

Liquisolid Technique: A Novel Approach to Enhance Solubility of Poorly Soluble Drugs

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Abstract: Bioavailability of any drug depends on the dissolution of the drug and its release from the dosage form. Solubility is the major challenge for pharmaceutical industries with the development of poorly soluble drugs. There are several approaches for solubility enhancement which includes micronisation, nanonisation, use of salt forms, surfactants, solid dispersions and supercritical fluid recrystallisation, etc. Liquisolid technique is a novel and efficient approach for solubility enhancement. According to this method the conversion of water insoluble drugs into dry looking, non-adherent, free flowing and acceptably compressible powder by incorporating into suitable nonvolatile solvents, carrier and coating materials (It is claimed that if hydrophobic carriers such as Eudragit RL and RS are used instead of hydrophilic carriers in liquisolid system, sustained release systems can be obtained). This free flowing powder is thus subjected to preformulation studies like differential scanning calorimetry, Fourier transformed infrared spectroscopy, angle of slide, flow properties, liquid retention potential, liquid load factor, etc. This powder is subjected to compression for tablet or filled in capsules. This mechanism for solubility enhancement includes increase in wettability and increase in surface of drug available for dissolution. This method is efficient, economic, viable for industrial production. Due to all these reasons liquisolid technique is most efficient and novel approach for solubility enhancement.

Keywords: Liquisolid, Carrier material, Coating material, Non polar solvent, Solubility

1. Introduction

Oral route is the most preferred route of drug administration because of patient compliance, ease and low cost of production and the drug must be presented in solution form for absorption through GIT when given orally. The dissolution of drug and its release from dosage form have a basic impact on bioavailability. With the development of new pharmaceutical products, solving solubility problems is the major challenge. Approximately 70% of new drug candidates and 40% of marketed new drugs in oral immediate release dosage form exhibit low aqueous solubility.

Solubility, polymorphism, salt form, particle size, complexation, wettability are various properties of drug that affect drug dissolution and can be used to enhance dissolution rate of poorly water soluble drugs.

Several methods are studied for increasing dissolution rate and bioavailability including micronisation, nanonisation, solid dispersions, complexation with cyclodextrins, liquisolid systems, etc.

Various methods used for enhancing solubility and thus bioavailability of drugs are:

- 1) Solid Dispersion:** These are commonly prepared by solvent or co precipitation method where both the guest solute and carrier solvent are dissolved in a common volatile solvent system like alcohol. The liquid solvent is removed by freeze drying or by evaporation under reduced pressure which results in amorphous precipitation of guest in a crystalline carrier.
- 2) Complex with Cyclodextrins:** The beta and gamma cyclodextrins and their several derivatives have unique ability to form molecular inclusion complexes with poorly water soluble hydrophobic drugs.

- 3) Micronization:** In this process, the size of drug particles is reduced to 1 to 10 micron by use of air attrition methods like fluid energy or by spray drying. The process is also known as 'micro milling'.
- 4) Nanonisation:** In this process, the drug powder is converted into nanocrystals having sizes 200-600nm.
- 5) Use of Surfactants:** Surfactants act as absorption enhancers and enhance both permeability of drug and dissolution rates. The dissolution rate is enhanced by increasing wetting and penetration of dissolution fluid into the solid drug particles.
- 6) Use of salt forms:** Salts have more improved solubility and dissolution than the original drug.
- 7) Supercritical Fluid Recrystallization:** Supercritical fluids (e.g. carbon dioxide) have temperature and pressure greater than their critical temperature (T_c) and critical pressure (P_c), so that it can assume properties of both liquid and gas. Supercritical fluids are highly compressible at near critical temperature, which allows moderate changes in pressure and can alter mass transport characteristics and density of a fluid that determines its solvent power. The drug particles may be recrystallized greatly at reduced particle sizes when they are solubilized in supercritical fluids.

2. Need of Liquisolid Technique

The oral route of drug administration is most preferred route due to convenience, it has less drug manufacturing cost and better patient compliance. When a drug is orally administered, it must get dissolved in gastric fluids, so that it will be absorbed into systemic circulation. But nowadays it is observed that, poor solubility is one of the major challenges in drug development. Because, 40% of most of the newly developed drugs are poorly soluble or insoluble in water.

The dissolution rate for poorly soluble drugs can be improved by increasing their surface area, decreasing particle size by creating nanoparticles or microparticles, by reducing their crystallinity etc. Fine drug particles have more tendency to form agglomerates due to the Vander Waals attraction forces or hydrophobicity, which helps to decrease the surface area over time.

On the other hand, drug adsorption on a high surface area carrier material can improve dissolution rate. In this technique, initially the drug is administered in a suitable non-volatile organic solvent followed by soaking of the solution with a high surface area carrier (eg. silica). Thus, drug binds to the carrier due to which agglomeration of drug particles is avoided. However, it is disadvantageous to use toxic solvents due to residual solvent present in drug formulation. Hence, to overcome such problems, the technique of 'liquisolid compacts' is an advanced and innovative approach for dissolution enhancement of poorly soluble drugs and for increasing their bioavailability.

The Overall Concept

The drug dissolved in a suitable liquid vehicle (non-volatile solvent) and then it is incorporated into a carrier material having closely matted fibers in its interior as cellulose and porous surface so that both absorption and adsorption take place. The liquid is initially absorbed in the interior of the particles and it is captured by its internal structure. Adsorption of the liquid in on the internal and on the external surfaces of the porous carrier particles occurs after saturation of previous process. The desirable flow properties of liquisolid system are obtained by coating material having large specific surface area and high adsorptive properties. See Figure 1.

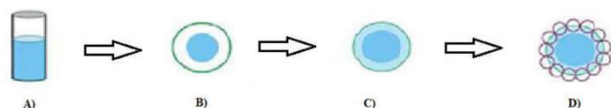


Figure 1

A-Liquid Drug, Drug Solution or Suspension

B-Carrier Particle

C-Carrier saturated with liquid

D- Addition of coating particles

3. Advantages

- 1) A large number of water-insoluble solid drug can be formulated into liquisolid systems.
- 2) Large number of Bio-Pharmaceutical classification (BCS) class -II drugs which are highly permeable, slightly or very slightly water soluble and practically insoluble liquids and solid drugs are possible to formulate by using liquisolid technique.
- 3) It helps to formulate the oily liquid drugs.
- 4) Dissolution medium has greater drug surface area available.
- 5) The drug is held in a solubilized liquid state in a tableted or encapsulated dosage form. It contributes to increased drug wetting properties and enhancing drug dissolution rate.

- 7) It helps to minimize excipients in formulation as compared to drug other formulations like solid dispersions, suspensions, etc.
- 8) It has simplistic way of processing.
- 9) It has lower manufacturing cost than that of soft gelatin capsules.
- 10) It has more viability of industrial production.
- 11) It omits the processing approaches like micronisation, nanonisation, etc.
- 12) The liquisolid systems help to formulate the immediate release or sustained release dosage forms.

Mechanism of Enhancement of Solubility

One of the proposed mechanisms for explaining enhanced solubility rates from liquisolid compacts is the wettability of compacts in the dissolution media. Non-volatile solvent present in liquisolid system decreases interfacial tension between tablet surface and the dissolution medium. This helps to facilitate the wetting of drug particles. Hence, the significant increase in effective surface area for dissolution and increase in wettability leads to enhancement of solubility of water insoluble drugs. Dissolution of a non-polar drug becomes a rate limiting step in absorption of drug in gastrointestinal tract. Hence, enhanced solubility and better bioavailability of an orally administered water-insoluble drug is gained when the drug is already in solution form. The drug release profile is determined mainly by the characteristics of drug, carrier material and vehicle used in process.

Thus it helped to improve following properties:

- It increased drug surface area for dissolution due to incorporation of non-volatile solvent (liquid vehicle).
- It increased the aqueous solubility of the drug by the diffusion of liquid vehicle with the drug candidate from liquisolid particles.
- It improved wetting property due to action of liquid vehicle as surface active agent or because of having low surface tension (which decreased angle of contact between water and liquisolid).

4. Classification of Liquisolid System

- 1) Based on the type of liquid drug incorporated, liquisolid systems is classified into three categories:
 - Powdered drug suspensions
 - Powdered drug solutions
 - Powdered liquid drugs
- 2) Based on the formulation technique, liquisolid systems is classified into two categories
 - Liquisolid compacts
 - Liquisolid Microsystems

5. Components of Liquisolid Formulations

Carrier material

These are compression-enhancing, preferably porous, relatively large particles possessing a sufficient absorption property which are involved in liquid absorption. E.g. various grades of cellulose, sorbitol, Avicel PH 102 and 200, starch, Eudragit RL and RS, amorphous cellulose etc.

Coating material

These are flow-enhancing, highly adsorptive, very fine (10 nm to 5,000 nm in diameter) coating particles (e.g. silica of various grades like Cab-O-Sil M5, Aerosil 200, etc.) which are involved in covering the wet carrier particles into a dry-looking powder by adsorbing any excess liquid.

Non-volatile solvents

These are inert, preferably water-miscible and not highly viscous organic solvent systems. They have high boiling points. Various non-volatile solvents used for the formulation of lquisolid systems include Polyethylene glycol 200 and 400, glycerin, polysorbate 80 and propylene glycol, liquid polyethylene glycols, etc.

Drug candidates

Examples of drug candidates include digitoxin, digoxin, prednisolone, hydrocortisone, hydrochlorothiazide, and other liquid medications such as chlorpheniramine, water insoluble vitamins, etc

Disintegrants

Mainly superdisintegrants increase rate of drug release, solubility of drug particles and wettability within short period of time. E.g. Sodium Starch Glycolate, Crosspovidone, etc.

6. Formulation of Lquisolids

This procedure is divided into following steps:

- I) Preformulation studies
- II) Formulation of lquisolid powder
- III) Precompression studies
- IV) Compression
- V) Post compression studies i.e. Evaluation of lquisolids

I) Preformulation Studies:

Pre-formulation Studies include

- a) Determination solubility of drug in different non-volatile solvents
- b) Determination of angle of slide
- c) Calculation of liquid load factor (Lf)
- d) Determination of flowable liquid retention potential (Φ value)
- e) Lquisolid compressibility test (LSC)

1) Determination solubility of drug in different non-volatile solvents: A saturated solution of drug in different solvents is prepared by adding excess amount of drug in non-volatile solvent. This solution is shaken with shaker for given period of time. Then, it is filtered and analyzed under UV spectrophotometer.

2) Determination of angle of slide: The required amount of carrier material is weighed and placed on side of a metallic plate. The plate is gradually raised till it is angular to the horizontal. The angle at which carrier slides from the plate is measured as angle of slide. It is used to measure the flow properties of powders. flow of powder have optimum angle of 330°.

3) Calculation of liquid load factor (Lf): The drug is dissolved in different concentrations of non-volatile

solvents. This prepared liquid medication is added to the carrier coating material admixture and blended well. The drug loading factors are determined by using given equation and used for calculating the amounts of carrier and coating materials used in each formulation prepared

$Lf = \text{weight of liquid medication} / \text{weight of carrier material}$

4) Determination of flowable liquid retention potential (Φ value):

The term "flowable liquid retention potential" (Φ -value) of a powder material defines 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,

$$\Phi \text{ value} = \text{weight of liquid} / \text{weight of solid}$$

5) Lquisolid compressibility test (LSC):

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

II) Formulation of lquisolid powder

- a) 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.
- b) 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.
- c) 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.
- d) For simple understanding of this step see Figure.2

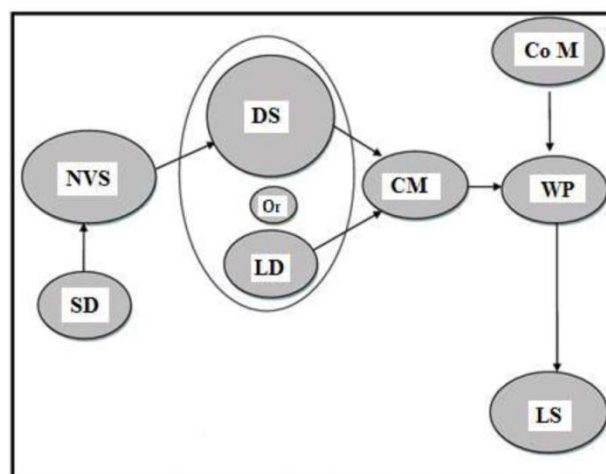


Figure 2 - Steps in formulation of lquisolid powder, where: (SD) Solid Drug; (NVS) Non volatile solvent; (DS) Drug solution or suspension; (LD) Liquid drug; (CM) Carrier material; (Co M) Coating Material; (WP) Wet particles; (LS) Lquisolid system i.e. Powder

III) Precompression studies

1) Flow properties of the liquisolid system: The flow properties of the liquisolid systems were estimated by determining the angle of repose, Carr's index, and Hausner's ratio. The angle of repose was measured by the free standing cone or fixed funnel method. The Bulk density and Tap densities were determined for the calculation of Hausner's ratio and Carr's Index.

A) Angle of repose: The angle of repose of physical mixtures of liquisolid compacts were determined by fixed funnel method. The accurately weighed physical mixtures of liquisolid compacts were taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touches the apex of the heap of the powder. The powder was allowed to flow through the funnel freely into the surface. The height and diameter of the powder cone was measured and angle of repose was calculated.

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

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

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

$$D_b = M / V_b$$

Where, M is the mass of powder and V_b is bulk volume of powder

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

$$D_t = M / V_t$$

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

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

$$CI (\%) = [(Tapped\ density - Bulk\ density) / Tapped\ density] \times 100$$

E) Hausner's Ratio: Hausner's ratio is an indirect index of ease of powder flow. It is calculated by the following formula, Hausner's Ratio = Tapped density (ρ_t) / Bulk density (ρ_b) Thus, estimation of flow properties of powder can be done. See Table No.1

Table 1

Flow	Angle of response	Compressibility Index	Hausner's ratio
Excellent	25-30	<10	1.0-1.11
Good	31-35	11-15	1.12-1.18
Fair	36-40	16-20	1.19-1.25
Possible	41-45	21-25	1.26-1.34
Poor	46-55	26-31	1.35-1.45
Very Poor	56-65	32-37	1.46-1.59
Very very poor	>66	>38	>1.60

2) X-ray diffraction studies (XRD):

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

3) Differential scanning calorimetry

It is necessary to indicate any possible interaction between excipients used in the formulation. This will also indicate growth 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 liquisolid formulation. Thus it shows that the drug is molecularly dispersed within the system.

4) Scanning electron microscopy (SEM):

Scanning electron microscopy (SEM) is used to assess the morphological characters of the raw materials and the drug-carrier systems. The presence or absence of the crystals in system is confirmed by this method.

IV) Compression

The previously produced dry looking, non-adherent liquisolid powder after precompression studies is subjected to compression or capsule filling. See Figure.3

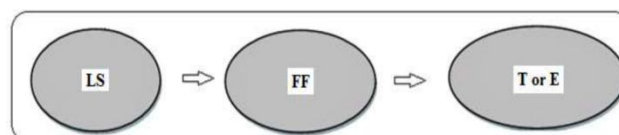


Figure 3 - Compression after precompression studies, where: (LS) Liquisolid system i.e. Powder; (FF) Final formulation after precompression studies; (T or E) Tableting or encapsulation.

V) Post compression studies i.e. Evaluation of liquisolids:

1) Thickness

Vernier Caliper instrument is used to measure thickness of tablet.

2) Hardness

Specific amount of hardness is necessary to prevent mechanical shock during handling, manufacturing and

shipping of tablets. Hardness is measured by Pfizer hardness tester.

3) Weight Variation Test

The weight variation test is a method used for determining drug content uniformity. The test is performed by weighing 10 tablets individually, calculating the average weight and comparing individual tablet weights with the average weights of 10 tablets. Not more than 2 tablets should vary from the average weight.

4) Disintegration Test

The process of breakdown of tablets into smaller particles is called disintegration. The USP device to test disintegration uses 3 inch long 6 glass tubes that are open at the bottom end of basket rack assembly. To test for disintegration time, one tablet is placed in each tube and the basket rack is positioned in a 1 litre beaker of water simulated gastric fluid at $37\pm 2^\circ$ C.

5) Contact angle measurement

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

6) Stability studies

In stability studies, drug content is determined by charging up the crystals of the drug to accelerated stability conditions. In this study, the samples are taken after each specific interval of the time. These samples are then analyzed by using differential scanning calorimetry or X-ray diffraction studies.

7) In vitro release

In vitro release of liquisolid tablets is carried out by using USP II apparatus at $37\pm 2^\circ$ C. During this study, it was observed that if there is low drug concentration in liquid formulation then there is rapid drug release from the formulation. If in-vitro release rates for liquisolid tablets are higher than the absorption rate will also be higher. This helps the drug to enhance bioavailability.

7. Applications

- 1) Liquisolid compact technology is an innovative method to improve bioavailability of water insoluble drug by their solubility enhancement. Various water insoluble drugs on dissolving in different non-volatile solvents have been formulated into liquisolid compacts.
- 2) Formulations prepared by liquisolid technique possess acceptable flowability and compressibility properties.
- 3) Release rates of many poorly water soluble drugs or water insoluble drugs are enhanced by using liquisolid system.
- 4) Designing of Sustained Release Tablets by the use of hydrophobic polymers such as Eudragit RL and RS is done practically in many industries.

- 5) Bioavailability of many class II and class IV drugs get enhanced by using liquisolid technique.

8. Conclusion

Different methods are studied to enhance water solubility and drug release, among which the liquisolid technology is one of the most promising approaches. With this method the 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 the excipients used like the carrier and the coating material. Highest drug release rates are observed with liquisolid compacts containing a drug solution as liquid portion. Thus, liquisolid compacts may be optimized by selection of the liquid vehicle and the carrier and coating materials. The addition of disintegrant improves rate of drug release from liquisolid compacts. The liquisolid technology is used for the preparation of sustained release dose form with zero order release pattern. Thus, constant plasma level will be reached, which is maintained throughout the dosing interval. An important role is played by the criteria of selection and concentration of used excipients such as liquid vehicle, carrier material and coating material for sustained release liquisolid formulations. Hence, the liquisolid technique is most preferable method for BCS class II and class IV formulations because of properties like the simple manufacturing process, low production costs and the possibility of industrial manufacture, good flow and compaction properties.

9. Future Scope

The future scope in this technique is that, we can use polymers like Avicel, HPMC which will decrease the density of dosage form (density lower than gastric fluid) so that we can make it a floating dosage form which will increase gastric emptying time of the drug.

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