (liquid)	--	**MCC & Colloidal Silica**
Famotidine	PG	**MCC & Colloidal Silica**
Fenofibrate	PEG 400	**MCC & Colloidal Silica**
Fenofibrate	PG	**MCC & Colloidal Silica**
Furosemide	Synperonic® PE/L 81	**MCC & Colloidal Silica**
Glibenclamide	PEG 400	**MCC & Colloidal Silica**
Griseofulvin	PEG 400	**MCC & Colloidal Silica**
Hydrochlorothiazide	PEG 200	**MCC + Magnesium carbonate & Colloidal Silica**
Hydrocortisone	PG	**MCC & Colloidal Silica**
Ibuprofen	PEG 300	**MCC & Colloidal Silica**
Indomethacin	PG	**MCC & Colloidal Silica**
Indomethacin	PEG 400	**MCC & HPMC**
Lamotrigin	PEG 400	**MCC & Colloidal Silica**
Methyclothiazide	PEG 400	**MCC & Colloidal Silica**
Naproxen	Cremophor® EL	**MCC & Colloidal Silica**
Piroxicam	Polysorbate 80	**MCC & Colloidal Silica**
Polythiazide	PEG 400	**MCC & Colloidal Silica**
Prednisolone	PG	**MCC & Colloidal Silica**
Prednisolone	N,N- dimethylacetamide/PEG400 (7:3 v/v)	**Various Silicas***
Prednisone	PG	**MCC & Colloidal Silica**

Repaglinide	Polysorbate 80	MCC & Calcium silicate

***: drug solution dispersed on various silicas (no compacts)**

PEG: polyethylene glycol; PG: propylene glycol;Synperonic® PE/L 81: polyoxyethylene-polyoxypropylene block copolymer

Cremophor® EL: polyoxyl 35 castor oil;MCC: microcrystalline cellulose;HPMC: hydroxypropyl methylcellulose

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 (*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 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[1-10] (**Table 3**).

Table 3: 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 molecularly dispersed drug (*FM*)
carrier and coating materials	high specific surface area	increased liquid load factor *Lf*)
addition of excipients	Polyvinylpyrrolidone (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

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) [32], hydrocortisone (ambient conditions, 10 months) [1], carbamazepine (25

°C/ 75 % R.H., 6 months)[45], indomethacin (25 °C/ 75 % R.H., 12 months)[12], piroxicam (25 °C/ 75 % R.H., 6 and 9 months, respectively)[34], or naproxen (20 °C/ 76 % R.H., 4 weeks)[48] 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.

IN VIVO EVALUATION OF IMMEDIATE RELEASE LIQUISOLID SYSTEMS

The liquisolid technology is a promising approach for the enhancement of drug release of poorly soluble drugs. The absorption characteristics of hydrochlorothiazide liquisolid compacts in comparison with commercial tablets were studies in beagle dogs[40]. 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.

The in vitro and in vivo performance of famotidine liquisolid compacts were investigated in comparison with directly compressed tablets and commercial famotidine tablets, respectively[46]. The dissolution rate of famotidine in 0.1 N HCl was shown to be enhanced with the liquisolid compacts compared to directly compressed tablets. The in vivo evaluation of famotidine liquisolid compacts was compared to that of commercial famotidine tablets using six healthy male volunteers aged between 20 and 40. It was found that there were no significant differences between the mean peak plasma concentrations (cmax), the mean times of peak plasma concentrations (tmax), 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 liquisolid compacts compared to directly compressed tablets could not be shown.

The poorly soluble antiepileptic drug carbamazepine drug release was measured from liquisolid compacts and commercial tablets[47]. It was observed that drug release from liquisolid compacts and that from commercial tablets is comparable. Furthermore, an oral dose of carbamazepine administered to mice led to less protection against an electroshock-induced convulsion with liquisolid compacts compared to the commercial product. This lower pharmacological activity of liquisolid compacts is probably due to the high drug concentration in the liquid vehicle and thus a precipitation of carbamazepine in the silica pores.

The bioavailability and biological activity (glucose tolerance in rabbits) of repaglinide formulated as liquisolid compacts and commercial tablets were investigated respectively[39]. It was found that the relative bioavailability of repaglinide from the liquisolid compacts was significantly higher than that from the commercial tablets. The increase in insulin blood level was more pronounced with the liquisolid compacts than with the commercial tablets indicating a higher bioavailability from the liquisolid compacts. Moreover, liquisolid compacts of repaglinide decreased blood glucose levels significantly more than the commercial tablets. These partially contrary results of bioavailability of liquisolid formulations show that still more in vivo data is needed to confirm the superiority of liquisolid compacts. The varying bioavailability of the above mentioned liquisolid formulations may be explained by a

different percentage of dissolved drugs in the liquid vehicle.

ADVANTAGES OF LIQUISOLID SYSTEMS[1-5]:

- Number of water-insoluble solid drugs can be formulated into liquisolid systems.
- Can be applied to formulate liquid medications such as oily liquid drugs.
- Better availability of an orally administered water insoluble drug.
- Lower production cost than that of soft gelatin capsules
- Production of liquisolid systems is similar to that of conventional tablets.
- Can be used for formulation of liquid oily drugs
- Exhibits enhanced in-vitro and in-vivo drug release as compared to commercial counterparts, including soft gelatin capsule preparations.
- Can be used in controlled drug delivery.
- 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.

LIMITATIONS[1-3]:

- Low drug loading capacities.
- Requirement of high solubility of drug in non-volatile liquid vehicles.

APPLICATIONS[1-5]:

- Rapid release rates are obtained in liquisolid formulations
- These can be efficiently used for water insoluble solid drugs or liquid lipophilic drugs.
- Sustained release of drugs which are water soluble drugs such as propranolol hydrochloride has been obtained by the use of this technique.
- Solubility and dissolution enhancement.
- Designing of controlled release tablets.
- Application in probiotics.

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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