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LIQUISOLID TECHNIQUE: A REVIEW

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Liquisolid, Poor water solubility, Carrier material, Coating material, water in-soluble/ soluble drugs

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ABSTRACT

This approach is suitable for immediate or sustain release formulations. Liquisoild technique is a novel concept for delivery of drugs through oral route. This approach of delivering drugs is suitable mostly for lipophilic drugs and poorly or water insoluble drugs. Poor bioavailability which is only caused by poor water solubility is a technological challenge represented by poorly soluble, highly permeable active pharmaceutical ingredients (BCS Class II drugs) resulting in low drug absorption.

The "Liquisolid" technique is a novel and capable addition towards such an aims for solubility enhancement and dissolution improvement, thereby it increases the bioavailability. Increasing the solubility by using a non-volatile solvent which is suitable for drug, there by dissolving the drug in the non-volatile solvent and this is termed as liquid medicament. Blending the liquid medicament with mixture of carrier and coating material, liquid medicament can be converted into non adhere, dry looking powder with acceptable flow properties and compression behaviour using suitable excipients and tabletting by direct compression method. This technique is an efficient method for formulating water insoluble and water soluble drugs. This technique is based upon the admixture of drug loaded solutions with appropriate carrier and coating materials.

INTRODUCTION[1,3]

Bioavailability is affected by the dissolution properties of a drug and its release from a dosage form. The rate of dissolution of a drug is a function of its intrinsic solubility and its particle size. Studies have demonstrated that particle size reduction to the sub-micron range of poorly soluble drugs can lead to an increase in dissolution rate and higher bioavailability.

The easiest way of administering drugs is oral drug delivery. Because of the greater stability, smaller bulk, accurate dosage and easy production, solid oral dosage forms offers many advantages over types of oral dosage forms. Therefore, most of the new chemical entities (NCE) under development these days are intended to be used as a solid dosage form originating an effective and reproducible in vivo plasma concentration profile after oral administration. In fact, most NCEs are poorly aqueous soluble drugs, hence not well-absorbed after oral administration, which can detract from the drug's inherent efficacy. Consequently, the incomplete release of these drugs in the gastrointestinal area will show low bioavailability problems. Therefore, one of the major current challenges to the pharmaceutical industry is related to improve the aqueous solubility of drugs. Drug release is an important and rate limiting step for oral bioavailability, particularly for drugs with low solubility and high permeability i.e. BCS class II drugs. By improving the drug release profile of BCS class II drugs, it is possible to enhance their bioavailability and reduce side effects[4]. Several studies have been carried out to increase the dissolution rate of drugs by decreasing the particle size, by creating micro-particle and nano-particles. However, the fine drug particle have tendency to agglomerate due to van-der Waals attraction or hydrophobicity, which 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 solvents.

1) BCS CLASSIFICATION[6,7,8]

Biopharmaceutics classification system (BCS) is a useful tool for making decision in formulation development from a biopharmaceutical point of view. As per BCS classification system drug substances is categorized into one of four classes depending on their solubility and intestinal permeability, and these four categories are defined as follows:

Class	Solubility	Permeability	Characteristic features
Class I	High	High	Well absorption orally
Class II	Low	High	Variable absorption due to solubility limitation.
Class III	High	Low	Variable absorption due to permeability limitation
Class IV	Low	Low	Meager absorbed due to both solubility & permeability limitation.

Table no: 1 Biopharmaceutical classification system

1.1) Principle concept behind BCS [6,7,8]

Principle concept behind BCS is that if two drugs products yield the same concentration profile along the gastrointestinal (GI) tract, they will result in the same plasma profile after oral administration. This concept can be summarized by application of Fick's first in the following equation

$$J = Pw\ Cw \quad \ldots\ldots\ldots\ldots\ldots\ldots (1)$$

Where J is the flux across the gut wall, Pw is the permeability of the gut wall to the drug, and Cw is the concentration profile at the gut wall In terms of bioequivalence, it is assumed that highly permeable, highly soluble drugs housed in rapidly dissolving drug products will be bioequivalent and that, unless major changes are made to the formulation, dissolution data can be used as a surrogate for pharmacokinetic data to demonstrate bioequivalence of two drug products.

Sr. No.	Drug property influencing absorption	Corresponding dimensionless parameter	Significance
1.	**Solubility:** A drug with high solubility is the one whose largest dosage strength is soluble in 250 ml or less of water over a pH range of 1-8.	**Dose number:** It is mass of drug divided by an uptake volume of 250ml and drug's solubility.	Ideally, dose ratio should be below 1if full dissolution is to be possible in principle. Obviously, higher doses will raise the ratio and absorption less likely.

2.	**Dissolution rate:** A drug product with rapid dissolution is the one when ≥ 85 % of the labelled amount of drug substance dissolves within 30 minutes using USP apparatus 1 or 2 in a volume of ≤900ml buffer solutions.	**Dissolution number:** It is the ratio of mean residence time to mean dissolution time.	Ideally, dissolution number should exceed 1. In the case of solid dosage forms, a combination of inadequate solubility or diffusivity, or density can increase the time needed for full dissolution and reduce this ratio.
3.	**Permeability:** A drug with high permeability is the one having extent of absorption greater than 90% of the administered dose given that the drug is stable in the gastrointestinal environment.	**Absorption number:** It is the ratio of the mean residence time of drug in the GIT to the absorption time.	Ideally, absorption number should excess 1. Longer absorption times resulting from lower permeability will reduce the ratio.

Table 2: BCS classification of drug based on solubility, dissolution rate, and permeability.[9]

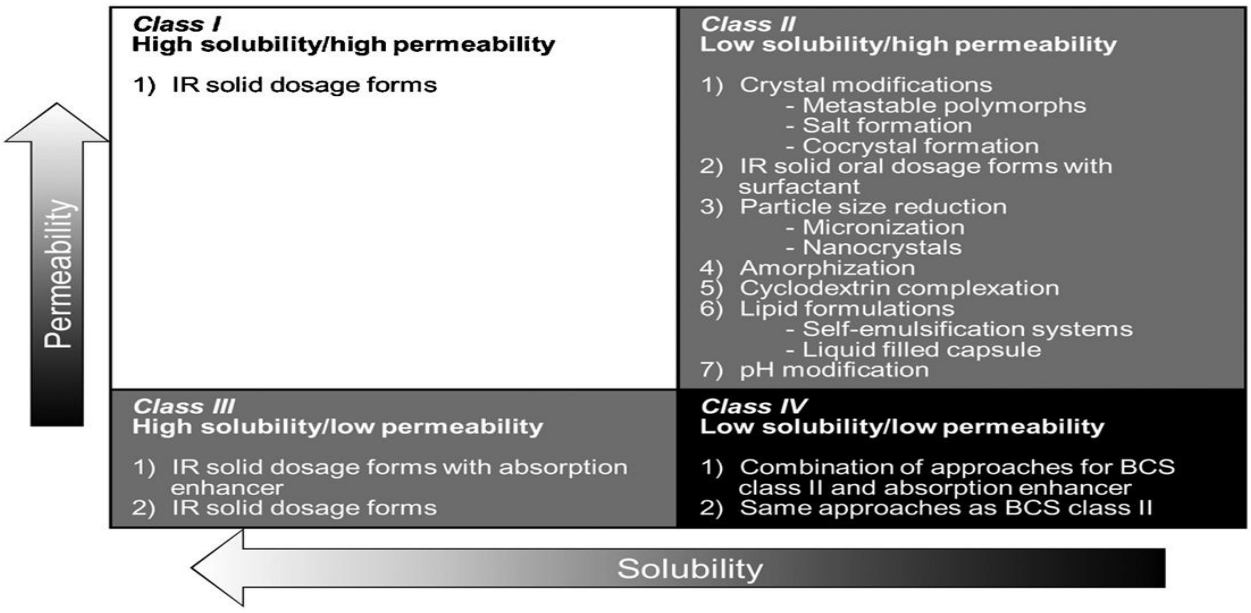


Figure 1: BCS and viable formulation option based on the BCS.

1.1.1 Formulations for BCS class I drugs :[10, 11,12,13,14,15]

BCS class I drugs are defined as being highly soluble and highly permeable. Metoprolol, Propranolol and Theophylline are categorized into this class. For BCS class I drugs, there is no rate-limiting step for oral absorption and bioavailability. BCS class I drugs possesses no major challenges for Immediate release (IR) form but Controlled release form need to limit drug release or dissolution since absorption of released drug is rapid.

1.1.2. Formulation for BCS class II drugs:

BCS class II drugs are identified as low solubility and high permeability. For example – Glibenclamide, Griseofulvin and Carbamezapine are categorized into class II. Generally, the bioavailability of a BCS class II drug is rate-limiting by its dissolution, so that even a small enhancement in dissolution rate sometimes results in a large increase in bioavailability. Therefore, an enhancement of the solubility and dissolution rate of the drug is found to be a key factor or improving the bioavailability of BCS class II drugs. Several physicochemical factors control the dissolution rate of the drugs. According to the modified Noyes – Whitney equation, the factor affecting the drug dissolution rate are defined as the effective surface area, the diffusion coefficient, the diffusion layer thickness, the saturation solubility, the amount of dissolution drug, and the volume of dissolution media[15]. Consideration of the modified Noyes – Whitney equation provides some keys as to how the dissolution rate of even very poorly soluble compounds might be improved to minimize the limitations to oral bioavailability:

$$dC/dt = \frac{ADK\,w/o\,(Cs - C)}{Vh} \ldots\ldots\ldots\ldots (1)$$

Where,

- **dC/dt** is the dissolution rate,
- **A** is the surface area available for dissolution
- **K $_{w/o}$** is the water/oil partition coefficient of the drug,
- **V** is the volume of dissolution medium,
- **h** is the thickness of the stagnant layer,
- **(Cs - C)** is the concentration gradient for diffusion of drug.

Increases in the saturation solubility and the effective surface area have a positive impact on the dissolution rate of the drugs, and can be increased by efforts of Preformulation study and formulation design. Crystal modification and co-crystal formation, particle size reductio, self – emulsification, pH modification, amorphiztion and salt formation are considered to be effective for improving the dissolution behavior of BSC class II drugs.

1.1.3. Formulations for BCS class III drugs:

Drug with high solubility and low permeability are classified as BCS class III. For example – Insulin, Atenolol, Ranitidine, Acyclovir, Neomycin B are categorized in BCS class III drugs. Gastrointestinal membrane permeability is the rate limiting step for the bioavailability of BCS class III drugs. Theoretically, there are three transepithelial pathways for the drugs absorption from the intestinal lumen to the bloodstream: transcellular carrier-mediated active or facilitated transport, transcellular passive transport, and paracellular transport. Most of the orally administered drugs are absorbed via transcellular passive transport process. In this case, the intrinsic lipophilicity of the drug is a determinant of the drug transport across the enterocytes, and highly lipophilic would have high membrane permeability. The intrinsic lipophilicity of a drug is determined by its chemical structure; hence, it is necessary to return to the lead optimization phase to increase the permeability via the transcellular route. Hydrophilic drugs generally penetrate the intestinal membrane via the paracellular route. Permeation enhancers, such as fatty acid, bile salts, surfactants, and polysaccharides, play a major role in enhancing the permeability of drugs via the paracellular pathway; however, some of them are known to have membrane damaging effects. Since far less is known about the efficacious and safe dosage options for BCS class III drugs, IR solid dosage forms should be practically designed for clinical use, although the absorption could be limited by membrane permeation.

1.1.4. Formulation for BCS class IV drugs:

BCS class IV drugs exhibit molecular properties such as low solubility and low permeability. Since both solubility and permeability are rate-limiting steps for absorption, it would be considered that physiological factors, for example, gastric emptying time and gastrointestinal transit time, highly influence the absorption of BCS class IV drugs. Therefore, the drugs categorized in BCS class IV could exhibit large inter- and intra-subject variability in terms of absorption. This variability in absorption could result in the challenging drug development of

BCS class IV drugs as well as their formulation design. There are viable formulation options focusing on improvement of the dissolution behavior that are commonly applied to BCS class II drugs. However, the approaches for enhancing their permeability are still at an early investigational stage, and their safety is not well established. In this context, formulation approaches similar to those for BCS class II drugs could be practically applied to BCS class IV drugs, even though the absorption could be limited by the poor permeability after dissolving in the gastrointestinal tract.

1.1.5. Formulation of BCS class V drugs:

Class V drugs are those that are metabolically or chemically unstable thus limiting their bioavailability. The various approaches to overcome these problems are aimed at enhancing their stability by use of methods such as:

1. Prodrug design
2. Enteric coating (Protection from stomach acid)
3. Enzyme inhibition or lymphatic delivery (to prevent pre-systemic metabolism)
4. Lipid technologies.

2) Solubility[21,22]

Basic consideration

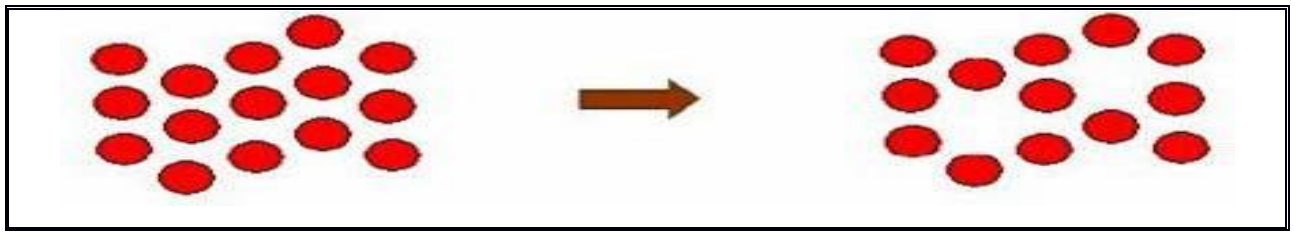
As per FDA, A drug substance is considered "highly soluble" when the highest dose strength is soluble in 250 ml or less of aqueous media over the pH range of 1–7.5 at 37^0C[7]. "Solubility in different solvents is an intrinsic material characteristic for a defined molecule". "Another definition of solubility of a given solute is the maximum concentration to which it can be dissolved in particular solvent to yield homogeneous monophasic system". When a solute dissolves, force of attraction between the solute and the solvent must overcome intermolecular force of attraction of substances. It represents breaking of solute-solute forces & solvent-solvent forces to achieve solute-solvent interaction. The solubility of a solute in a given solvent is determined at fixed temperature (normally a little higher than room temperature). The U. S. Pharmacopoeia (USP) gives the following definition of solubility (USP/NF 2008) as enlisted in [Table 2].

Descriptive term	Parts of solvent required for 1 part of solute
Very soluble	Less than 1
Freely soluble	From 1 to 10
Soluble	From 10 to 30
Sparingly soluble	From 30 to 100
Slightly soluble	From 100 to 1,000
Very slightly soluble	From 1,000 to 10,000
Practically insoluble	From 10,000 and over.

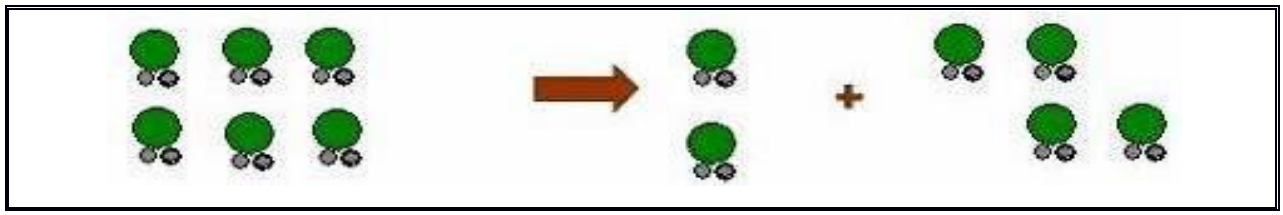
Process of Solubilization[23]

Solubility process is depend on the bonding between the solute and solvent molecule. The bonds involved in solubilization are mainly dipole interaction, London forces, hydrogen bonding, ionic bonding etc.

Step 1: Holes open in the solvent



Step 2: Molecules of the solid breaks away from the bulk



Step 3: The free solid molecules are integrated into solvent holes

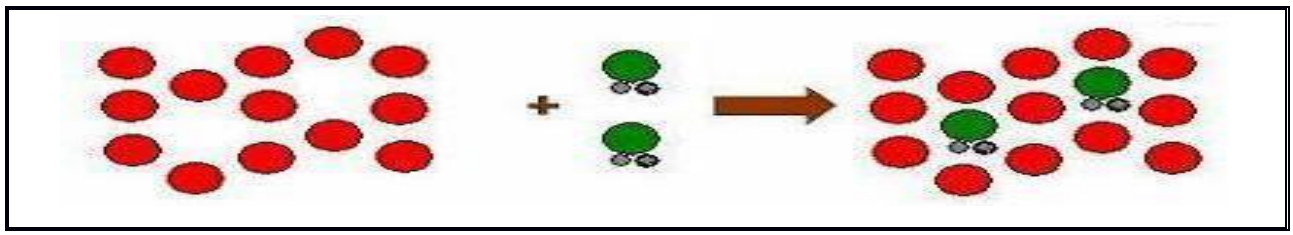


Fig- mechanism of solubility

Tab - Factor affecting Solubilization[36]

Particle Size	The solubility of drug is often intrinsically related to drug particle size; as a particle becomes smaller, the surface area to volume ratio increases. The larger surface area allows a greater interaction with the solvent.
Pressure	For solids and liquid solutes, changes in pressure have practically no effect on solubility but for gaseous solutes, an increase in pressure, increases solubility and a decrease in pressure, decrease the solubility. Nature of the solute and solvent only 1 gram of lead (II) chloride can be dissolved in 100 grams of water at room temperature while 200 grams of zinc chloride can be dissolved. The great difference in the solubility's of these two substances is the result of differences in their natures.
Temperature	Temperature will affect solubility. If the solution process absorbs energy then the solubility will be increased. If the solution process releases energy then solubility will decrease with increase in temperature. The situation is different for gases with increase of temperature they become less soluble in each other and in water but more soluble in organic solvents. Organic compounds nearly always become soluble as temperature raised in most of the solvents
Molecular Size	The solubility of the substance is decreased when molecules have higher molecular weight and higher molecular size because larger molecules are more difficult to surround with solvent molecules in order to solvate the substance.
Polarity	Polarity of the solute and solvent molecules will affect the solubility. Generally dissolves like means non-polar solute molecules will dissolve in non-polar solvents and polar solute molecules will dissolve in polar solvents. The polar solute molecules have a positive and a negative end to the molecule. If the solvent molecule is also polar then positive ends of solvent molecules will attract negative ends of Solute molecules. This is a type of intermolecular force known as dipole-dipole interaction. The other forces called London dispersion forces where the positive nuclei of the atoms of the solute molecule will attract the negative electrons of the atoms of a solvent molecule. This gives the non polar solvent a chance to solvate the solute molecules.
Polymorphs	Polymorphs can vary in melting point. Since the melting point of the solid is related to solubility, so polymorphs will have different solubility's. Generally the range of solubility differences between different polymorphs is only 2-3 folds due to relatively small differences in free energy.

3) Methods of Determination of Solubility

There are several methods available for determination of solubility of a drug. Some of these are;

A. Equilibrium method

B. Non-equilibrium method

C. Intrinsic dissolution method

D. Partition coefficient measurement

E. Calculation based on melting point and Octanol-Water partition coefficient.

A. Equilibrium method:

This method is the most common method of determining the solubility of any compound at laboratory scale. According to this method an excess amount of the compound is dissolved in particular medium filled in vials and allow to shake for specified period of time at specified sets of temperature condition, until equilibrium is achieved, after specified time intervals the solubilized compound is taken from the supernant and quantity dissolved is determined by validated analytical procedure such as HPLC or Spectrophotometric methods. In this method multiple sets of vials are to be placed and when two sets of vials give same result at particular time, it can be said equilibrium has been achieved.

Application:

This method is most suitable for estimating equilibrium solubility.

Advantages:

Simple and easy method.

Disadvantage:

1) Lack of sensitive analytical procedures during early stages of drug discovery.

2) Measurement of solubility requires the time period of 24-48 hrs or sometimes a week also, i.e. Time consuming.

3) Addition of excess amount of drug which is expensive for pharmaceutical industries.

B. Non Equilibrium method/ shake flask method:

The method includes Solubilization of 10 µg/ml of the compound in 25ml of DMSO and pouring around 1 µg/ml of solution of compound in chloride free buffer solution of pH 7.4 until the compound precipitates out from the solution. Hence the method does not require equilibrium to be attained between solute and solvent. The precipitation can be characterized by rapid change in absorbance of solution.

C. Intrinsic dissolution rate method:

The dissolution rate is directly proportional to the equilibrium solubility if the appropriate experimental conditions such as the once used for intrinsic dissolution rate measurements are selected. The rotating-disc method is the most useful and most widely used technique for measuring intrinsic dissolution rate. Intrinsic dissolution means the dissolution of drug without its formation in any suitable dosage form which is nearly equivalent to that of solubility of drug in pure form, so measuring intrinsic dissolution rate by selecting appropriate experimental condition will give equilibrium solubility of the drug.

The intrinsic dissolution rate method is most useful where the equilibrium method cannot be used. For example, when one wishes to examine the influence of crystal habit, solvates and hydrates, polymorphism, and crystal defects on apparent solubility, the intrinsic dissolution rate method will usually avoid the crystal transitions likely to occur in equilibrium methods.

D. Determination of partition coefficient:

When the compound is highly lipophilic and it is practically impossible to dissolve it in any suitable solvent, measurement of partition co-efficient is a suitable method for predicting solubility. Once the solubility of these compounds in some typical organic solvents has been measured, solubility in aqueous solvents can be measured by measuring partition coefficient of the compound in the mixture of aqueous phase and organic phase. The method has another application for the drug and Prodrug having instability in aqueous medium.

Advantage:

Simplicity and rapid determination of partition co-efficient of the compound simply by vigorous shaking for few minutes followed by separation of two phases by gravity.

E. Calculation based on melting point and Octanol-Water partition coefficient:

Imperial formula is available based on Octanol-Water partition coefficient and melting point to measure the solubility of any compound by considering the transfer of a solute from the solid state to Octanol followed by its transfer to the aqueous phase.

$\text{Log } S_{aq} = -\log P_o/w - 0.01MP + 1.05$…… (4)

Where, S_{aq} is the aqueous solubility of the drug, P_o/w is the Octanol/water partition coefficient, and MP is the melting point. As it is an imperial formula it does not work for all type of compounds but it is suitable for few compounds.

Approach to Enhance the Solubility[25]

Principally all the methods are classified into two main headings as;

1. **Physical approach**
2. **Chemical approach**

Further classification into each category depends on whether the techniques are of conventional or novel origin. Detailed classification of various solubility enhancement techniques

1. Physical approach

A. Particle size

1. Particle size reduction
2. Nanosuspension / Nanoparticles

B. Modification of crystal habit

C. Polymorphs

D. Pseudo-polymorphs (including solvates)

E. Complexation/ Solubilization

1. Use of surfactants, Microemulsion & Self-Emulsifying System
2. Co-solvents & Co-solvency
3. Use of Cyclodextrin
4. Hydrotrophy

F. Drug Dispersion Into Carriers

1. Eutectic mixtures
2. Solid dispersions
3. Solid solutions

G. Chemical approach

1. Soluble Prodrug
2. Salt formation.

4) Introduction of Liquisolid Technique[3]

Many techniques are being employed for the solubility enhancement of poorly soluble drugs to resolve the bioavailability issue due to inadequate dissolution rate. Various approaches make use of hydrophilic polymers as solubility enhancers acting through a variety of mechanisms such as amorphization, co-solvency, micelle formation or inclusion complexes.

These techniques impart many advantageous effects in the formulation development. But usually these approaches show lack of stability and decreasing success rate over a period of storage. One of the remarkable demerits of solid dispersions, glass solutions, eutectic mixtures and inclusion complexes is formation of sticky and hygroscopic mass resulting in the poor flow characteristics. Due to this set-back, industrial feasibility of the final dosage form becomes very difficult.

The liquisolid technology emerged as a new drug delivery system distinguished by its characteristics and ability to deliver variety of drugs. Liquisolid drug delivery system has gained attention of pharmaceutical researchers due to its contribution in the solubility enhancement as well as dissolution retarding approaches depending on the need and design of the formulation.

Three major components in the formulation of liquisolid compacts are liquid medication, carrier and coat material. Other excipients such as use of disintegrant or release retarding polymers for modification of release profile are used as per the objective and need of the formulation.

5) Concept of liquisolid system[(3)]

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 such as celluloses, both absorption and adsorption take place. The liquid initially absorbed in the interior of the particles is captured by its internal structure. After the saturation of this process, adsorption of the liquid onto the internal and external surfaces of the porous carrier particles occurs. Then, the coating material having high adsorptive properties and large specific surface area provides the liquisolid system the desirable flow characteristics. In liquisolid systems, the drug is already in solution form in liquid vehicle, while at the same time, it is carried by powder.

The wettability of the compacts in the dissolution media is one of the proposed mechanisms for explaining the enhanced dissolution rate from the liquisolid compacts. Non-volatile solvent present in the liquisolid system facilitates wetting of drug particles by decreasing interfacial tension between dissolution medium and tablet surface. Thus, due to substantial increase in wettability and effective surface area for dissolution, liquisolid compacts may be expected to reveal enhanced release profiles of water-insoluble drugs. 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.

However, the drug release profile entirely depends on the characteristics of drug, carrier and vehicle used. Thus by altering these variables, liquisolid technique can be used for enhancing or retarding the drug release.

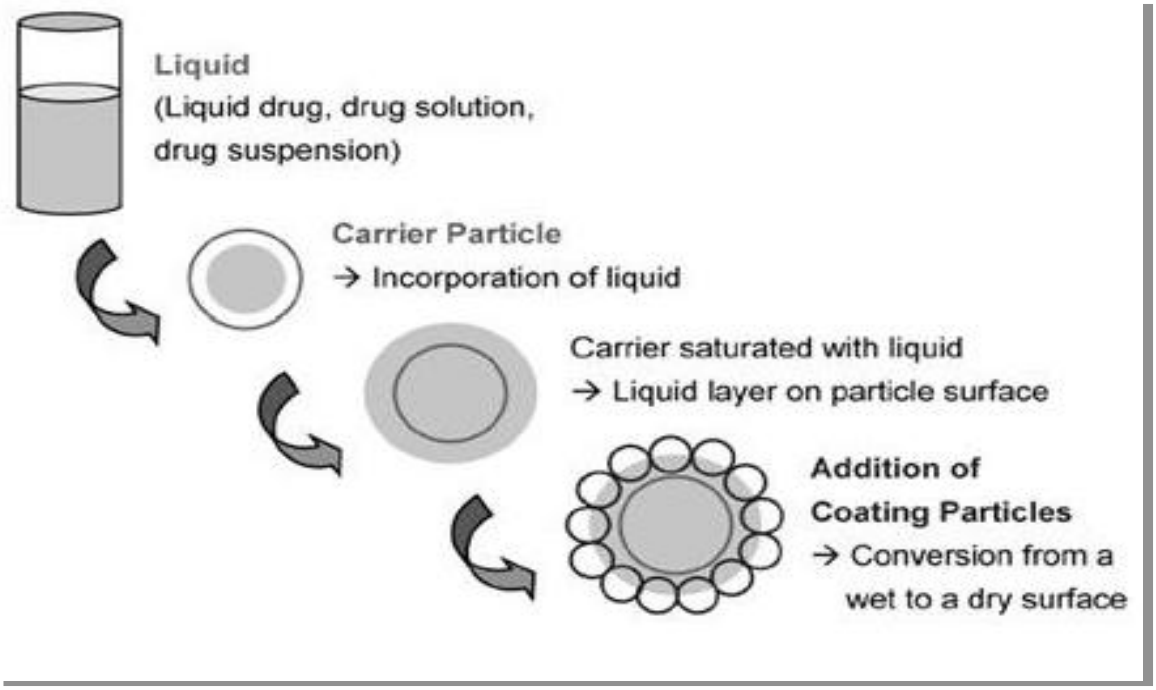


Fig- Concept of Liquisolid formulation

Advantages-

1) Drugs such as Digitoxin, Prednisolone and Hydrocortisone etc. i.e. practically water-insoluble liquid and solid drugs 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 tabletted or encapsulated dosage form it is held in a solubilised liquid state, which consequently contributes to increased drug wetting properties, thereby enhancing drug dissolution.

4) Production cost 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) Greater drug surface area is exposed to the dissolution medium.

7) It is used in controlled drug delivery systems.

8) Drug can be molecularly dispersed in the formulation.

9) Drug release can be modified using suitable formulation ingredients.

10) Capability of industrial production is also possible.

11) Enhanced bioavailability can be obtained as compared to conventional tablets.

12) Differentiate the dosage form by admixture of colour into liquid vehicle.

13) To minimize excipients in formulation compare with other formulations like solid Dispersions.

14) Omit the process approaches like nanonisation, micronization techniques.

Disadvantages

1. Formulation of high dose lipophilic drugs the liquisolid tablet is one of the limitations of this technique.

2. In order to achieve acceptable flowability and compactability for liquisolid powder formulation, high levels of carrier material and coating materials should be added. This will increase the weight of tablets to above one gram which makes them difficult to swallow. Consequently, it is impossible with conventional tablet methods to convert high dose to liquisolid tablets with a tablet weight of less than 50mg. Dissolution profile enhancement occurs in the presence of low levels of hydrophilic carrier, where coating material is not significant.

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

Classification of Liquisolid system:[26,27]

A. Based on the Type of liquid Medication:

Based on type of liquid medication used in the formulation, Liquisolid systems may be classified into four subgroups:

1. Powdered drug solutions

2. Powdered drug suspensions

3. Powdered drug emulsions

4. Powdered liquid drugs

The first three may be produced from the conversion of drug solutions or drug suspensions and emulsions, the later from the formulation of liquid drugs into Liquisolid systems.

Since non-volatile solvents are used to prepare the drug solution or suspension, the liquid vehicle does not evaporate and thus, the drug carried within the liquid system, remains dispersed throughout the final product.

B. Based on the Formulation Technique:

Depending on the technique used, Liquisolid systems may be classified into two categories:

1. Liquisolid compacts

2. Liquisolid microsystem

Liquisolid compacts are prepared using the previously outlined method to produce tablets or capsules, whereas the Liquisolid microsystems are based on a new concept which employs similar methodology combined with the inclusion of an additive e.g. PVP, in the liquid medication which is incorporated into the carrier and coating materials to produce an acceptably flowing admixture for encapsulation. The advantage stemming from this new technique is that the resulting unit size of Liquisolid microsystems may be as much as five times less than that of Liquisolid compacts.

Components of Liquisolid System[(4)]

Component	Examples
Non Volatile Liquids	Poly Ethylene Glycol 200, Poly Ethylene Glycol 300, Poly Ethylene Glycol 400, Glycerine, Propylene Glycol, fixed oils.
Carrier Materials	Microcrystalline Cellulose PH 101, Microcrystalline Cellulose PH 200, Lactose, Methyl Cellulose, Ethyl Cellulose, Starch1500, Ethocel, Eudragit RL, Eudragit RS 12, Hydroxy Propyl Methyl Cellulose K4M, Hydroxy Propyl Methyl Cellulose K100M, Xanthum Gum, Guar gum

Coating Materials	Aerosil 200, Silica (Cab-O-Sil M5), Syloid 244FP, and Colloidal Silicon Dioxide.
Disintegrants	Sodium Starch Glycolate , Croscarmellose Sodium, Cross Polyvinyl Pyrrolidine, Pregelatized Starch.
Glidant	Talc.
Lubricant	Magnesium Stearate.
Release retardant material	Eudragit RS, RL, Hydroxy Propyl Methyl Cellulose K100M, K15M, K4M.

6) Method of preparation of liquisolid system[28,29,30]

A liquid drug can be converted into dry-looking liquisolid system without being further chemically modified. If liquisolid system of a solid water-insoluble drug is to be formulated, it should be initially dissolved or suspended in a suitable non-volatile solvent system to produce a drug solution or drug suspension of desired concentration.

Next, a certain amount of the prepared drug solution or a liquid drug itself is incorporated into a specific quantity of carrier material which should be preferably of a porous nature and possessing sufficient absorption properties. The resulting wet mixture is then converted into a dry-looking, non adherent, free-flowing and readily compressible powder by the simple addition and mixing of a calculation amount of coating material. Excipients possessing fine and highly adsorptive particles are suitable for this step.

Before compression or encapsulation, various adjuvant like lubricants and disintegrants (immediate release) or binder (sustained release) may be added to final liquisolid system to produce liquisolid compact i.e. tablet or capsule.

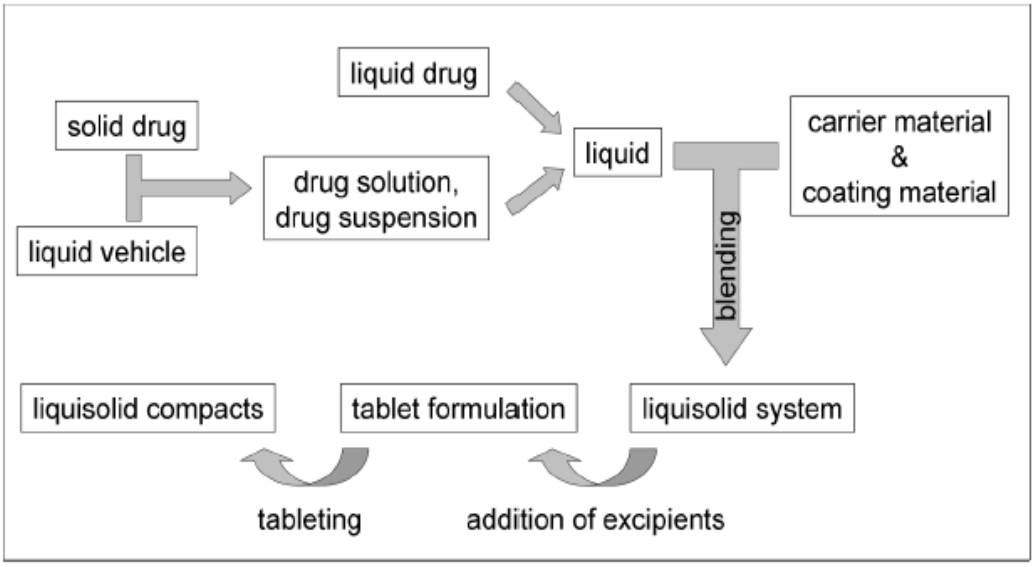


Figure 5: General method of preparation liquisolid systems

The Mathematical Model for Designing the Liquisolid Systems[4]

To achieve good flow behavior and compressibility of liquisolid systems a mathematical model designed by Spireas. was used as formulation design model for the liquisolid tablets. Prerequisites for this include suitable drug candidate, suitable non-volatile solvent, carrier and coating materials. The Spireas et al's model is based on new fundamental properties of powder called "flowable liquid retention potential" (ϕ value) and "compressible liquid retention potential" (ψ value) of powdered excipients used in the formulation. The ϕ value is defined as the maximum weight of liquid that can be retained per unit weight of powder material in order to produce an acceptably flowing liquid/powder admixture while the ψ 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 compressible liquid or powder admixture i.e. being able to yield tablets of satisfactory mechanical strength without presenting any liquid squeezing out of liquisolid mass during compression**.** The excipients ratio (*R*) or the carrier: coating material ratio is represented as follows:

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

Where,

R is ratio of carrier (*Q*)

and coating materials (*q*).

For, a successful formulation design, this ratio *R* should be suitably selected. Another term called Liquid load factor (Lf) is defined as ratio of weight of liquid medication (W) to weight of carrier material (*Q*) in system.

$$\mathbf{Lf = W / Q \ldots \ldots \ldots (2)}$$

The ϕ value was used to calculate excipient quantities. Equation derived for this is as follows:

$$\mathbf{Lf = \phi + \phi\,(1 / R) \ldots \ldots \ldots (3)}$$

where, ϕ and ϕ are the constant ϕ values of carrier and coating materials, respectively. By calculating Lf and W, we can calculate the amount of Q and q required for the liquisolid system.

7) Mechanisms of Enhanced Drug Release from Liquisolid Systems [35,4]

1) Increased Aqueous Solubility,

2) Increased Drug Surface Area ,

3) Increased Wettability.

The mechanisms are described as :

1) 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 decreases.

2) 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 cosolvent.

3) 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 surface. shows lower contact angle of liquisolid compacts than the conventional tablets and thus improved wettability. Figure represents the comparison of wettability between a conventional tablet and a liquisolid tablet.

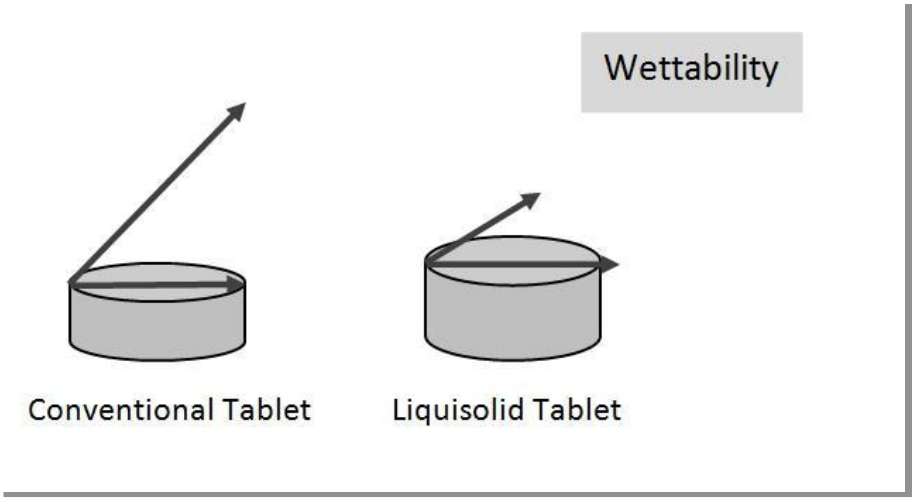


Fig- Comparison of Wettability between a Conventional tablet and a Liquisolid tablet

8) Preparation of Liquisolid Tablets[4]

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 above binary mixture disintegrant like sodium starch glycolate, other reaming additives were added according to their application and mixed for a period of 10 to 20 min. in a mortar.

4) Final mixture was compressed using the manual tableting machine to achieve tablet hardness.

5) Characterize the final liquisolid granules for solubility, dissolution, flowability, compressibility and other physicochemical properties.

8) Limitations of liquisolid technology[26,27]

a) Not suitable for formulation of high dose water insoluble drugs.

b) It does not require chemical modification of drug.

c) If more amount of carrier is added it increase the flow properties of powder, it may increase the tablet weight too, hence it is difficult to swallow.

d) Acceptable compression may not be achieved because the liquid drug may be squeezed out during compression resulting in unsatisfactory tablet weight.

9) Applications[4]

1. Liquisolid compact technology is a powerful tool to improve bioavailability of water insoluble drugs. Several water insoluble drugs on dissolving in different non-volatile solvents, have been formulated into liquisolid compacts.

2. Literature cites different drugs successfully incorporated into liquisolid compacts.

3. Rapid release rates are obtained in liquisolid formulations.

4. These can be efficiently used for water insoluble solid drugs or liquid lipophilic drugs.

5. Sustained Release of drugs which are water soluble drugs such as propranolol hydrochloride has been obtained by the use of this technique.

6. Solubility and dissolution improvement

7. Flowability and compressibility

8. Designing of Controlled Release Tablets

9. Bioavailability Enhancement

10. Application in probiotics.

CONCLUSION

In this technique drug is dissolved in a non volatile solvent and their by this liquid medicament is converted to non adherent, dry looking and free flowing by using suitable carrier and coating material. In This Liquisolid technique gives a design to enhance the absorption as well as dissolution rate their by it may enhance the bio availability of a poorly soluble, insoluble or lipophilic drug and to formulate them into immediate release or else sustain release by selection of suitable solvent and carrier. Because of the presence of drug in the state of solubilised or moleculary dispersed state, so solubility of insoluble drug is enhanced.

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