

Liquisolid Compacts: An Effective Approach towards Enhancement of Dissolution Rate of Poorly Soluble Drugs

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ABSTRACT

Poorly water-soluble drugs involve many difficulties in the development of pharmaceutical dosage forms for oral delivery systems due to their low bioavailability. Therapeutic effectiveness of a drug depends upon the bioavailability which is dependent on the solubility and dissolution rate of drug molecules. It is believed that better bioavailability of poorly soluble drugs could be achieved when drug is present in solution. "Liquisolid compact technique" is a novel and most promising technology that can enhance the dissolution rate of water insoluble drugs by keeping the drug in a molecularly dispersed form. The technique is based upon the admixture of drug loaded solutions (or) liquid drug with appropriate carrier and coating materials. Addition of the additives improves the technique. The liquisolid approach has been successfully applied in release enhancement of low dose poorly soluble drugs.

Keywords: Liquisolid compacts, Solubility enhancement, loading factor, Non-volatile solvents, direct compression.

INTRODUCTION

The poor dissolution rate of water insoluble drugs is still a substantial problem confronting the pharmaceutical research industries. A great number of new and possibly, efficient and useful chemical entities do not reach the public merely because of their poor oral bioavailability due to inadequate dissolution. Dissolution is an important factor for absorption of drugs especially in case of water insoluble or poorly soluble drugs. In order for a drug to be bioavailable, that is administered orally, it must be soluble as well as it must cross through the biological membrane of gastrointestinal tract (GIT). If the rate of dissolution of drug is slower than the rate of absorption then it is said to be dissolution limited^{1,2}.

There are different types of techniques are available to increase the solubility of poorly water soluble drugs like Micronization, Lyophilisation, Solid dispersions, use of complexing agents, co solvency, chemical modification, pH adjustment, solubilisation by surfactants, solid solutions, inclusion of liquid drug into the soft gelatin capsules, salt formation etc. All these techniques have certain limitations. All these limitations can be overcome by a new and promising technique called "Liquisolid technique" which promotes dissolution rate of insoluble drugs^{3,4}.

LIQUID SOLID COMPACTS

Liquisolid compact technique is a new and promising method that can improve the

dissolution rate of drugs. It has been used to enhance the dissolution rate of poorly water-soluble drugs⁵. The new "liquisolid 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 nonvolatile liquid vehicles) into powders suitable for tableting or encapsulation. Since, the liquisolid tablets contain a solution of the drug in suitable solvent; the drug surface available for dissolution is tremendously increased. Liquisolid systems involves conversion of liquid lipophilic drugs or water insoluble solid drugs dissolved in non-volatile solvent and this liquid medication can be converted into free-flowing, non adherent, dry looking, and readily compressible powders with the use of carrier and coating materials. "liquisolid systems" is formulated by converting liquid lipophilic drugs, or drug suspensions or solutions of water-insoluble solid drugs in suitable non-volatile solvent systems, into "dry" (i.e., dry-looking), nonadherent, free-flowing and readily compressible powder admixtures by blending with selected carrier and coating materials⁶.

The term liquisolid compacts a novel technique described by Spireas et.al indicates that immediate or sustained release tablets or capsules that are prepared using the technique of "liquisolid systems" combined with inclusion of appropriate adjuvants required for tableting or encapsulation such as lubricants and for rapid or sustained release action, such as disintegrants or

binders, respectively. Lquisolid compacts prepared by using different solvents which dissolves the poorly soluble drug and gives better bioavailability. It has been observed that the drug release superiority of lquisolid tablets is inversely proportional to the aqueous solubility of the contained drug⁷.

In case of water soluble drugs, the sustained release can be obtained. The release rate can also be enhanced by encapsulation of drug particles by hydrophobic carrier. Therefore, it leads to poor wettability resulting in slow disintegration and further prolonged drug release. The non-volatile solvents reduce the glass transition temperature (T_g) of polymers and impart flexibility. If the temperature is above T_g, the coalescence of polymer particles occurs and forms a fine network and a matrix with lower porosity & higher tortuosity. The liquid vehicle may also affect the drug release. A comparison of drug release from conventional matrix tablets and lquisolid compacts, both containing Eudagit RS & RL as matrix forming material showed the retardation effect of lquisolid compacts with polysorbate 80 as liquid vehicle is much more pronounced than conventional matrix tablets. This confirms the important role of liquid vehicle in sustained drug release from lquisolid matrix systems⁸.

CLASSIFICATION

A. Based on the type of liquid medication contained therein, lquisolid 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. Nateglinide solution in propylene glycol) or drug suspensions (e.g. gemfibrozil suspension in Tween 80), and the latter from the formulation of liquid drugs (e.g. clofibrate, valproic acid, liquid vitamins, etc.), into lquisolid systems⁹.

B. Based on the formulation technique used, lquisolid systems may be classified into two categories, namely,

- Lquisolid compacts
- Lquisolid microsystems

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

DESIGNING OF LIQUISOLID SYSTEMS^{10,11}

Before designing the lquisolid, the Preformulation studies

Should be performed first, these include:

1. Determination of solubility of drug in various liquid vehicles.
2. Determination of angle of slide
3. Determination of flowable liquid retention potential (Ø value)
4. Calculation of liquid load factor (L_f)
5. Liquid solid compressibility test (LSC)

Solubility determination

It includes determination of solubility of drug in different non-volatile solvents by preparing saturated solutions. Saturated solutions are prepared by adding excess amount of drug to the solvent and placed in orbital shaker for 48hr at 25⁰c. Then the solutions were filtered, diluted and analyzed by U.V spectrophotometer.

Angle of slide

The required amount of carrier material is weighed and placed on a slide and gradually raise the slide till the slide is angular to the horizontal. The angle at which carrier slides from the slide is measured as angle of slide. It is used to measure the flow properties of powders. The 33⁰ is optimum for flow of powders.

Flowable liquid retention potential

It is defined as maximum weight of liquid that can be retained per unit powder material in order to produce an acceptably flowing liquid/powder admixture. This Ø-value of powders may be determined using a new procedure, the lquisolid flowability (LSF) test. This test is basically a titration-like procedure in which 25-30 grams of mixtures of the powders under investigation, with increasing amounts of a non-volatile solvent (i.e., liquid/solid weight composition), such as, for example, poly ethylene glycol, light mineral oil and clofibrate, are prepared using a standard mixing process which ensures uniformity, and their flow rate and consistency are assessed using a recording powder flow meter (RPF)¹².

$$L_f = \frac{W}{R} + \frac{W}{R} (1/R)$$

Where, Ø and Ø are the constant liquid retention potential values of carrier and coating materials, respectively. By calculating L_f and W, we can calculate the Q and q required for lquisolid systems.

Liquid load factor (Lf)

It is defined as ratio of weight of liquid medication (W) to weight of carrier material (Q). Different concentrations of nonvolatile solvents are taken and the drug is dissolved and the carrier coating material is added and blended.

$$Lf = W/Q$$

Where W is ratio of weight of liquid medication and Q is weight of carrier material¹³.

Liquid solid compressibility test

This test is useful to determine the ϕ values¹⁴.

SELECTION OF INGREDIENTS FOR A LIQUISOLID COMPACT TABLET

Drug: The drug used in liquisolid systems must be water insoluble, low dose drugs. It must be in BCS class I and IV. Eg: Digoxin, Digitoxin, Prednisolone, Hydrocortisone, Water insoluble vitamins, Fish oil etc .

Non-volatile solvent: It must be inert water-miscible, not highly viscous and should have high boiling point. E.g: PEG 200 and 400, Glycerin, N, N dimethyl acetamide, Span 80 &19, Tween 80&19 Propylene glycol and Fixed oils etc¹⁵.

Carrier materials: These are highly porous materials & have a wide surface area and the recommended to absorb the drugs on to them. Eg: Cellulose (microcrystalline & amorphous), starch, sorbitol, Lactose, MCC (Avicel PH102), DCP, Eudragit RS&RL¹⁶.

Coating materials: There are fine materials having a particle size range from 10 nm to 4560 nm in diameter. These must be highly

adsorptive to cover the carrier particles and show dry look.

Eg: Silica of various grades like cab-o-sil M5, Aerosil200 and Syloid 244fp etc¹⁷.

Disintegrants: These are used to break the compacts to smaller particles. Eg: Crosscarmellose sodium, Crosspovidone, Explotab and Pre gelatinized starch etc¹⁸.

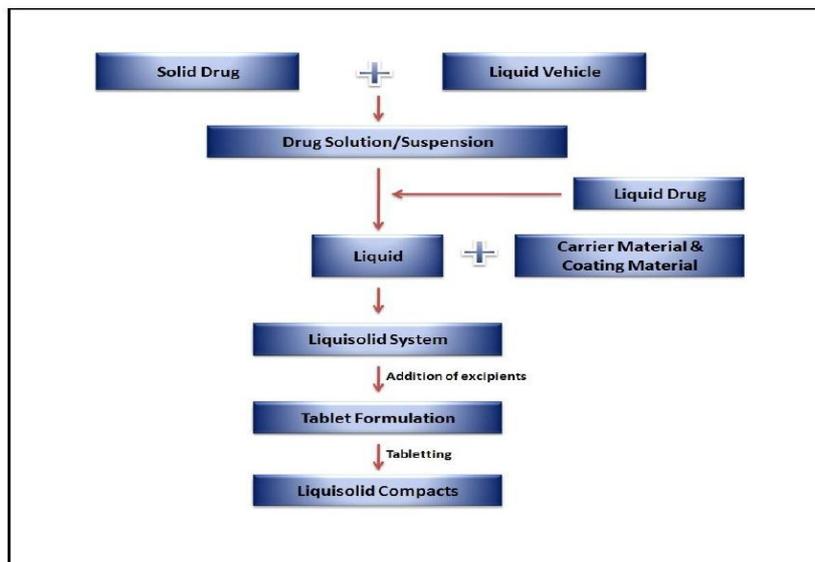
Lubricants: These are intended to reduce the friction. Eg: Stearic acid, Stearic acid salts and Talc etc.

Glidants: Intended to promote the flow between particles by reducing the friction. Eg: Silica derivatives, Talc and Corn starch etc¹⁹.

PREPARATION OF LIQUISOLID TABLETS

Calculated quantities of drug are added to the non-volatile solvent, and then it is heated to dissolve the drug. This liquid drug solution is added to the carrier and coating materials and then it is mixed properly. The mixing process is carried out in three steps as described by Spireas et al.

- The system is blended at a rate of one rotation per second for approximately one minute in order to distribute the drug evenly in liquid.
- This admixture is evenly spread over the motor surface and left standing for 5min. to absorb the drug into the powder particle.
- Then powder is scraped off and then blended with other excipients for another 30sec. similar to first step. This gives the final formulation of liquisolid tablets^{20,21}



Schematic representation of preparation of Liquisolid compacts

MECHANISMS OF ENHANCED DRUG RELEASE FROM LIQUISOLID SYSTEMS

The different mechanisms supposedly responsible for enhancement of drug release from liquisolid compacts are described below:

Increased Drug Surface Area

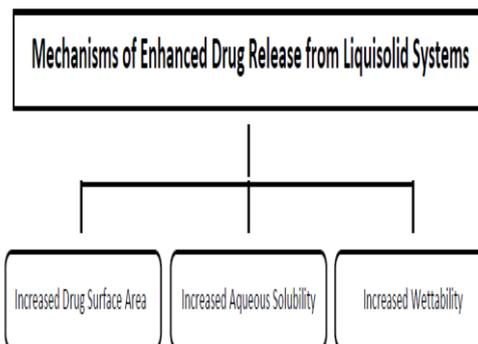
If the drug within the liquisolid system is completely dissolved in the liquid vehicle it is located in the powder substrate still in a solubilized, molecularly dispersed state. Therefore, the surface area of drug available for release is much greater than that of drug particles within directly compressed tablets. Accordingly, with increasing drug content exceeding the solubility limit and thus, increasing fraction of undissolved drug in the liquid vehicle the release rate decreases²².

Increased Aqueous Solubility of the Drug

In addition to the first mechanism of drug release enhancement it is expected that 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 cosolvent²³.

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 times. Nonvolatile solvent present in the liquisolid system facilitates wetting of drug particles by decreasing interfacial tension between dissolution medium and tablet surface²⁴.



Different mechanisms for enhancement of drug release from a liquisolid system

PRE-COMPRESSSION STUDIES^{25, 26}

Flow property

Flow property is important in formulation and industrial production of tablet dosage form in order to reduce high dose variations. Angle of repose, Carr's index, compressibility index, tapped density etc., have to be performed.

Differential Scanning Calorimetry (DSC)

It is used to determine the interactions between drug and excipients, which indicates the success of stability studies. The drug has a characteristic peak, absence of this peak in DSC thermogram indicates that the drug is in the form of solution in liquid formulation and it is molecularly dispersed within the system.

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.

X-ray diffraction (XRD)

XRD studies are used to determine the whether the drug is solubilised or in amorphous form. The disappearance of characteristic peaks of drug and their by appearance of peaks which belongs to carrier is observed.

In vitro release studies

The *in vitro* release studies are performed to estimate the amount of drug release in a certain period of time.

Scanning electron microscopy (SEM)

SEM analysis is performed to determine the crystallinity of drug in liquisolid system. The

disappearance of crystalline nature of drug indicates that the drug is solubilised in the system.

ADVANTAGES ^{27,28}

1. Improved bioavailability of orally administered water insoluble or poorly soluble drugs.
2. This technique is also useful for the formulation of oily drugs/liquid drugs.
3. Drug release can be modified using different carriers and additives like PVP, PEG 60000, HPMC, Eudragit etc..
4. A number of poorly soluble drugs can be formulated in to the system.
5. Industrially applicable.
6. Production cost is low compared to that of preparation of soft gelatin capsules.
7. Method of preparation is very simple and it is similar to that of conventional tablets preparation.
8. Enhances the bioavailability when compared to that of conventional tablets.
9. It does not involve the operations like micronization, nanonization of particles, which are complex and require advanced equipments.

DISADVANTAGES/LIMITATIONS ²⁹

1. Only applicable to low dose drugs and only water insoluble or poorly soluble drugs.
2. High solubility of drug in the non volatile liquid drugs for the improvement of dissolution rate and bioavailability.
3. It only requires excipients of high adsorption properties and high specific surface area.
4. It requires more number of excipients.
5. During compression sometimes liquid drug may be squeezed out of the tablet result in improper hardness.

APPLICATION OF LIQUISOLID TECHNIQUE **Solubility and dissolution improvement**

This technique was successfully applied for low dose water insoluble drugs. However, formulation of the high dose insoluble drugs as liquisolid tablets is one of the limitations of the liquisolid technique. In fact, when the therapeutic dose of drug is more than 50mg, dissolution enhancement in the presence of

low levels of hydrophilic carrier and coating material is not significant. But by adding some materials such as polyvinyl pyrrolidone (PVP) to liquid medication (microsystems), it would be possible to produce dry powder formulations containing liquid with high concentration of drug. By adding such materials to the liquid medication, low amount of carrier is required to obtain dry powder with free flowability and good compatibility³⁰.

Flowability and compressibility

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, whereas silicas of very fine particle size can be used as coating materials. In order to have acceptable flowability and compactability for liquisolid powder formulation, high levels of carrier and coating materials should be added and that in turn will increase the weight of each tablet above 1 gm which is very difficult to swallow. Therefore, in practice it is impossible with conventional method to convert high dose drugs to liquisolid tablet with the tablet weight of less than 1 gm. In such systems, the drug existed in a molecular state of subdivision and systems were free flowing, non-adherent, dry looking powders. In further studies, compression enhancers were added to these powdered solutions like microcrystalline cellulose. However, the compression of these latter systems resulted in a significant "Liquid Squeezing Out" phenomenon³¹.

Bioavailability improvement

In the liquisolid and powdered solution systems the drug might be in a solid dosage form, it is held within the powder substrate in solution, or in a solubilized, almost molecularly dispersed state. Therefore, due to their significantly increased wetting properties and surface of drug available for dissolution, liquisolid compacts of water insoluble substances may be expected to display enhanced drug release properties, and consequently, improved bioavailability³².

Examples of some drugs formulated using Liquisolid technique^{24,29}

S. No.	Drug	Nonvolatile solvent	Carrier & Coating Material	Application
1.	Glibinclamide	PEG-400	Avicel PH 102 & Aerosil	Enhancement of release rate
2.	Gemfibrozil	Tween 80	Avicel PH 200 & Cab-o-sil M5	Improvement of dissolution rate compared to commercial tablets
3.	Indomethacin	Propylene Glycol	Avicel & Colloidal Silica	Enhanced dissolution rate upto 60%
4.	Indomethacin	2-Pyrrolidone	Kollidon-CL & Aerosil 300	Improvement of dissolution rate
5.	Methylclothiazide	PEG400	Avicel & Colloidal Silica	Enhancement, of dissolution rate of commercial tablets upto 40%
6.	Carbamazapine	PEG200	Avicel(MCC) & Cab-o-sil	Enhancement of dissolution rate, Improvement of bioavailability
7.	Piroxicam	Polysorbate 80 (Tween 80)	MCC & Colloidal silica	Increased Dissolution rate, improvement of bioavailability
8.	Hydrocortisone	PG	Avicel PH 200 & Cab-O-sil	Improved dissolution rate that is independent of volume of dissolving medium
9.	Prednisolone	PG	AvicelPH101, Lactose and Cab-O-Sil	Solubility and dissolution improvement
10.	Famotidine	PG	MCC & Colloidal Silica	Improvement of solubility and dissolution rate

For designing of sustain release tablet

Development of sustained release oral dosage forms is beneficial for optimal therapy in terms of efficacy, safety and patient compliance. Ideally, a controlled release dosage form will provide therapeutic concentration of the drug in the blood that is maintained throughout the dosing interval. 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 simplicity and low cost. To achieve this aim, several methods have been developed such as preparation of salt form of drug, coating with special materials and incorporation of drugs into hydrophobic carriers. Liquisolid technique is a new and promising method that can change the dissolution rate of drugs. It is claimed that if hydrophobic carriers such as Eudragit RL and RS are used instead of hydrophilic carries in liquisolid systems, sustained release systems can be obtained. Therefore, it is suggested that the method have the potential to be optimized for the reduction of drug dissolution rate and thereby production of sustained release systems²³.

CONCLUSION

This technique is a promising alternative for formulation of BCS class-II and class-IV drugs, which are poorly soluble. The method is simple and effective and can be used on an industrial scale. The production of Liquisolid compacts does not involve the application of any specialized equipments, hence it is an economical, yet very effective tool for enhancement of dissolution rate of poorly soluble drugs. The various drugs formulated

using this technique have shown a rapid drug release than the conventional tablets. This enhanced dissolution may be due to the increasing in absolute surface area, increased wettability due to the dissolution or dispersion of drug molecularly in the nonvolatile solvent. Moreover addition of disintegrating agents further increases the release rates. By using some hydrophobic carriers the release rates of drugs can be modified. Therefore the liquisolid compacts have the potential to be used on a greater scale in the formulation of modified release as well as immediate release tablets.

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