LIQUISOLID TECHNOLOGY: AN UNIQUE APPROACH TO IMPROVE BIOAVAILABILITY OF POORLY WATER SOLUBLE DRUGS

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ABSTRACT

Liquisolid technology is novel concept for oral drug delivery system, described by Spireas et al. (1998).This technique was used for water insoluble drugs as solubility is major problem in most of the drugs in their development phase. The liquisolid system is formulated by conversion of drug into drug solution, drug suspension using non-volatile solvent and this liquid medication converted into dry, free flowing, non-adherent, and compressible powder using simple physical blending with selected carrier and coating materials which causes increase in bioavailability of poor water soluble drugs. The use of non-volatile solvent causes improved wettability and molecular dispersion of drug in the formulation and leads to enhance solubility.

INTRODUCTION

In most of the pharmaceutical industry major challenges in the drug development is poor water solubility of drugs. New Chemical Entities (NCE) do not entered in market due to their poor solubility. Liquisolid technique is new method used to change the dissolution rate of poor soluble drugs. The dissolution is the rate limiting steps for the drug absorption for BCS class II (low solubility and higher permeability) drugs and BCS class IV (low solubility and low permeability) drugs in the Biopharmaceutical Classification System.[1]

<table>
<thead>
<tr>
<th>BCS class</th>
<th>Solubility</th>
<th>Permeability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Class II</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Class III</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Class IV</td>
<td>Low</td>
<td>Low</td>
</tr>
</tbody>
</table>

Different techniques have been reported in many literatures to improve the dissolution rate such as

a. Reduce particle size i.e. Nanonization, Micronization
b. To increase surface area
c. Use of surfactant
d. Use of Prodrug and drug Derivatisation
e. Formulation of solid solution and amorphous form
f. Microencapsulation.

Among the various techniques are used to overcome the solubility issue. Several researcher reported that formulation of liquisolid tablet is one of the most promising technique for drug dissolution.[2]
Liquisolid Technique is categories on the basis of the liquid medications[5][6]

1. Powder drug
2. Powder drug solution
3. Powder drugs suspension

Based on the formulation techniques

1. Liquid solid compact
2. Liquid solid Microsystem

Concept of Liquisolid Formulation

When the drug dissolved in the liquid vehicle is incorporated into a carrier material which has a porous surface and closely matted fibers in its interior as cellulose, both absorption and adsorption take place.

The liquid initially absorbed in interior of the particle is capture by its internal structure. After saturation adsorption of the liquid on to the internal external surface of the porous carrier particle occurs. Then the coating materials having high adsorption properties and large specific surface area that provides the Liquisolid system the desirable flow Characteristics.

Non-volatile solvent present in the Liquisolid system provides wetting of the drug particle by reducing surface tension between dissolution medium and tablet surface thus the increasing in wettability and effective surface area for dissolution, which enhance the bioavailability of the drugs[6][7]

Theory of liquisolid compacts:[8][9][10]

The powder can retain only limited amounts of liquid while maintaining acceptable flow and compression properties. To calculate required amounts of powder excipients (carrier and coating material) a mathematical approach for formulation of liquisolid systems has been developed by Spireas et al this approach is based on flowable (Φ-value) and compressible (Ψ-value) liquid retention potential introducing constants for liquid/powder combination.

The Φ-value of a powder represents the maximum amount of a given non-volatile liquid that can be retained inside its bulk [w/w] while maintaining an acceptable flowability. The flowability may be determined from the powder flow or by measurement of the angle of repose. The Ψ-number of a powder is defined as the maximum amount of liquid the powder can retain inside its bulk [w/w] while maintaining acceptable compactability resulting in compacts of sufficient hardness with no liquid leaking out during compression[3]. The compactability may be determined by the so-called “pactisity” which describes the maximum (plateau) crushing strength of a one-grain tablet compacted at sufficiently high compression forces. The terms “acceptable flow and compression properties” imply the desired and thus preselected flow and compaction properties which must be met by the final liquisolid formulation.

Depending on the excipient ratio (R) of the powder substrate an acceptably flowing and compressible liquisolid system can be obtained only if a maximum liquid load on the carrier material is not exceeded. This liquid/carrier ratio is termed “liquid load factor LF [w/w] and is defined as the weight ratio of the liquid formulation (W) and the carrier material (Q) in the system:

\[ LF = W/Q \]

R represents the ratio between the weights of the carrier (Q) and the coating (q) material present in the formulation:

\[ R = Q/q \]

The liquid load factor that ensures acceptable flowability (Lf) can be determined by:

\[ Lf = \Phi + \psi \cdot \left(1/R \right) \]

Where Φ and ψ are the Φ-values of the carrier and coating material, respectively. Similarly, the liquid load factor for production of liquisolid systems with acceptable compactability (ΨLf) can be determined by:

\[ \Psi Lf = \Phi + \psi \cdot \left(1/R \right) \]

Where Ψ and ψ are the Ψ-numbers of the carrier and coating material, respectively. In Table II examples of liquisolid formulation parameters of various powder excipients with commonly used liquid vehicles are listed. Therefore, the optimum liquid load factor (Lo) required to obtain acceptably flowing and compressible liquisolid systems are equal to either ΦLf or ΨLf, whichever represents the lower value. As soon as the optimum liquid load factor is determined, the appropriate quantities of carrier (Qo) and coating (qo) material required to convert a given amount of liquid formulation (W) into an acceptably flowing and compressible liquisolid system may be calculated as follows:

\[ Qo = W/Lo \]

\[ qo = Qo/R \]

The validity and applicability of the above mentioned principles have been tested and verified by producing liquisolid compacts possessing acceptable flow and compaction properties.

Table II Liquisolid formulation parameters of various powder excipients with commonly used liquid vehicles

<table>
<thead>
<tr>
<th>Powder excipient or system</th>
<th>Φ-values</th>
<th>Ψ-numbers</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Propylene glycol</td>
<td>PEG 400</td>
</tr>
<tr>
<td>Avicel PH 102</td>
<td>0.16</td>
<td>0.224</td>
</tr>
<tr>
<td></td>
<td>0.005</td>
<td>0.242</td>
</tr>
<tr>
<td>Avicel PH 200</td>
<td>0.26</td>
<td>0.299</td>
</tr>
<tr>
<td></td>
<td>0.02</td>
<td>0.232</td>
</tr>
<tr>
<td>Cal-O-Sil M5 (silica) with</td>
<td>3.31</td>
<td>0.560</td>
</tr>
<tr>
<td>Avicel PH 102</td>
<td>3.26</td>
<td>0.653</td>
</tr>
<tr>
<td>Cal-O-Sil M5 (silica) with</td>
<td>2.57</td>
<td>0.712</td>
</tr>
<tr>
<td>Avicel PH 200</td>
<td>2.44</td>
<td>0.717</td>
</tr>
</tbody>
</table>
Composition of Liquisolid tablet

Carrier materials: Carrier material should possess porous surface and matted fibers in interior, which involved in sorption process and improve the effective surface area for dissolution. Examples, Starch, Lactose, Sorbitol, various grades of cellulose.[11]

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. Coating materials are very fine (10nm – 5000nm) examples colloidal silica, cab-o-sil MS, Aerosil 200, Syloid 244FFP.

Non-volatile solvent: It should be inert, ability to dissolve the amount of drug, high boiling point, water miscible and not viscous in organic solvent system. Examples polyethylene glycol, Liquid PEG, polysorbate (Tween 80), fixed oil etc.[12]

Disintegrants: which are used to solubility enhancement of drug. Examples Crospovidone, sodium starch glycolate (pumogel, Explotab)

Drugs: Drugs should be poorly soluble or insoluble in water specially BCS class II and BCS class IV drugs. [13]

Mechanism of Enhanced Drug Release From Liquisolid Tablet

Increase drug surface area: Drug within the liquisolid system is completely dissolved in liquid vehicle it is located in the powder substrate still in a solubilised, molecularly dispersed state therefore surface area of drug available for release is much more than that of drug particles within directly compressed tablets.

Increased water solubility of the drug: The solubility of the drug increased with Liquisolid system. The solid / liquid interface between and individual liquisolid primary particle and the release medium it is possible that in this microenvironment the amount of liquid diffusing out of the single liquisolid particle together with the drug molecules sufficient to increase the aqueous solubility of the drug if the liquid vehicle act as co-solvent.[14]

Evaluation of the Liquisolid system

Flow behaviour: Flow properties are the essential in the formulation and industrial production of tablet dosage form. Angle of repose is characteristic to the flow rate of powder. In general, values of angle of repose ≥ 40° indicate powders with poor flowability.

Differential Scanning Calorimetry (DSC): It is necessary to determine any possible interaction between excipients used in the formulation. DSC is used to stability studies of the drug and excipients. If the characteristic peak for the drug is absent in the DSC Thermogram, this is the indication that the drug is in the form of solution in Liquisolid formulation and hence it is molecularly dispersed within the system.[16]

X-ray diffraction (XRD): The disappearance of characteristic peaks of drug in the Liquisolid formulation and retaining peaks of carrier material is observed. It showthat drug gets converted to amorphous form or insolubilized form in the Liquisolid formulation.

Scanning Electron Microscopy (SEM): After SEM study, complete disappearance of crystals of drug which confirms that drug is totally solubilized in Liquisolid system and this ensures the complete solubility.

Fourier Transform Infrared Spectroscopy (FTIR): FTIR studies are used to determine the chemical interaction between the drug and excipients in the formulation. The presence of drug peaks in the formulation and absence of extrapeaks indicates there is no chemical interaction.

Estimation of drug content: The Liquisolid compacts are powdered well and powder equivalent to 10 mg of the drug is accurately weighed and suitably diluted using methanol/sulphuric acid. The drug content is calculated by at wavelength using UV-Visible spectrophotometer.[17]

Contact angle measurement: 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, so-called imaging method. A saturated solution of the drug indissolution 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.

In-vitro drug release study: Generally the in-vitrodissolution study is carried out for a period of hour using USP type-II
Advantages:[20][21]

1. Production cost is less as compared to the soft gelatin capsule because production is same as to conventional tablet.
2. Liquisolid system is applicable for low dose of water insoluble drugs.
3. Absolute bioavailability of liquisolid tablet is 15% greater than conventional.
4. Slightly and very slightly water soluble and practically water insoluble liquid and solid drugs can be formulated into liquisolid system.
5. Water insoluble solid and liquid drugs formulated into immediate, Sustained and Controlled release formulation.
6. Liquisolid system specially applicable for the powder liquid medication.
7. Drugs formulated in tablet or encapsulated dosage form and is held in solubulised liquid state which enhance the wetting properties therefore improves the drug dissolution profile.
8. Drug release can be modified changing other suitable ingredients.
9. Scale up of production is possible.
10. To reduce the excipients in formulation as compared to the solid dispersion technique.

Disadvantages

1. Liquisolid technique is not applicable for drugs having high doses.
2. It requires the mathematical calculations.[22]

Literature review of liquisolid formulation which increase drug dissolution.[23][24][25][26][27][28]

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Drug</th>
<th>Non-volatile solvent</th>
<th>Carrier material</th>
<th>Coating material</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Indomethacin</td>
<td>PEG 200, Glycerine</td>
<td>MCC</td>
<td>Silica</td>
<td>Enhance bioavailability due to increase wetting properties. Improving the bioavailability of drug.</td>
</tr>
<tr>
<td>2</td>
<td>Hydrochlorothiazide</td>
<td>PEG 200, Avicel PH 101</td>
<td></td>
<td>Aerosils</td>
<td>Increase dissolution rate by decrease crystallinity. Higher dissolution rate than conventional by direct compression tablet.</td>
</tr>
<tr>
<td>3</td>
<td>Glimepiride</td>
<td>PG, Avicel PH 101</td>
<td>MCC</td>
<td>Silica</td>
<td>Improve bioavailability of drug.</td>
</tr>
<tr>
<td>4</td>
<td>Famotidine</td>
<td>PG</td>
<td>MCC</td>
<td>Silica</td>
<td>Increase dissolution rate. Improve bioavailability of drug.</td>
</tr>
<tr>
<td>5</td>
<td>Carbamazepine</td>
<td>PEG 200, 400, MCC</td>
<td>Lactose</td>
<td>Silica</td>
<td>Increase dissolution rate. Improve bioavailability of drug.</td>
</tr>
<tr>
<td>6</td>
<td>Ketoprofen</td>
<td>PEG 200</td>
<td>Avicel PH 101</td>
<td>Silica</td>
<td>Increase dissolution rate. Improve bioavailability of drug.</td>
</tr>
</tbody>
</table>

Fig 3 Contents of liquisolid tablet used for dissolution enhancement

From the above graph (fig 3) it is concluded that non-volatile solvent PEG, coating material such as Silica and carrier material i.e. MCC (Microcrystalline cellulose) are the mostly used for the enhancement of drug dissolution.

**Marketed formulations of Liquisolid tablet:**[24]

<table>
<thead>
<tr>
<th>Sr.No.</th>
<th>Brand Name</th>
<th>Generic Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Mepron</td>
<td>Atorvastatin</td>
</tr>
<tr>
<td>2</td>
<td>Maxalt</td>
<td>Rizatrpinten Benzoate</td>
</tr>
<tr>
<td>3</td>
<td>Infasurf</td>
<td>Clofibrate</td>
</tr>
<tr>
<td>4</td>
<td>Noritrate</td>
<td>Metronidazole</td>
</tr>
<tr>
<td>5</td>
<td>Angeliq</td>
<td>Drosiprenone and Istradiol</td>
</tr>
<tr>
<td>6</td>
<td>Renova</td>
<td>Trizetone cream</td>
</tr>
<tr>
<td>7</td>
<td>Proair HFA</td>
<td>Albetenol sulphate inhalation</td>
</tr>
<tr>
<td>8</td>
<td>Dermotic oil</td>
<td>Fluocinolone/Acetamide oil Ear drops</td>
</tr>
</tbody>
</table>

**CONCLUSION**

The conclusion of the Liquisolid technique is most effective technique among the various water solubility enhancement methods. The authors [Khalid U. Shaskh et al.] have demonstrated the application of Liquisolid Technology in improving the bioavailability of poorly water-soluble drugs through various case studies and illustrations, showing significant improvements in dissolution and bioavailability compared to conventional methods. The technique involves the use of non-volatile solvents, specific carrier materials, and coating techniques to enhance the dissolution rate and bioavailability of drugs that are otherwise insoluble in water. The effectiveness of Liquisolid Technology is further highlighted through literature review and marketed formulations, indicating its potential application in enhancing the bioavailability of a wide range of drugs.
technique due to increasing the wetting properties of the drug by using non-volatile solvent, cost effectiveness than conventional tablet, thus it is applicable for the industrial production.

References


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