ABSTRACT

The bioavailability and solubility were major challenge for the pharmaceutical industry with developments of new pharmaceuticals. The liquisolid technique is a new and promising method that can change the dissolution rate of water insoluble drugs. Generally, Water-miscible organic solvent systems with high boiling point like propylene glycol, polyethylene glycols, or glycerine are used as liquid vehicles for improved wettability and ensures molecular dispersion of drug in the formulation and leads to enhance solubility in liquisolid technique. When the carrier is saturated with liquid, a liquid layer is formed on the particle surface which is instantly adsorbed by the fine coating particles forming a dry, free flowing and compressible powder. Generally, Micro Crystalline Cellulose is used as carrier and silicon dioxide as coating material in liquisolid technique. Liquisolid compacts of poorly soluble drugs containing a drug solution or drug suspension in a solubilising vehicle show enhanced drug release with increased surface area of drug release, increased aqueous solubility and improved wettability of the drug particles. There are various methods but liquisolid technique is a new and promising method that can change the dissolution rate of water insoluble drugs. In liquisolid technique, suspension and solution of solid drugs in non-volatile solvent systems and liquid drug convert into solid dosage form by using carriers and coating materials. Liquisolid system is characterized by flow behaviour pattern, wettability, powder bed hydrophilicity, saturation solubility, drug
content, differential scanning calorimetry, Fourier transform infra red spectroscopy, powder X-ray diffraction, scanning electron microscopy, in-vitro release and in-vivo evaluation. By applying this novel and capable technique, solubility and dissolution rate can be enhanced, sustained drug delivery systems be developed for the water soluble drugs. It contains liquid medications in powdered form. This technique is an efficient method for formulating water insoluble and water soluble drugs.

KEYWORDS: Liquisolid technology, Free flowing, and Wettability.

INTRODUCTION
The oral route of administration offers several advantages like ease of administration, patient compliance, safe and effective. The solid dosage forms having the greatest importance because of their good dosability, packaging, transportability, stability, and ease of administration. Solubility of the compound influences the drug absorption, bioavailability, pharmacokinetic profile. The “Liquisolid” technique most commonly intended for solubility enhancement, dissolution improvement and increases the bioavailability of drugs. Low aqueous solubility is the major problem encountered with formulation development of new chemical entities as well as for the generic development. The insufficient dissolution rate of the drug is the limiting factor in the oral bioavailability of poorly water soluble compounds \[^{[1]}\]. In this technique, liquid may be converted into a free flowing, readily compressible dry powder by physical blending with suitable carrier and coating material \[^{[2-4]}\].

Definitions \[^{[5]}\]
The term ‘liquid medication’ refers to liquid lipophilic (oily) drugs or water-insoluble solid drugs dissolved in suitable water-miscible non-volatile solvent systems termed as the liquid vehicle.

The term ‘liquisolid compacts’ refers to immediate or sustained-release tablets or capsules that are described under “liquisolid systems”.

The term ‘liquisolid Microsystems’ refers to capsules prepared by “liquisolid systems” plus the inclusion of an additive resulting in a unit size that may be as much as five times less than that of a liquisolid compact.

The term ‘Liquid load factor (Lf)’ refers to the ratio of the amount of liquid medication (W) over the quantity of carrier material (Q) in the system.
The term ‘Carrier: Coating Material Ratio (R)’ refers to Ratio between the quantities of carrier (Q) and coating materials (q) present in the formulation. The term ‘Carrier’ refers to a preferably porous material possessing sufficient absorption properties. The term “Coating Material” refers to a material possessing fine and highly adsorptive particles.

**Advantages**\(^{[5]}\)
1. It is suitable technique for drugs with high permeability and poorly water soluble.
2. It is suitable technique for practically insoluble liquids and solid drugs.
3. It is suitable technique for enhancement of bioavailability of poorly water soluble drugs.
4. It is suitable technique for enhancement of dissolution profiles.
5. It is suitable technique for improvement of exposed drug surface area to the dissolution medium.
6. It is suitable technique, specifically for powdered liquid medications.
7. It is suitable technique for formulate into immediate release or sustained release dosage forms.
8. In this liquisolid technique, production expenditure is low compared to soft gelatin capsules.
9. It is used in controlled drug delivery systems.
10. Drug can be molecularly dispersed in the formulation
11. Drug release can be modified using suitable formulation ingredients.
12. Differentiate the dosage form by admixture of colour into liquid vehicle.
13. Capability of industrial production is also possible.
14. To minimize excipients in formulation compare with other formulations like solid dispersions.
15. Omit the process approaches like nanonisation, micronization techniques.
16. Drug is formulated in a tablet form or encapsulated dosage form and is held in solubilized liquid state, which confers developed or enhanced drug wetting properties thereby improving drug dissolution profiles.

**Disadvantages**\(^{[5]}\)
1. Liquisolid system require low drug loading capacities.
2. It requires more efficient excipients which have higher adsorption capacities and it should provide faster drug release with smaller tablet size.
3. Higher amounts of carrier and coating materials are required for maintain acceptable flowability and compatibility.

4. Liquisolid system require high solubility of drug in non-volatile liquid vehicles

5. Liquisolid system is most commonly for water insoluble drugs.

6. Liquisolid system is not suitable for formulation of high dose water insoluble, lipophilic drugs.

**Formulation Of Liquisolid System** [6-15]

Liquisolid technique is based upon the admixture of drug loaded solutions with suitable carrier and suitable coating materials. The use of non-volatile solvent (hydrophobic carrier) causes improved wettability and ensures molecular dispersion of drug in the formulation and leads to improve solubility. By using hydrophobic carriers (non-volatile solvents) one can modify release (sustained release) of drugs by this technique.

**Components**

1. Drug
2. Non-Volatile solvent
3. Carrier
4. Coating material
5. Super Disintegrates
6. Lubricants
7. Glidants

**Drug**

They may be poorly soluble or insoluble in water. The drug used in liquisolid systems should be water insoluble or poorly soluble and low dose drugs. It should be in BCS class II or IV.

**Non-Volatile solvent**

The common application of non-volatile solvent in liquisolid system causes improved wettability and ensures molecular dispersion of drug in the formulation and leads to enhance solubility. The use of hydrophobic carriers (non-volatile solvents) one can modify release (sustained release) of drugs by this technique. They may be either hydrophilic or lipophilic in nature based on selection of type of formulation like immediate or sustained release. The most commonly preferably water-miscible, inert high boiling point and not highly viscous organic solvent systems. The common application of non-volatile solvents are used to
dissolve the drug the liquid vehicle does not evaporate so the drug carried as it is throughout the product. It must be inert water miscible, not highly viscous and should have high boiling point. Poly Ethylene Glycol (PEG)-400, PEG- 200, PEG- 4000, PEG- 6000, Tween–80,Span 20, Propylene Glycol (PG), N, N dimethylacetamide, Fixed oils, glycerine etc, used as vehicles in liquisolid system.

**Carrier**

They are favoured to be coarser granular for acceptable flow. These are as porous substance possessing adequate absorption properties. These are highly porous materials & have a wide surface area and the recommended to absorb the drugs on to them. MCC, starch, sorbitol and lactose used as carrier materials. Eudragit RL and RS , Ethocel , Methyl cellulose (MC), Ethyl cellulose(EC), HPMC K4M etc, for sustained release.

**Coating material**

It is a substance possessing very fine (10 nm to 5,000 nm in diameter) and highly adsorptive coating particles for enhancing the flow. These are contributes in covering the wet carrier particles and displaying a dry-looking powder by adsorbing any excess liquid. Aerosil® PH 200, Colloidal silica, Talc , Syloid244FP and Cab-O-sil RTM M5 used as coating material.

**Super Disintegrates**

These are used to break the compacts to smaller particles. Sodium starch glycolate (SSG), Explotab, Pre gelatinized starch, Crospovidone and Sodium Croscarmellose used as Super Disintegrates.

**Lubricants**

These are intended to reduce the friction. Eg: Stearic acid, Stearic acid salts and Talc etc.

**Glidants**

These are intended to promote the flow between particles by reducing the friction. Eg: Silica derivatives, Talc and Corn starch etc.,
<table>
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<tr>
<th>S.No.</th>
<th>Drug</th>
<th>BCS class</th>
<th>Non-Volatile solvent</th>
<th>Carrier</th>
<th>Coating material</th>
<th>Super Disintegrates</th>
<th>Reference</th>
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<td>Aerosil-200</td>
<td>Cross povidone</td>
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<td>2</td>
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<td>II</td>
<td>Propylene glycol, PEG 400, Tween 80, Cremophor EL and Capryol 90</td>
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<td>Aerosil-200</td>
<td>SSG</td>
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<td>Cross Carmellose Sodium</td>
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<td>Cross povidone, SSG and Cross carmellose Sodium</td>
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<td>Furosemide</td>
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<td>Synperonic® PE/L 81, Caprol® PGE-860 and Polyethylene glycol 400</td>
<td>Avicel® pH-101</td>
<td>Cab-O-Sil® M-5</td>
<td>Potato starch</td>
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<td>Atovastatin calcium</td>
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<td>Aerosil-200</td>
<td>Explotab</td>
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<td>II</td>
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<td>Avicel®p^H^ 101 and Avicel®p^H^ 200</td>
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<td>Silica</td>
<td>Starch</td>
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<td>Aerosil-200</td>
<td>SSG</td>
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<tr>
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<td>Excipients</td>
<td>Binder</td>
<td>Coating</td>
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<td>15</td>
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<td>MCC</td>
<td>Silica</td>
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<td>PG</td>
<td>MCC</td>
<td>Colloidal silica</td>
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<td>Cremophor EL</td>
<td>MCC</td>
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<td>Cab-o-silM5</td>
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<td>Avicel p&lt;sub&gt;H&lt;/sub&gt; 190</td>
<td>Cab-o-silM5</td>
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<td>Cab-o-sil</td>
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<td>Cab-o-sil M5</td>
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<td>-</td>
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<td>Avicel PH 101</td>
<td>Cab-O-Sil® M-5P</td>
<td>Cross Carmellose</td>
<td>[38]</td>
</tr>
</tbody>
</table>
Mechanisms Of Improvement Of Drug Release [6-15]

Several mechanisms are developed to enhance the drug release. Three important mechanisms includes

1. An increase in effective drug surface area,
2. An increase in aqueous solubility
3. An improved wettability of drugs.

I. Enhancement of surface area:
By increasing the effective surface area of drug leads to the dissolution of drug with the liquid vehicle is increased.

II. Enhancement of aqueous solubility
A relatively small quantity of liquid vehicle is not sufficient to solubilize the total quantity of drug. But at the solid liquid interface between the particles and dissolution medium, it is possible that a little amount of liquid vehicle diffuses from the total quantity along with drug and this less amount of liquid is sufficient to increase the aqueous solubility of drug if it acts as a co solvent.

III. Enhancement of wetting properties
The liquid vehicle can enhances the wettability of liquisolid primary particle by acting as a surface active agent (or) by reducing the surface tension. Wettability of liquisolid systems has been demonstrated by measurement of contact angles and water rising times.

Classification Of Liquisolid Systems
Method Of Preparation

Calculated quantities of drug substance was initially dispersed in the nonvolatile solvent systems (Polysorbate 80, Polyethylene glycol-200) termed as liquid vehicles with different drug: vehicle ratio and then it is heated to dissolve the drug. 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(SSG) and other reaming additives were added according to their application and mixed for a period of 10 to 20 minutes in a mortar. The liquisolid systems made into compacts by the addition of excipients, lubricants and disintegrants are used for sustained release liquisolid systems. The final blend was compressed using the manual tableting machine to achieve require tablet hardness. Evaluate the final liquisolid granules for solubility, dissolution, flowability, compressibility and other physicochemical properties.

Characterization

Liquisolid system is characterized by flow behavior, wettability, powder bed hydrophilicity, saturation solubility, drug content, differential scanning calorimetry(DSC), Fourier transform infra red spectroscopy(FTIR), powder X-ray diffraction(XRD), scanning electron microscopy(SEM), in-vitro release and in-vivo evaluation.

Flow behaviour of liquisolid system

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.

\[ \tan \Theta = \frac{h}{r} \]

\[ \text{Carr's index} = \frac{\text{Tapped density} - \text{bulk density} \times 100}{\text{Tapped density}} \]

\[ \text{Hausner’s ratio} = \frac{\text{Tapped density}}{\text{Bulk density}} \]

Fourier Transform Infra Red Spectroscopy (FT-IR)

These studies are performed to estimate the chemical interactions between excipients and drug. Potassium bromide (KBr) pellet method is employed and background spectrum is collected under identical situation. Each spectrum is derived from single average scans.
collected in the region 400 - 4000 cm\(^{-1}\) against background interfereogram. If there is the presence of characteristic peaks and absence of extra peaks in formulation indicates that there are no chemical interactions.

**X-ray diffraction (XRD)**

These studies are performed to estimate crystalline properties. For the characterization of crystalline state, X-ray diffraction (XRD) patterns are determined for physical mixture of drug and excipients used in formulation and for the prepared liquisolid compacts. Absence of constructive specific peaks of the drug in the liquisolid compacts in X-ray diffractogram specify that drug has almost entirely converted from crystalline to amorphous or solubilized form. Such lack of crystallinity in the liquisolid system was understood to be as a result of drug solubilization in the liquid vehicle i.e., the drug has formed a solid solution within the carrier matrix. This amorphization or solubilization of drug in the liquisolid compacts it may contribute to the consequent improvement in the apparent solubility and enhancement of dissolution rate of the drug.

**Differential scanning calorimetry**

These studies are performed to estimate interaction studies and polymorphism. Differential scanning calorimetry (DSC) is performed in order to assess the thermotropic properties and the thermal behaviours of the drug, excipients used in the formulation of the liquisolid system. Inclusive disappearance of characteristic peaks of drug indicates the formation of drug solution in the liquisolid powdered system, i.e., the drug is molecularly dispersed within the liquisolid matrix.

**Scanning electron microscopy (SEM)**

Scanning electron microscopy (SEM) is utilized to assess the morphological characteristics of the raw materials and the drug-carrier systems.

**Contact angle measurement**

For assessment of wettability, contact angle of liquisolid tablets is measured according to the imaging method. The commonly used method is to measure contact angle directly for a drop of 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.
**In vivo evaluation of liquisolid systems**

This liquisolid technology is a promising tool for the enhancement of drug release of poorly soluble drugs. The absorption characteristics of hydrochlorothiazide liquisolid compacts in comparison with commercial tablets were studied in beagle dogs. Significant differences in the area under the plasma concentration-time curve, the peak plasma concentration and the absolute bioavailability of the liquisolid and the commercial tablets were observed. However, for the mean residence time, the mean absorption time, and the rate of absorption no significant differences were found. The absolute bioavailability of the drug from liquisolid compacts was 15% higher than that from the commercial formulation.

**In vitro dissolution studies**

Works of many researchers revealed that technique of liquisolid compacts could be a promising alternative for formulation of water-insoluble drugs. This technique of liquisolid compacts has been successfully employed to improve the in-vitro release of poorly water soluble drugs as hydrocortisone, Prednisolone, Carbamazepine, Piroxicam. Also several water insoluble drugs nifedipine, gemfibrozil, and ibuprofen, have shown higher bioavailability in rats as compared to their commercial counterparts.

**Stability Studies**

The stability studies are conducted to identify the shelf life of the products. Shelf life is defined as the time required falling the concentration of the reactant to 90 percent of its initial concentration. To distinguish the information on the stability of liquisolid systems, the effect of storage on drug release profile and the crushing strength of liquisolid compacts were investigated. Stability studies of liquisolid systems containing hydrocortisone (ambient conditions, 10 months), Piroxicam (24°C/76% R.H., 4 weeks), carbamazepine (24°C/76% R.H., 6 months), Indomethacin (24°C/76% R.H.,12 months) showed that storage at different conditions may not affect the hardness and drug release profile of liquisolid compacts. This indicates that the technology is a promising technique to enhance the release rate without any physical stability problems.

**Applications**

<table>
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<th>S.No.</th>
<th>Drug</th>
<th>Applications</th>
<th>References</th>
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<td>Amlodipine besylate and Valsartan</td>
<td>Improvement of the dissolution rate</td>
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<tr>
<td>2</td>
<td>Candensartan cilexetil</td>
<td>Improvement of the dissolution rate</td>
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<td>3</td>
<td>Tamoxifen citrate</td>
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<tr>
<td></td>
<td>Drug</td>
<td>Improvement</td>
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<td>------------------------------------------------------------------------------</td>
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<tr>
<td>4</td>
<td>Accelofenac</td>
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<tr>
<td>5</td>
<td>Diltiazem</td>
<td>To make sustained release dosage forms</td>
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<td>Formulating as immediate release solid dosage forms and dissolution rate enhancement</td>
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<td>19</td>
<td>Nimesulide</td>
<td>Increasing wetting properties and surface area of drug available for dissolution.</td>
<td>[28]</td>
</tr>
<tr>
<td>20</td>
<td>Candesartan</td>
<td>Immediate Release</td>
<td>[37]</td>
</tr>
<tr>
<td>21</td>
<td>Rofecoxib</td>
<td>Flowability and compressibility and Enhancement of the dissolution rate</td>
<td>[38]</td>
</tr>
</tbody>
</table>

**CONCLUSION**

This Liquisolid technique is capable method for formulation of water insoluble solid drugs and liquid lipophilic drugs. This Liquisolid technique gives a design to enhance the absorption as well as dissolution rate their by it may enhance the bioavailability of a poorly soluble, insoluble or lipophilic drug and to formulate them into immediate release or sustain or control release by selection of suitable solvent and carrier. This Liquisolid formulations are designed to contain liquid medications in powdered form and hence possess drug delivery mechanisms similar to that of soft gelatin capsule preparations, containing liquids. Liquisolid formulations show better compressibility, flowability, improve solubility, dissolution and hence better absorption. The technique is also used to design sustained release systems by means of hydrophobic carriers instead of hydrophilic carries in liquisolid systems.
REFERENCES


