

LIQUISOLID COMPACT: A NEW TECHNIQUE FOR ENHANCEMENT OF DRUG DISSOLUTION

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ABSTRACT

The dissolution properties of a drug and its release from a dosage form have a basic impact on its bioavailability. Solving solubility problems is a major challenge for the pharmaceutical industry with developments of new pharmaceutical products. There are various methods but liquisolid technique is a new and promising method that can change the dissolution rate of water insoluble drugs. According to the new formulation method of liquisolid 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.

Keywords: Bioavailability, Insoluble drugs, Non-volatile liquid, liquisolid compacts.

INTRODUCTION

The dissolution properties of a drug and its release from a dosage form have a basic impact on its bioavailability. Solving solubility problems is a major challenge for the pharmaceutical industry with developments of new pharmaceutical products, since nearly half of the active substances being identified through the new paradigm in high-throughput screening are either insoluble or poorly soluble in water¹. The rate of dissolution of a drug is a function of its intrinsic solubility and its particle size. Studies with poorly soluble drugs have demonstrated that particle size reduction to the sub-micron range can lead to an increase in dissolution rate and higher bioavailability¹⁻⁴.

Nearly one-third of drugs in development are water insoluble and one-half fail in trials

because of underprivileged pharmacokinetics⁵. These poorly water soluble drugs are allied with slow drug absorption leading to inadequate and variable bioavailability and gastrointestinal mucosal toxicity of drugs⁶. Poorly water soluble drugs belong to BCS class II and class IV⁷ group of compounds. In the process of absorption of drug from oral route; dissolution is the rate limiting step for lipophilic drugs; therefore it is necessary to enhance dissolution of these drugs to ensure maximum therapeutic utility of these drugs. Dissolution is a process by which a solid substance goes into solution. The extent to which the dissolution proceeds, under a given set of conditions is referred to as the solubility of the substance in the solvent i.e. rate of solution (dissolution) and amount that can be

dissolved (solubility) are not same. The dissolution rate of a drug is directly proportional to its solubility as per Noyes-Whitney equation and therefore solubility of a drug substance is a major factor that determines its dissolution rate and hence its absorption and bioavailability eventually⁸. The various properties of drug that affect drug dissolution and its rate includes solubility, particle size, polymorphism, salt form, complexation, wettability and can be targeted to enhance dissolution of poorly water soluble drugs⁹.

There are several techniques such as solid dispersion, inclusion complex, steam-aided granulation, cogrinding or comicronization, lipid-based formulations, melt-granulation, direct compaction, solvent evaporation by ultra-rapid freezing (URF), coevaporate system or coprecipitation, ordered or interactive mixing, solvent deposition, adsorption of drugs onto high surface area carriers and liquisolid compacts etc reported in literature for formulation of hydrophobic drugs with enhanced dissolution rate. These techniques are carefully selected on the basis of properties of drug, excipients and dosage forms.

Micronization is the most common method to increase the drug surface area. But, in practice, the effect of micronization is often disappointing, especially when the drugs are encapsulated or tableted¹⁰⁻¹². The most promising method for promoting dissolution is the formation of liquisolid tablets¹³⁻¹⁵. Formulating liquid medications into solid compacts has been the object of many studies. Jarowski et al^{16,17} and Spireas et al¹³⁻¹⁵ on producing solid solutions and liquisolids based on the concept of blending liquid medications with selected powder excipients to produce free flowing, readily compressible powders. A liquisolid system refers to formulations formed by conversion of liquid drugs, drug suspensions or drug solution in non-volatile solvents, into dry, non-adherent, free-flowing and compressible powder mixtures by blending the suspension or solution with selected carriers and coating materials¹³. Various grades of cellulose, starch¹⁸ lactose, sorbitol¹⁹ may be used as the carrier; whereas very fine particle size silica powder may be used as the coating material.

Advantages of Liquisolid Compact

1. A great number of slightly and very slightly water-soluble and practically water-insoluble liquid and solid drugs such as Digitoxin, Prednisolone and Hydrocortisone etc. can be formulated into liquisolid systems using the new formulation-mathematical model.
2. Better availability of an orally administered water-insoluble drug is achieved when the drug is in solution form.
3. 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.
4. Production cost of liquisolid systems is lower than that of soft gelatin capsules.
5. Advantage of liquisolid systems, particularly for powdered liquid drugs, during dissolution of a liquisolid 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, liquisolid systems exhibit enhanced drug release.
6. Optimized rapid-release liquisolid tablets or capsules of water-insoluble drugs exhibit enhanced in-vitro and in-vivo drug release as compared to their commercial counterparts.
7. Optimized sustained-release liquisolid 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 tablets²⁰.

Disadvantages of Liquisolid System

1. The liquisolid systems have low drug loading capacities and they require high solubility of drug in non-volatile liquid vehicles¹⁹.
2. It requires more efficient excipients which have higher adsorption capacities which provide faster drug release with a

smaller tablet size to improve liquisolid formulations²¹.

3. To maintain acceptable flowability and compatibility for liquisolid powder formulation high levels of carrier and coating materials are required and that in turn will increase the weight of each tablet above 1 gm which is very difficult to swallow¹⁹.

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 40% of all newly developed drugs are poorly soluble or insoluble in water²². In addition, up to 50% of orally administered drug compounds suffer from formulation problems related to their low solubility and high lipophilicity²³⁻²⁵. 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 microparticles.

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 solvents²⁵⁻²⁷.

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, whereas 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, non-adherent, dry looking powders²⁸⁻²⁹. 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 Carbamazepine¹⁹, Famotidine³⁰, Piroxicam²⁸, Indomethacin²⁹, Hydrocortisone¹⁴, Naproxen³¹ and Prednisolone¹³.

Concept

When the drug dissolved in the liquid vehicle is incorporated into a carrier material which has a porous surface and closely matted fibers in its interior as cellulose, both absorption and adsorption take place; i.e. the liquid initially absorbed in the interior of the particles is captured by its internal structure, and after the saturation of this process, adsorption of the liquid onto the internal and external surfaces of the porous carrier particles occur. Then, the coating material having high adsorptive properties and large specific surface area gives the liquisolid system the desirable flow characteristics Fig. 1³⁰.

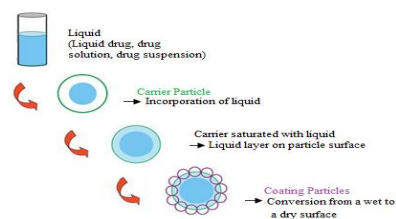


Fig.1: Steps in Formulation of Liquisolid²¹.

The wettability of the compacts by the dissolution media is one of the proposed mechanisms for explaining the enhanced dissolution rate from the liquisolid compacts. Nonvolatile solvent present in the liquisolid system facilitates wetting of drug particles by decreasing interfacial tension between dissolution medium and tablet surface¹⁹. Fig. 2 shows lower contact angle of liquisolid compacts than the conventional tablets and thus improved wettability.

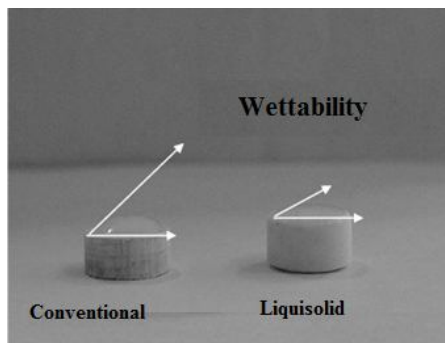


Fig. 2: Comparison of wettability between Conventional tablet and liquisolid compacts.

Classification of liquisolid systems

A. Based on the type of liquid medication contained therein, liquisolid systems may be classified into three subgroups

1. Powdered drug solutions
2. Powdered drug suspensions
3. Powdered liquid drugs

The first two may be produced from the conversion of drug solutions or (e.g. prednisolone solution in propylene glycol¹³ drug suspensions (e.g. gemfibrozil suspension in polysorbate 80³², and the latter from the formulation of liquid drugs (e.g. clofibrate, liquid vitamins, etc.) into liquisolid systems.

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

1. Liquisolid compacts
2. Liquisolid Microsystems

Components of Liquisolid Compact Formulation

Liquisolid compact mainly includes

1. Non volatile solvent
2. Disintegrant
3. Drug candidate
4. Carrier material
5. Coating material

Non volatile Solvent

Non volatile Solvent should be Inert, high boiling point, preferably water-miscible and not highly viscous organic solvent systems and compatible with having ability to solubilise the drug. The non volatile solvent acts as a binding agent in the liquisolid formulation³³.

Various non-volatile solvents used for the formulation of liquisolid systems include Polyethylene glycol 200 and 400, glycerin, polysorbate 80 and propylene glycol¹⁹.

Disintegrant

Superdisintegrants increases the rate of drug release, water solubility and wettability of liquisolid granules. Mostly superdisintegrants like sodium starch glycolate and croscarmellose are used³³.

Drug candidates

This technique was successfully applied for low dose BCS class II and class IV drugs which are poorly water soluble and have slow dissolution rate³⁴.

Examples of drug candidates include carbamazepine¹⁹, famotidine³⁰, piroxicam²⁸, indomethacin²⁹, hydrocortisone¹⁴, naproxen³¹ and prednisolone¹³, digoxin, digitoxin, prednisolone, hydrocortisone, spironolactone, hydrochlorothiazide, polythiazide, and other liquid medications such as chlorpheniramine, water insoluble vitamins, fish oil etc^{20,35}.

Carrier Materials

Carrier material should be porous material possessing sufficient absorption properties which contributes in liquid absorption. The carrier and coating materials can retain only certain amounts of liquid and at the same time maintain acceptable flow and compression properties hence, increasing moisture content of carrier's results in decreased powder flowability³⁴.

These include grades of microcrystalline cellulose such as avicel PH 102 and avicel PH 200^{20,35}, lactose¹⁹, eudragit RI and eudragit RS12 (to sustain drug delivery)³⁶ etc.

Coating Materials

Coating material should be a material possessing fine and highly adsorptive particles which contributes in covering the wet carrier particles and displaying a dry-looking powder by adsorbing any excess liquid. Coating material is required to cover the surface and so

maintain the powder flowability³⁴. Coating material includes silica (Cab-O-Sil) M5^{20,35} Aerosil 200³⁰, Syloid, 244FP^{20,35} etc.

Formulation of Lquisolid Compact

The formulation part of lquisolid compact mainly includes Pre-formulation studies and Formulation of lquisolid compact system.

Pre-formulation Studies

Pre-formulation Studies includes

1. Determination solubility of drug in different non-volatile solvents
2. Determination of angle of slide
3. Determination of flowable liquid retention potential (Φ value)
4. Calculation of liquid load factor (Lf)
5. Lquisolid compressibility test (LSC)

Solubility studies

Solubility studies are carried out by preparing saturated solutions of drug in non-volatile solvent and analyzing them spectrophotometrically¹³. Saturated solutions are prepared by adding excess of drug to non volatile solvent and shaking them on shaker for specific time period under constant vibration. After this, the solutions are filtered and analyzed spectrophotometrically³⁶.

Determination of angle of slide

Angle of slide is used as a measure of the flow properties of powders. Determination of angle of slide is done by weighing the required amount of carrier material and placed at one end of a metal plate with a polished surface. The end is gradually raised till the plate becomes angular to the horizontal at which powder is about to slide.

This angle is known as angle of slide. Angle of 33° is regarded as optimum³⁷.

Determination of flowable liquid retention potential (Φ value)³⁷

The term "flowable liquid-retention potential" (Φ -value) of a powder material describes its ability to retain a specific amount of liquid while maintaining good flow properties. The Φ -value is defined as the maximum weight of liquid that can be retained per unit weight of the powder material in order to produce an acceptably flowing liquid/powder admixture.

The Φ values are calculated according to equation

$$\Phi \text{ value} = \text{weight of liquid} / \text{weight of solid} \dots (1)$$

Calculation of liquid load factor (Lf)¹⁹

Different concentrations of non-volatile solvents are taken and the drug is dissolved. Such liquid medication is added to the carrier-coating material admixture and blended. Using equation (2) drug loading factors are determined and used for calculating the amounts of carrier and coating materials in each formulation.

$$\text{Lf} = \text{weight of liquid medication} / \text{weight of carrier material} \dots (2)$$

Lquisolid compressibility test (LSC)^{20,35}

Lquisolid compressibility test is used to determine Φ values and involves steps such as preparing carrier coating material admixture systems, preparing several uniform liquid or powder admixtures, compressing each liquid or powder admixtures to tablets, assessing average hardness, determination of average liquid content of crushed tablets, as well as determining plasticity, sponge index and Φ value and Lf .

Preparation of Lquisolid Tablets

General method of preparation of lquisolid³⁸

1. A drug substance was initially dispersed in the nonvolatile solvent systems (Polysorbate 80, Polyethylene glycol-200) termed as liquid vehicles with different drug: vehicle ratio.
2. Then a mixture of carrier or different polymers and excipients were added to the above liquid medication under continuous mixing in a mortar. These amounts of the carrier and excipients are enough to maintain acceptable flow and compression properties.
3. To the above binary mixture disintegrant like sodium starch glycolate and other reaming additives were added according to their application and mixed for a period of 10 to 20 min. in a mortar.
4. The final mixture was compressed using the manual tableting machine to achieve tablet hardness.
5. Characterize the final lquisolid granules for solubility, dissolution, flowability, compressibility and other physicochemical properties.

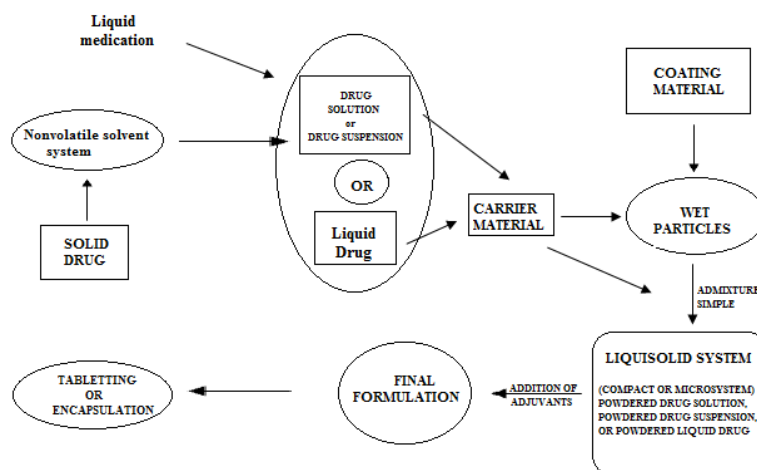


Fig. 3: General method for formulation of liquisolid compact³⁹

Evaluation of Liquisolid Systems

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 powder. In general, values of angle of repose $\geq 40^\circ$ indicate powders with poor flowability⁴⁰.

Differential Scanning Calorimetry (DSC)

It is necessary to determine any possible interaction between excipients used in the formulation. This will also indicate success of stability studies⁴¹. 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 liquisolid formulation and hence it is molecularly dispersed within the system³⁰.

X-ray diffraction (XRD)

Generally, disappearance of characteristic peaks of drug in the liquisolid formulation and retaining peaks of carrier material is observed³⁰. This indicates that drug gets converted to amorphous form or in solubilized form in the liquisolid formulation.

Scanning Electron Microscopy (SEM)

After SEM study, complete disappearance of crystals of drug which confirms that drug is totally solubilized in liquisolid system and this ensures the complete solubility.

After complete formulation, Tablets are evaluated by carrying out tests for weight variation, uniformity of tablet thickness and diameter, humidity content using Karl Fisher method, friability, hardness, disintegration, dissolution, and content uniformity. All these tests are carried out in triplicate and according to the compendial specifications^{42,43}.

For content uniformity test tablets should contain not less than 95% and not more than 105% of the labeled potency⁴³.

The disintegration test was carried out on six tablets in distilled water at $37 \pm 2^\circ\text{C}$ using the USP disintegration apparatus⁴².

Dissolution studies of Liquisolid tablet

Generally Dissolution studies of Liquisolid tablet are carried out using dissolution apparatus USP II at $37^\circ\text{C} \pm 2^\circ\text{C}$. Many researchers^{13, 30, 31, 37} revealed that at low drug concentrations in liquid medication, more rapid release rates are observed. The consistent and higher dissolution rate displayed by liquisolid compacts will improve the absorption of drug from gastrointestinal tract.

In vivo evaluation of Liquisolid tablets

The improvement in oral bioavailability was confirmed by estimating the pharmacokinetic parameters in various animals such as rabbit⁴⁴ beagle dog⁴⁵.

Results show that absolute bioavailability of drug from liquisolid tablets was much higher than marketed tablets⁴⁴.

Application of Liquisolid Techniques
Table 1: Examples and Application of Liquisolid Technique

Sr. No	Drug	Applications	Reference
1.	Prednisolone	Solubility and dissolution improvement	13
2.	Famotidine	Solubility and dissolution improvement	30
3.	Naproxen	Solubility and dissolution improvement	31
4.	Bromhexine Hydrochloride	Solubility and dissolution improvement	47
5.	Methchrothiazide	Bioavailability improvement	15
6.	Carbamazepine	Bioavailability improvement	19
7.	Piroxicam	Bioavailability improvement	28
8.	Propranolol	For designing of sustain release tablet	36
9.	Hydrochlorothiazide	For designing of sustain release tablet	46
10.	Atorvastatin	Flowability and compressibility	44

CONCLUSION

Liquisolid formulations are designed to contain liquid medications in powdered form and hence possess drug delivery mechanisms similar to that of soft gelatin capsule preparations, containing liquids. This novel technique is found to be efficient method for formulation of water insoluble solid drugs and liquid lipophilic drugs. Rapid disintegration rates are observed compared to conventional tablets and therefore, they show improved release rates and hence greater bioavailability. The use of nonvolatile solvent in the formulation causes increased wettability of water insoluble drugs and ensures molecular dispersion of drug in the formulation. Modification of formulation by use of certain agents cause sustained release of drugs from the liquisolid tablets.

Liquisolid Formulations shows better Flowability, Compressibility, improves solubility, Dissolution and hence better absorption.

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