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# LIQUISOLID COMPACT TECHNIQUE; A PROMISING APPROACH FOR SOLUBILITY ENHANCEMENT

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## ABSTRACT

The solubility of poorly water-soluble drugs remains a critical challenge in pharmaceutical formulation, significantly impacting bioavailability and therapeutic efficacy. With an increasing number of lipophilic drug candidates in development, the need for effective solubility enhancement techniques has become more pressing. This review examines various strategies for enhancing drug solubility, including pH adjustment, complexation, solid dispersion, co-solvency, hot-melt extrusion, Sonocrystallization, solvent evaporation, and micronization. Among these, the liquisolid compact technique has emerged as a promising approach for enhancing the dissolution rate of poorly soluble drugs. This method involves converting liquid medications into dry, free-flowing powders using suitable carrier and coating materials, thereby improving wettability, surface area and aqueous solubility. The mechanisms, advantages, limitations and recent advancements in liquisolid technology are discussed, along with their potential for industrial application. The review also highlights recent studies demonstrating the effectiveness of liquisolid systems in enhancing drug dissolution and bioavailability, positioning them as a viable alternative to conventional formulation techniques.

**KEYWORDS:** Solubility enhancement, Liquisolid technique, poorly soluble drug, bioavailability, Dissolution rate.

## INTRODUCTION

Out of the numerous challenges in the design of pharmaceutical dosage forms, the most important is the solubility enhancement of poorly water-soluble drugs and improvement of bioavailability. However, most of these drugs are highly lipophilic and poorly water-soluble. About 40% of the newly developed drugs and nearly 60% of the synthesised chemical entities suffer from solubility issues.[1]

Nowadays, the synthesis of poorly soluble drugs is increasing steadily. Therapeutic effectiveness of a drug depends upon the bioavailability which is dependent on the solubility and dissolution rate of drug molecules. The drugs which are poorly water soluble will be inherently released at a slow rate owing to their limited solubility within the GI contents.[2]

**Ex:** Ketoconazole, Mefenamic acid, Nifedipine, Nicardipine, Felodipine, Piroxicam.[3]

### Biopharmaceutical classification systems

The BCS is a scientific framework for classifying a drug substance based on aqueous solubility and intestinal permeability. When combined with the *In-Vitro* dissolution characteristics of the drug product the BCS takes into account 3 major factors: solubility, intestinal permeability and dissolution rate, all of which govern the rate and extent of oral drug absorption from IR solid-oral dosage form.[4]

**Table 1: Biopharmaceutical classification system (1)**

| Sl. No | BCS class | Solubility | Permeability | Example |
|---|---|---|---|---|
| 1 | I | High | High | Metoprolol, Verapamil, Propranolol, Diltiazem. |
| 2 | II | Low | High | Danazol, Nifedipine, Ketoprofen, Naproxen. |
| 3 | III | High | Low | Atenolol, Captopril Ranitidine, Acyclovir. |
| 4 | IV | Low | Low | Taxol, Furosemide. |

### Solubility enhancement

**Solubility:** Solubility may be defined as solute dissolve in particular solvent at certain temperature. More than 90% of drug administered as orally drug absorption, bioavailability and pharmacokinetic profile are dependent on solubility parameter. Solubility of drug can be increase by increasing of dissolution rate.[5]

### Solubility enhancement techniques

1. Ph Adjustment
2. Complexation

3. Solid dispersion
4. Co- Salvency
5. Hot Melt Extraction
6. Sonocrystallization
7. Salvent evaporation method
8. Micronization
9. Liquisolid Technique

**1. pH Adjustment**

PH is required for the solubility of drug more ionic drug can easily solubilize. PH is main parameter of drug to maintain the solubility and for the purposed of pharmacological response. PH is required for the purposed of administration of drug. The drug having low solubility can precipitate in the blood it cannot soluble in the blood because blood has acidic in nature which effect in the blood. The suitable PH should require for the absorption of drug. PH of stomach is 1 -2 and duodenum is 5- 6 the degree of solubility is responsible to pass to body.[6]

**2. Complexation**

In complexation extraordinarily at the risk forces inclusive of London forces, hydrogen bonding and hydrophobic interactions concerned. frequently enough drug solubilization may be received with the aid of using which include most effective complexing agent in aq. form, or a strong drug product, however occasionally complex of greater than the complexing agent is wanted to acquire favored solubility.[7]

**3. Solid dispersion**

The Noyes-Whitney equation provides indication on how the dissolution rate can be used to improve the solubility of poorly soluble drugs. By increasing the surface area and decreasing the particle size of the compound, dissolution can occur. Also, a greater rate of dissolution will happen by increasing the wettability of the surface compound and by decreasing its' thickness.

$$\frac{dc}{dt} = \frac{AD(Cs - C)}{h}$$

Where,

dC= Rate of dissolution A = Surface area

Cs = Solubility od's the compound in the dissolution medium C = Concentration

T = Time

h = thickness[8]

### 4. Co- salvency

The solubility of a poorly water-soluble drug can be increased frequently by the addition of a water miscible solvent in which the drug has good solubility known as cosolvents. Co-solvents are mixtures of water and one or more water miscible solvents used to create a solution with enhanced solubility for poorly soluble compounds. Historically, this is one of the most widely used techniques because it is simple to produce and evaluate. Examples of solvents used in co- solvent mixtures are PEG 300, propylene glycol or ethanol.[9]

### 5. Hot Melt Extrusion

Hot melt extrusion is essentially the same as the fusion method except that intense mixing of the components is induced by the extruder. Just like in the traditional fusion process, miscibility of drug and matrix can be a problem. High shear forces resulting in high local temperature in the extruder is a problem for heat sensitive materials.[10]

### 6. Sonocrystallization

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 characterized by a frequency range of 20-100 kHz for inducing crystallization. It's not only enhancing 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.[11]

### 7. Salvent evaporation method

In solvent evaporation method we dissolve both the drug and the carrier in a common solvent and then evaporate the solvent under vacuum to produce a solid solution.[15] Tachibechi and Nakumara were the first to dissolve both the drug (β- carotene and the carrier PVP) in a common solvent and then evaporate the solvent under vacuum to produce a solid dispersion. Commonly use solvent such as ethanol, chloroform, or a mixture of ethanol and dichloromethane. In some case cosolvant may use because large volume of solvents as well as heating may be required to enable complete dissolution of drug and carrier.[12]

### 8. Micronization

Reduction of particle size occur so as increase of surface area which increase the dissolution rate and bioavailability of drug. The particle size after micronization is 1-10 microns. This method involves spray drying and attrition method. Applying of shear force. By this phenomenon drugs particles get dispersed. Homogenization depends on pressure and nature of drug.[5]

### Factors affecting Solubility enhancement

- **Particle size:** Size of the solid particle affects solubility since for example element becomes smaller; surface areas volume ratio raises of surface area, which allows to leads greater communication/interact through the solvent.
- **Temperature:** Rising in temperature of solubility material enhancement is normally probable.
- **Nature of solute and solvent:** The drug solubility is owing to the polarity of the solvent, which is dipole-dipole movement, and the addition of H-bonding between the solute and solvent is needed.
- **Pressure:** The solids and liquids solubility not affected by water in higher pressure. Solubility of gases knowingly rises by pressure. When the increase in solubility is directly proportional to the increase in pressure.
- **Polymorphs:** Volume for material to crystallize in which there is more than one crystalline form is polymorphism. Polymorphs can also differ in the melting point.
- **PH:** Maximum of drugs is weak electrolytes and the weak bases and weak acids undertake ionization in the solution. The drugs which have more soluble in water when they are in ionised form. Poorly water-soluble drug is Unionised drug.[7]

### Liquisolid System

The liquisolid technique refers to powdered forms of liquid medications formulated by changing liquid lipophilic drugs or drug suspensions or solutions of water insoluble solid drugs in suitable non-volatile solvent systems into dry-looking, non- adherent, free moderately flowing.[13]

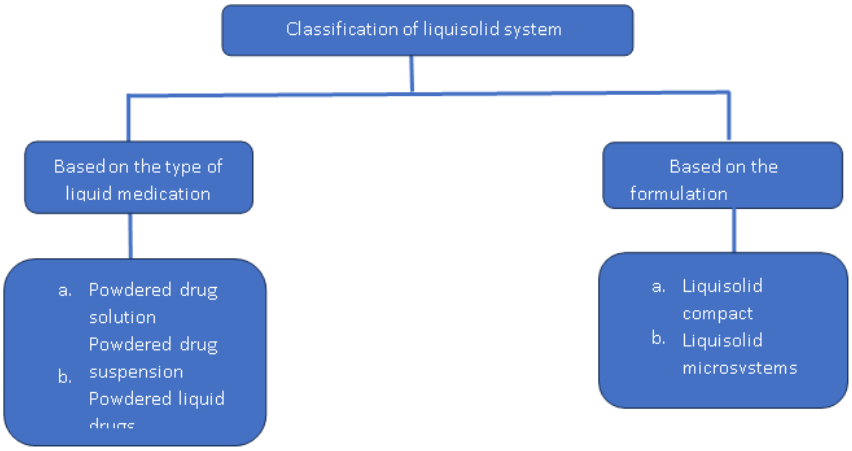


**Fig No. 1: Based on the formulation technique used, liquisolid systems may be classified into two categories.**[14]

**Liquisolid Compact**

Liquisolid compacts are one of the most promising and new technique which promotes the dissolution rate of water insoluble drugs. The term liquisolid compact refers to immediate release or sustained release tablets or capsules, combined with the inclusion of appropriate adjuvant required for tableting or encapsulating.[15]

**Components of liquisolid Compact**

1) Drug
2) Non-volatile solvent
3) Carrier materials
4) Coating materials
5) Disintegrants
6) Lubricants

**1. Drug**

The drug must be poorly water soluble and having biopharmaceutical classification system II and IV.

**2. Non-volatile solvent**

- Inert
- High boiling point
- Preferably water-miscible
- Less viscous organic solvent systems

eg., propylene glycol, liquid polyethylene glycols, polysorbates, glycerin, N, N- dimethyl acetamide, fixed oils, PEG 600 and 400, Tween80 and 20, Span80 and 20, Glycerin.

**3. Carrier material**

- Materials with porous surface
- Closely matted fibres in their interior
- Sufficient absorption properties

e.g. Microcrystalline and amorphous cellulose, Starch, Lactose, MCC (Avicel PH 102), DCP dibasic calcium phosphate, Eudragit RL and RS.

**4. Coating materials**

Fine and highly adsorptive particles Contributes in covering the wet carrier particles and displaying a dry-looking powder Particle size range of about 10 nm to 5,000 nm in diameter. Amorphous silicon dioxide (silica 2), HPMC, silica (Cab-O-Sil M5), Syloid etc.

**5. Disintegrants**

Sodium starch glycolate, cross carmelose sodium, cross povidine, explotab, Pregelatinized Starch etc.[16]

**6. Lubricants**

Most commonly used lubricant is magnesium state.[2]

**Preparation of liquisolid compact**

Calculated quantities of drug and non-volatile solvent is accurately weighed in 20 ml glass beaker and then heated to dissolve the drug in that solvent. The resulting hot medication is incorporated into calculated quantities of carrier and coating materials. Mixing process is carried out in three steps as described by Spirea's et al.

(1) During the first stage, the system is blended at an approximate mixing rate of one rotation per second for approximately one minute in order to evenly distribute liquid medication in the powder.
(2) In the second stage, the liquid/powder admixture is evenly spread as a uniform layer on the surfaces of a mortar and left standing for approximately 5 min to allow drug solution to be absorbed in the interior of powder particle.
(3) In the third stage, the powder is scraped off the mortar surfaces by means of aluminium

spatula and then blended with sodium starch glycolate for another 30 seconds in a similar way to the first stage. This gives final formulation of liquisolid tablets.[17]

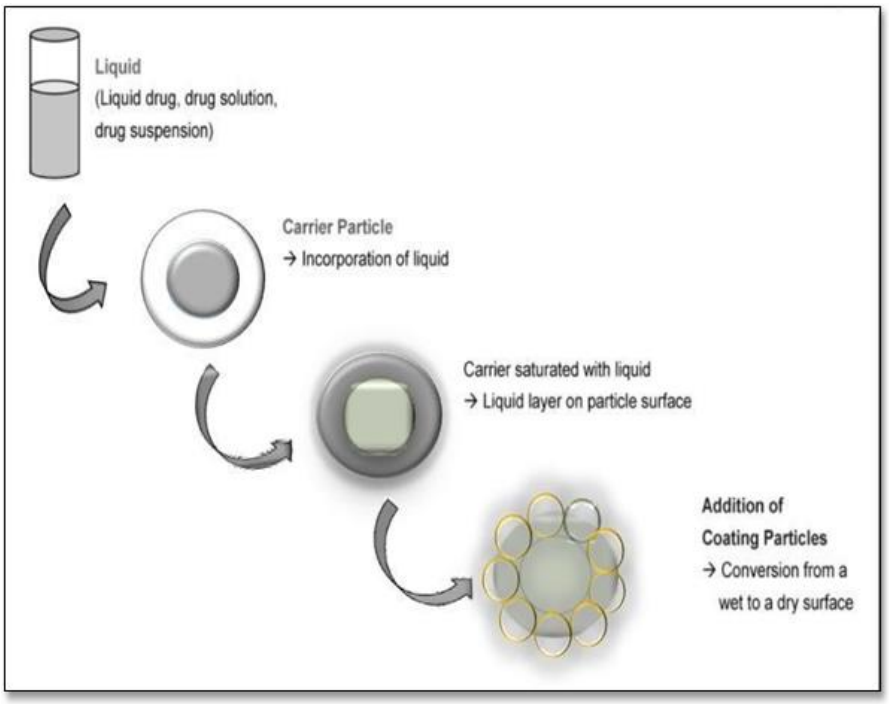


**Fig No. 2 Schematic representation of liquisolid system(15)**

**Mechanism of liquisolid compact**

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

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 enhance 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.[18]

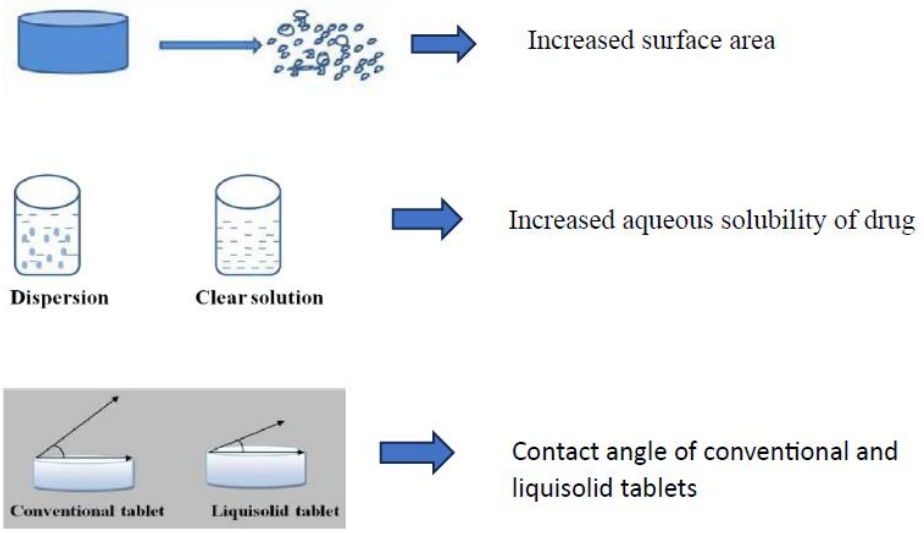


**Fig. No. 3 Schematic representation of mechanism of liquisolid compact.**

### Advantages of liquisolid compact

- Liquisolid systems are low-cost formulations than soft gelatin capsules.
- Production of them is similar to that of conventional tablets.
- Drug release can be modified using suitable formulation ingredients.
- Drug can be molecularly dispersed in the formulation.
- Capability of industrial production is also possible.
- Enhanced bioavailability can be obtained as compared to conventional tablets.[19]
- Sustained release liquisolid tablets or capsules of water insoluble drugs exhibit constant dissolution rates (zero-order release) comparable only to expensive commercial preparations that combine osmotic pump technology and laser- drilled tablets
- Can be applied to formulate liquid medications such as oily liquid drugs.
- Better availability of an orally administered water insoluble drug.
- Several slightly and very slightly water-soluble and practically water-insoluble liquid and solid drugs, can be formulated into liquisolid systems.

### Disadvantages / limitations

- 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.
- Hydrotrophy is suggested to be superior to other solubilization method, such as miscibility, micellar solubilization, cosolvency and salting in, because the solvent character is independent of pH, has high selectivity and does not require emulsification.
- It only requires mixing the drug with the hydrotrope in water.

**Table No. 2: Published works on liquisolid delivery systems showing dissolution, solubility and bioavailability.[20]**

| Drug | Non- volatile liquid used | Carrier/coating material | Improvement over marketed brand (%) | Presentation/ application | Reference |
|---|---|---|---|---|---|
| Valsartan | Propylene glycol | Avicel Ph 102/Aerosil 200 | Over 15% in dissolution efficiency | As liquisolid compact | Chella *et al.*[44] |
| Ro suvastatin | PEG 400 | Neusilin US2/Aerosil 200 | Fast disintegration and enhanced dissolution profiles | As liquisolid tablet | Vraníková *et al.*[29] |
| Ritonavir | PEG 400 | MCC/crospovidone | Improved dissolution by over 40% | As liquisolid pellets | De Espíndola *et al.*[45] |
| Telmisartan | Transcutol HP | Avicel PH102/Aerosil 200 | Significant improvement | Liquisolid compacts | Chella *et al.*[46] |
| Efavirenz | Transcutol HP | Neusilin US2 and corn starch/Aerosil | Improved dissolution profile with almost 100% release in 60 min | Liquisolid tablet | Jaydip *et al.*[47] |
| Olmesartan Medoxomil | Acrysol El 135 (Polyoxyl 35 castor oil) | Avicel PH 102, Fujicalin and Neusilin/Aerosil | Significant higher drug release rates | Liquisolid compact | Prajapati *et al.*[37] |
| Olanzapine | Kolliphor EL | Avicel/ Aerosil | Formulations showed good/excellent flow properties and compressibility AUC of optimized liquisolid formulation was higher than marketed tablet | Liquisolid tablet | Korni and Gonugunta[48] |
| Meloxicam | PEG 400 | Avicel PH102/Aerosil | Higher dissolution with more than 80% drug | Liquisolid tablets | Dias *et al.*[38] |

| | | | | | |
|---|---|---|---|---|---|
| | | | release within 10 min | | |
| Fexofenadine hydrochloride | Propylene glycol or Cremophor ®E L | Aerosil® 200 Avicel® PH102/ | Increased oral drug bioavailability by 62% and reduced Tmax to 2.16 hrs | Liquisolid tablets | Yehia *et al.*[49] |
| Itraconazole | PEG 600 | Afacel PH200/ Aerosil | Higher drug dissolution, Cmax an AUC | Liquisolid compact | Thakkar *et al.*[36] |
| Prednisolone | PEG 400, glycerin, propylene glycol | MCC/Silica | Higher dissolution rate with enhanced bioavailability | Liquisolid compact | Spireas and Sadu[27] |
| Indomethacin | PEG 200, glycerin | Avicel PH101/ Nano-sized amorphous silica | Liquisolid formulations exhibited significantly higher drug dissolution rates than directly compressed tablet | Liquisolid compact | Saeedi *et al.*[42] |
| Famotidine | Propylene glycol | Avicel® PH 102/ Aerosil® 200 | Optimized liquisolid formula had 39% higher release than directly compressed tablets during the first 10 min | Liquisolid tablet | Fahmy and Kassem[50] |
| Carbamazepine | PEG 200, PEG 400 | MCC or Lactose/ Nano-sized amorphous silica and PVP or HPMC or PEG35000 Added to reduce quantity of carrier-coating mixture used | Liquisolid formulations containing PVP showed significantly higher drug dissolution rates over that prepared as directly compressed compacts technique Improved dissolution as carrier-coating ratio reduced from 20 to 10 but decreased when reduced to 5 10 | Liquisolid compact | Javadzadeh *et al*[34] |
| Furosemide | Castor oil, cremophor EL and PEG 400 in ratio 1:6:3 | (Avicel PH101) and coating materials (Aerosil 200) | 2-folds increase in drug release | SNEDDS delivered as liuisolid tablets | Dalal *et al.*[40] |
| Atorvastatin | PEG 400 | Avicel PH 101 OR Avicel PH 102 OR Neusilin US2 as carriers and Aerosil 200 as coating material | Optimized liquisolid tablets showed higher dissolution compared to marketed tablets | Liquisolid tablets | Windriyati *et al.*[51] |
| Clopidogrel | Propylene glycol and water in ratio 2:1 | Maize starch, microcrystalline cellulose/colloidal silicondioxide | Formulation showed higher solubility in HCl buffer pH 2 | Liquisolid tablet | Ali *et al.*[52] |

## CONCLUSION

Enhancing the solubility of poorly water-soluble drugs remains one of the major challenges in pharmaceutical formulation. Various conventional techniques such as pH adjustment, complexation, solid dispersion, co-solvency and micronization have been effectively used to improve solubility and bioavailability. However, among the modern approaches, the liquisolid compact technique stands out as a simple, cost-effective, and industrially feasible method for improving dissolution rate and drug absorption. By converting liquid drugs or drug solutions into free-flowing, compressible powders, this system enhances surface area, wettability, and aqueous solubility. Despite certain limitations for high-dose drugs, the liquisolid technique has shown significant potential in improving the bioavailability of BCS Class II and IV drugs. Therefore, it represents a promising platform for the development of novel oral dosage forms with enhanced therapeutic performance.

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