LIQUISOLID TECHNOLOGY: TECHNIQUE FOR FORMULATION WITH ENHANCED BIOAVAILABILITY

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ABSTRACT
Liquisolid technique is also known as powder solution technology. It is the technique which deals with the solubility enhancement of poorly soluble drugs. As these days there are many drugs in the market with poor solubility which leads to poor dissolution and bioavailability, so solubility is becoming rate limiting factor in the development of new drugs. 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 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. With Liquisolid technique liquid formulations such as solutions or suspensions of poorly soluble drugs in a non-volatile liquid vehicle are converted into acceptably flowing and compressible powders by simple physical blending with selected excipients named the carrier and the coating material. The liquisolid approach has been successfully applied in release enhancement of low dose poorly soluble drugs.

KEYWORDS: Liquisolid, bioavailability, dissolution, sustained release.

INTRODUCTION[5, 2]
The bioavailability of many poorly water-soluble drugs is limited by their dissolution rates which are internal controlled by the effective surface present for dissolution. The enhancement
of oral bioavailability of poor water soluble drugs remains one of the most challenging aspects of drug development. Various formulation parameters that play a vital role for successful formulation includes, aqueous solubility, stability at ambient temperature and humidity, photostability, compatibility with different solvents & excipients etc. Out of these parameters solubility is the most important for developing the formulation. There have always been certain drugs for which solubility has presented a challenge to the development of a suitable formulation for oral administration. Compounds exhibiting dissolution rate limited bioavailability are considered class-II, according to BCS classification. Poor water soluble compounds show decreased release rate & poor bioavailability. However, the most attractive option for increasing the release rate is improvement of the solubility through formulation approaches. There are three major approaches in overcoming the bioavailability problems due to such causes are,

- **a. The pharmaceutical approach**
  Modification of formulation, manufacturing process or the physicochemical properties of the drug without changing the chemical structure.

- **b. The pharmacokinetic approach**
  Pharmacokinetics of the drug is altered by modifying its chemical structure.

- **c. The biological approach**
  Route of drug administration may be changed such as changing from oral to parenteral route.

**BCS CLASSIFICATION**[^8,9]

1) **Class I: High Permeability and Solubility**
   The bioavailability of class-I compounds is determined only by delivery of the drugsolution to the intestine. Examples: Benzapril, Loxoprofen, Sumatriptan etc.

2) **Class II: High Permeability but Low Solubility**
   The bioavailability of class-II compounds is limited by drug solubility/dissolution. Examples: Albendazole, Aceclofenac, Diazepam, Eprosartan, Erythromycin etc.

3) **Class III: low Permeability but High Solubility**
   The bioavailability of class-III compounds is limited by intestinalpermeability. Examples: Gabapentine, Topiramate, Atropine etc.

4) **Class IV: Low Permeability and Low Solubility**
   The bioavailability of class-IV compounds is limited both by solubility or dissolution and intestinal permeability.
Solving solubility problems is a major challenge for the pharmaceutical industry with developments of new pharmaceutical products.

**METHODS OF SOLUBILITY ENHANCEMENT**

(1,10s)
- Particle Size Reduction
  - Conventional methods
  - Micronization
  - Nanosuspension
- Solid Dispersion
- pH adjustment
- High Pressure Homogenization
- Supercritical fluid recrystallization (SCF)
- Sonocrystallisation
- Inclusion Complex Formation-Based Techniques
  - Kneading Method
  - Lyophilization/Freeze-Drying Technique
  - Microwave Irradiation Method
- Liquisolid technique
- Salt formation

**Particle size reduction**

The solubility of drug is often intrinsically related to drug particle size as a particle becomes smaller, the surface area increases. The larger surface area allows a greater interaction with the solvent which cause increase in solubility. By reducing particle size, increased surface area improves the dissolution properties.

**TECHNIQUES OF PARTICLE SIZE REDUCTION**

**Conventional methods:** Conventional methods of particle size reduction, such as spray drying, rely upon mechanical stress to disaggregate the active compound. Particle size reduction is thus permitting an economic, reproducible, and efficient means of solubility improvement. However, the mechanical forces natural to comminution, such as milling and grinding, often impart significant amounts of physical stress upon the drug product which may induce degradation. The thermal stress which may occur during comminution and spray drying is also a consider when processing of thermo sensitive or unstable active agents. Only
by using traditional methods of solubility enhancement it is not possible to increase the solubility of poorly soluble drugs up to desirable level.

**Micronization:** Micronization is another conventional technique for the particle size reduction. Micronization increases the dissolution rate of drugs through increased surface area; by decreasing particle size, it does not increase equilibrium solubility. Micronization of drugs is done by milling techniques using jet mill, rotor stator colloid mills and so forth. Micronization is not suitable for drugs having a high dose number because it does not change the saturation solubility of the drug.

**Nanosuspension:** This technology is applied to poorly soluble drugs that are insoluble in both water and oils. A pharmaceutical nanosuspension is biphasic systems consisting of Nano sized drug particles stabilized by surfactants for either oral and topical use or parenteral and pulmonary administration. The particle size distribution of the solid particles in nanosuspensions is usually less than one micron with an average particle size ranging between 200 and 600 nm.

**Hydrotropy:** Hydrotropy is a solubilization phenomenon whereby addition of large amount of a second solute results in an increase in the aqueous solubility of existing solute. Concentrated aqueous hydrotropic solutions of sodium benzoate, sodium salicylate, urea, nicotinamide, sodium citrate, and sodium acetate have been observed to enhance the aqueous solubilities of many poorly water-soluble drugs.

**Cosolvency:** The solubility of poorly soluble drugs in water can be increased by mixing it with some water miscible solvent in which the drug is readily soluble. This process is known as cosolvency and the solvent used in combination are known as cosolvent. Cosolvent system works by reducing the interfacial tension between the aqueous solution and hydrophobic solute. It is also commonly known as solvent blending. There is a dramatic change in the solubility of drugs by addition of organic co-solvent into the water. The co-solvents are having hydrogen acceptor or donor groups with a small hydrocarbon region. The hydrophobic hydrocarbon region usually interferes with the hydrogen bonding network of water which consequently reduces the intermolecular attraction of water while the hydrophilic hydrogen bonds ensures water solubility.
**Solubilization by Surfactants:** Surfactants are molecules with distinct polar and nonpolar regions. Most surfactants consist of a hydrocarbon segment connected to a polar group. The polar group can be anionic, cationic, zwitterionic or nonionic. When small polar molecules are added they can accumulate in the hydrophobic core of the micelles. This process of solubilization is very significant in industrial and natural processes. The addition of surfactants may decrease the surface tension and increase the solubility of the drug within an organic solvent. The use of surfactants to improve the dissolution performance of poorly soluble drug products is possibly the fundamental, chief, and the oldest method. Surfactants are the agent which reduces surface tension and enhance the dissolution of lipophilic drugs in aqueous medium. The surfactants are also used to stabilize drug suspensions. When the concentration of surfactants more than their critical micelle concentration (CMC, which is in the range of 0.05–0.10% for most surfactants), micelle formation occurs which entrap the drugs within the micelles. This is known as micellization and generally results in enhanced solubility of poorly soluble drugs.

**Solid Dispersion:** Solid dispersion as group of solid products consisting of at least two different components, generally, a hydrophilic matrix, and a hydrophobic drug. The matrix can be either crystalline or amorphous. The drug can be isolated molecularly, in amorphous particles or in crystalline particles. Solid dispersion can also be referred as the dispersion of one or more active ingredients in an inert matrix at solid state prepared by the melting, solvent, and melting solvent method. The most commonly used hydrophilic carriers for solid dispersions include polyvinylpyrrolidone, polyethylene glycols, Plasdone-S630. Many times surfactants may also used in the formation of solid dispersion. Surfactants like Tween-80, Docusate sodium, Myrj-52, Pluronic-F68 and Sodium Lauryl Sulphate are used.

**pH adjustment:** Poor water soluble drug may potentially dissolve in water by applying a pH change. To access the solubility of this approach, the buffer capacity and tolerability of the selected pH are important to consider. Solubilized excipients that increase environmental pH within the dosage form to a range higher than pKa of weekly acidic drugs increase the solubility of that drug, those excipients that act as alkalizing agents may increase the solubility of weekly basic drugs.

**High Pressure Homogenization:** High-pressure homogenization has been used to prepare nanosuspension of many poorly water soluble drugs. In this method, the suspension of a drug and surfactant is forced under pressure through a nanosized aperture valve of a high pressure
homogenizer. The principle of this method is based on cavitation in the aqueous phase. The cavitation forces within the particles are sufficiently high to convert the drug microparticles into nanoparticles. The concern with this method is the need for small sample particles before loading and the fact that many cycles of homogenization are required.

**Supercritical fluid recrystallization (SCF):** Those fluids are referred to as supercritical fluids which are having temperature and pressure greater than its critical temperature and critical pressure so as they are acquire properties of both gas and liquid. The best example of this is carbon dioxide. SCF are highly compressible at critical temperatures and allows alteration in density and mass transport characteristics which determines its solvent power due to moderate changes in pressure. As the drug gets solubilized within SCF they can be recrystallized with reduced particle size of drug.

**Sonocrystallisation:** Recrystallization of poorly soluble materials using liquid solvents and antisolvents has also been employed successfully to reduce particle size. The novel approach for particle size reduction on the basis of crystallization by using ultrasound is Sonocrystallisation. Sonocrystallisation utilizes ultrasound power characterised by a frequency range of 20–100 kHz for inducing crystallization. It’s not only enhances the nucleation rate but also an effective means of size reduction and controlling size distribution of the active pharmaceutical ingredients. Most applications use ultrasound in the range 20 KHz-5 MHz.

**Complexation:** Complexation of drugs with cyclodextrins has been used to enhance aqueous solubility and drug stability. Cyclodextrins of pharmaceutical relevance contain 6, 7 or 8 dextrose molecules (α, β, γ-cyclodextrin) bound in a 1,4-configuration to form rings of various diameters. The ring has a hydrophilic exterior and lipophilic core in which appropriately sized organic molecules can form noncovalent inclusion complexes resulting in increased aqueous solubility and chemical stability. Complexation relies on relatively weak forces such as London forces, hydrogen bonding and hydrophobic interactions.

**Co-precipitate method:** Active drug is dissolved in ethanol at room temperature and suitable polymer is dissolved in distilled water. Different molar ratios of active drug and suitable polymers are mixed respectively. The mixture is stirred at room temperature for one hour and the solvent is evaporated. The resultant mass is pulverized and passed through sieve no. 80 and stored in a desiccators.
**Spray Drying:** The solvent evaporation of drug and polymer solution in different ratio is carried out by using spray dryer. The solutions are prepared by dissolving drug in methanol and polymer in distilled water and mix both solutions, which produces a clear solution. The solvent evaporated by using evaporator. The spray dried mixture of drug with polymer is obtained in 20–30 min.

**Inclusion Complex Formation-Based Techniques:** Among all the solubility enhancement techniques, inclusion complex formation technique has been employed more precisely to improve the aqueous solubility, dissolution rate, and bioavailability of poorly water soluble drugs. Inclusion complexes are formed by the insertion of the nonpolar molecule or the nonpolar region of one molecule (known as guest) into the cavity of another molecule or group of molecules known as host.

**MICRO-EMULSION**
A micro emulsion is an optically clear pre-concentrate, isotropic, thermo dynamically stable transparent (or translucent) system, containing a mixture of oil, hydrophilic surfactant andhydrophilic solvent which dissolves a poorly water soluble drug. Upon contact with water, the formulations spontaneously disperse (or ‘self emulsifies’) to form a very clear emulsion of exceedingly small and uniform oil droplets containing the solubilized poorly soluble drug. Micro-emulsions have been employed to increase the solubility of many drugs that are practically insoluble in water, along with incorporation of proteins for oral, parenteral, as well as percutaneous/transdermal use.

**Self-Emulsifying Drug Delivery Systems:** Self-emulsifying or self-micro emulsifying systems use the concept of in situ formation of emulsion in the gastrointestinal tract. The mixture of oil, surfactant, co-surfactant, one or more hydrophilic solvents and co- solvent forms a transparent isotropic solution that is known as the self-emulsifying drug delivery system (SEDDS).

**Salt formation:** Dissolution rate of particular salt is usually different from that of parent compound. Sodium and potassium salt of week acid dissolve more rapidly than that of pure salt. Limitation of salt formation includes epigastric distress due to high alkalinity, reactivity with atmospheric water and carbon dioxide leads to precipitation, patient compliance and commercilation.
LIQUISOLIDTECHNOLOGY\textsuperscript{[6,3]}

Liquisolid technique is a new and promising method that can change the dissolution rate of water insoluble drugs. The liquisolid technique as described by Spires. It is a novel concept of drug delivery that can change the dissolution rate of water insoluble drugs. It is also called as "powdered solution technology, applied to prepare water-insoluble drugs into rapid-release solid dosage forms. In this, a liquid may be transformed into a free flowing, readily compressible and apparently dry powder by simple physical blending with selected carrier and coating material.

The liquid portion, which can be a liquid drug, a drug suspension or a drug solution in suitable non-volatile liquid vehicles, is incorporated into the porous carrier material. A liquid layer is formed on the particle surface which is instantly adsorbed by the fine coating particles. Thus, an apparently dry, free flowing, and compressible powder is obtained.

NEED OF LIQUISOLIDSYSTEM\textsuperscript{[4]}

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 water. In addition, up to 50\% of orally administered drug compounds suffer from formulation problems related to their low solubility and high lipophilicity. 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 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, 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.

CLASSIFICATION OF LIQUISOLID SYSTEMS\textsuperscript{[4]}

Based on the type of liquid medication contained therein, liquisolid systems may be classified into three sub-groups.

- Powdered drug solutions
- Powdered drug suspensions
Powdered liquid drugs

Powdered drug solutions and suspensions may be produced from the conversion of drug solutions or drug suspensions into liquisolid systems. Powdered liquid drugs are produced from the formulation of liquid drugs into liquisolid systems.

Simultaneously, based on the formulation technique used, liquisolid systems may be classified into two categories namely,

- Liquisolid compacts
- Liquisolid Microsystems

The term “liquisolid compacts” refers to immediate or sustained release tablets or capsules prepared, combined with the inclusion of appropriate adjuvants required for tableting encapsulation, such as lubricants, disintegrates or binders.

The term “liquisolid Microsystems” refers to capsules prepared by combining the drug with carrier and coating materials, combined with inclusion of an additive e.g., PVP in the liquid.

ADVANTAGES

- Number of water-insoluble solid drug can be formulated into liquisolid systems.
- Can be applied to formulate liquid medication such as oily liquid drugs.
- Simplicity.
- Better availability of an orally administered water-insoluble drug.
- Lower production cost than that of soft gelatin capsules.
- Production of liquisolid system is similar to that of conventional tablets.
- Viability of industrial production.
- Can be used for formulation of liquid oily drugs.
- Exhibits enhanced in-vitro drug release as compared to commercial counterpart including soft gelatin capsule preparations.
- Can be used in controlled drug delivery.
- Optimized sustained release, liquisolid tablets or capsules of water insoluble drugs demonstrate constant dissolution rates (zero order release).
- Drug can be molecularly dispersed in the formulation.
DISADVANTAGES

- Not applicable for formulation of high dose insoluble drugs, if more amount of carrier is added to produce free-flowing powder, the tablet weight increases to more than one gram which is difficult to swallow.
- Acceptable compression properties may not be achieved since during compression liquid drug may be squeezed out of the liquisolid tablet resulting in tablets of unsatisfactory hardness.
- Introduction of this method on industrial scale and to overcome the problems of mixing small quantities of viscous liquid solutions onto large amounts of carrier material may not be feasible.

COMPONENTS OF LIQUISOLID COMPACT FORMULATION

Liquisolid compact formulation mainly includes:

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

1. Non-volatile solvent

Non-volatile solvent should be Inert, having high boiling point, preferably water-miscible and not highly viscous organic solvent systems and compatible with having ability to solubilize the drug. The nonvolatile solvent acts as a binding agent in the liquisolid formulation. E.g. Polyethylene glycol 200 and 400, glycerin, polysorbate 80 and propylene glycol.

2. Disintegrant

Superdisintegrants increase the rate of drug release, water solubility and wettability of liquisolid granules. Mostly superdisintegrants like sodium starch glycolate and crosspovidone are used.

3. Drug candidates

Liquisolid technique was successfully applied for low dose BCS class II and class IV drugs which are poorly water soluble and have slow dissolution rate. E.g. carbamazepine, famotidine, piroxicam.
4. 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 flowability. E.g. Grades of microcrystalline cellulose such as Avicel PH 102 and avicel PH 200, lactose.

5. 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 flowability. E.g. SilicaM5, Aerosil 200.

MECHANISMS OF ENHANCED DRUG RELEASE FROM LIQUISOLID SYSTEM
✓ Increased Aqueous Solubility.
✓ Increased Drug Surface Area.
✓ Increased Wettability.

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.

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 liquisolidsystems. 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.

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.

![Wettability](image)

**Figure 1: Comparison of wettability between a conventional tablet and a liquisolid tablet**

**FORMULATION OF LIQUISOLID COMPACT**

The formulation part of liquisolid compact mainly includes Pre-formulation studies and Formulation of liquisolid 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. Liquisolid compressibility test (LSC)

**1. Solubility studies**

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

3. Determination of flowable liquid retention potential (Φ value)
- The term “flowable liquid-retentional 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 or powder admixture.

4. Calculation of liquid load factor (Lf)
- 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.

5. Liquisolid compressibility test (LSC)
- Liquisolid 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.

PREPARATION OF LIQUISOLID COMPACTS

Liquisolid compacts of poorly water soluble drugs containing a drug solution or drug suspension in a solubilizing vehicle illustrate enhanced drug release due to an increased surface area of drug available for release, an increased aqueous solubility of the drug, and an improved wettability of the drug particles. Therefore, this enhanced drug release may result in a higher drug absorption in the gastrointestinal tract and thus, an improved oral bioavailability. Microcrystalline cellulose is used as carrier material and amorphous silicon dioxide (colloidal silica) as coating material usually. Various excipients such as lubricants
and disintegrates (immediate release) or matrix forming materials (sustained release) may be added to the liquisolid system to produce Liquisolid compacts.

**STEPS INVOLVED IN THE PREPARATION OF LIQUISOLID COMPACTS**

- 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.
- 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.
- To the above binary mixture disintegrant like sodium starch glycolate and other remaining additives were added according to their application and mixed for a period of 10 to 20 min. in a mortar.
- The final mixture was compressed using the manual tableting machine to achieve tablet hardness.
- Characterize the final liquisolid granules for solubility, dissolution, flowability, compressibility and other physicochemical properties.

![Schematic Diagram Representing Preparation of Liquisolid Compacts](image)

**Figure 2**: schematic diagram representing preparation of liquisolid compacts
EVALUATION OF LIQUISOLID SYSTEM\(^{(6)}\)

**Flow behavior**
The flowability of a powder is of critical importance in the production of pharmaceutical dosage forms in order to reduce high dose variations. Angle of repose, Carr’s index and Hausner’s ratio were used in order to ensure the flow properties of the liquisolid systems.

**Pre compression studies of the prepared liquisolid Powder systems**
In order to ensure the suitability of the selected excipients, Fourier Transform Infra-Red Spectroscopy, Differential scanning Calorimetry, X-ray Diffraction and Scanning Electron Microscope studies are to be performed. In addition, flowability studies are also to be carried out.

**Dissolution studies**
In-Vitro release profiles of drug from the preferred tablets were studied using dissolution apparatus and compared with the formulated Liquisolid tablet. Drug release, % drug dissolved can be calculated of both the formulation results are estimated.

**Differential scanning calorimetry**
This is prerequisite to know if any possible interaction present between the excipients and the drug used in the formulation. The characteristic peak in the DSC thermo gram belongs to a drug absent that indicates that the drug is present in molecularly dispersed in this system.

**X- ray diffraction**
To get justification that the drug is in the solubilized state or converted into amorphous form because of disappearance of characteristic peaks belongs to drug and their by appearance of peaks which belongs to carrier is absorbed.

**Scanning electron microscopy**
This study confirms that there are any crystals present, or else drug is present in the solubilized form by absence of crystals of drug.

**Stability studies**
Drug content was determined after the crystals were charged for accelerated stability studies according to ICH guidelines. Samples were taken and analyzed for specified intervals. 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 liquid resting on a plane surface of the solid, the so-called imaging method. A saturated solution of the drug in dissolution media is prepared and a drop of this solution is put on the surface of tablets. The contact angles are calculated by measuring the height and diameter of sphere drop on the tablet.

OPTIMIZATION OF LIQUISOLID FORMULATIONS WITH ENHANCED DRUG RELEASE\textsuperscript{[6]}

The Liquisolid Technique has been successfully useful to low dose, poorly water soluble drugs. The formulation of a high dose, poorly soluble drug is one of the limitations of the Liquisolid Technique. As the release rates are directly proportional to the fraction of molecularly dispersed drug in the liquid formulation a higher drug dose requires higher liquid amounts for a desired release profile. Therefore, to obtain liquisolid systems with acceptable flowability and compactability high levels of carrier and coating materials are required. However, this results in an increase in tablet weight ultimately leading to tablet sizes which are difficult to swallow. Therefore, to overcome this and various other problems of the Liquisolid Technique several formulation parameters may be optimized as shown in Table

<table>
<thead>
<tr>
<th>Sr. no.</th>
<th>Formulation parameters</th>
<th>Optimization</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Liquid vehicle</td>
<td>High drug solubility in vehicle</td>
<td>Increased fraction of the molecularly dispersed drug (FM)</td>
</tr>
<tr>
<td>2.</td>
<td>Carrier and coating material</td>
<td>High specific surface area</td>
<td>Increased Liquid load factor (Lf)</td>
</tr>
<tr>
<td>3.</td>
<td>Addition of excipient</td>
<td>Polyvinyl pyrrolidone (PVP) Superdisintegrant</td>
<td>Increased liquid load factor (Lf), Increased viscosity of liquid.</td>
</tr>
<tr>
<td>4.</td>
<td>Exipient ratio</td>
<td>High R-Value</td>
<td>Fast Disintegration Inhibition of precipitation.</td>
</tr>
</tbody>
</table>
DRUGS THAT CAN BE INCORPORATED INTO LIQUISOLID SYSTEM\textsuperscript{[4]}

**Antihistaminic:** chlorpheniramine

**Antiarrhythmic:** digoxin, digitoxin

**Antihypertensive:** nifedipine

**Antilipidemics:** clofibrate, gemfibrozil

**Antiepileptic:** Carbamazepine, valproic acid.

**Chemotherapeutic agent:** etoposide.

**Diuretics:** Hydrochlorothiazide, methylchlorthiazide,

**Glucocorticoids:** prednisolone, hydrocortisone, prednisone.

**NSAIDS:** piroxicam, indomethacin, ibuprofen.

**Water-insoluble vitamins:** vitamin A, D, E, and K\textsuperscript{[9]}

Table 2: Drug solutions used in liquisolid formulation for immediate release\textsuperscript{(7)}

<table>
<thead>
<tr>
<th>Drug</th>
<th>Cosolvent</th>
<th>Carrier material</th>
<th>Coating material</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indomethacin</td>
<td>Propylene glycol</td>
<td>MCC</td>
<td>Silica</td>
<td>60% enhanced dissolution rate</td>
</tr>
<tr>
<td>Methyclothiazide</td>
<td>PEG 400</td>
<td>MCC</td>
<td>Silica</td>
<td>40% enhanced dissolution than commercial tablets</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>PEG 200</td>
<td>MCC</td>
<td>Cab-o-sil</td>
<td>Enhanced dissolution than commercial tablets which is not affected by storage</td>
</tr>
<tr>
<td>Hydrocortisone</td>
<td>Propylene glycol</td>
<td>Avicel PH200</td>
<td>Cab-o-sil</td>
<td>Enhanced dissolution rates which is independent of the volume of the dissolving medium</td>
</tr>
<tr>
<td>Hydrochlorthiazide</td>
<td>PEG 200</td>
<td>Avisel PH101/102</td>
<td>Aerosil</td>
<td>Absolute bioavailability of the drug from liquisolid tablets</td>
</tr>
</tbody>
</table>
was 15% higher than commercial tablets

Table 3: Drug suspensions used in liquisolid formulation for immediate release

<table>
<thead>
<tr>
<th>Drug</th>
<th>Co-solvent</th>
<th>System</th>
<th>Carrier material</th>
<th>Coating material</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gemfibrozil1</td>
<td>Tween80</td>
<td>DS</td>
<td>Avicel PH 200</td>
<td>Cab-o-sil M5</td>
<td>Improvement in dissolution rate when compared to commercial tablets.</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>PEG 400</td>
<td>DS</td>
<td>Avicel PH 200</td>
<td>Cab-o-sil M5</td>
<td>Improvement in dissolution rate when Compared to commercial soft gelatincapsules.</td>
</tr>
<tr>
<td>Glibenclamide</td>
<td>PEG 400</td>
<td>DS</td>
<td>Avicel PH 102</td>
<td>Aerosil</td>
<td>Enhanced drug release rates.</td>
</tr>
</tbody>
</table>

APPLICATIONS[6]

- 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.
- Literature cites different drugs successfully incorporated into liquisolid compacts.
- Rapid release rates are obtained in liquisolid formulations.
- These can be efficiently used for water insoluble solid drugs or liquid lipophilic drugs.
Sustained Release of drugs which are water soluble drugs such as propranolol hydrochloride has been obtained by the use of this technique.

Solubility and dissolution improvement

Flowability and compressibility.

Designing of Controlled Release Tablet.

CONCLUSION

It is well established that the inadequate dissolution of water-insoluble drugs is the major reason for their poor and erratic bioavailability since it is the rate determining step in the absorption of nonpolar molecules. Liquisolid formulations were designed to contain liquid medications in powdered form, thereby possessing mechanisms of drug delivery similar to those of soft gelatin capsule preparations containing liquids. The liquisolid technique could be a promising alternative technique to increase the dissolution of water insoluble drugs and thereby enhance their absorption characteristics.

REFERENCES


