Available online on 15.09.2018 at http://jddtonline.info

Journal of Drug Delivery and Therapeutics

Open Access to Pharmaceutical and Medical Research



Open Access Review Article

# A PROMISING TECHNIQUE TO IMPROVE THE SOLUBILITY BY LIQUISOLID COMPACTION TECHNOLOGY

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## ABSTRACT

About 60-70% of the drugs synthesized are poorly soluble and comes under BCS Class-II&IV. Now it is a challenging situation during the development of different dosage forms for pharmaceutical industries because solubility of the drug is the rate limiting step. Based on the solubility, the dissolution, bioavailability & therapeutic effect is dependent. To overcome this consequence a novel technique -Liquisolid compact is used by dissolving the poorly soluble drug in a non-volatile solvent that improves wettability & decreases the surface tension and ensures drug molecular dispersion in the formulation to increase the solubility of the drug. This admixture of drug loaded solution is blended with carrier adsorption & coating material (adsorption) that has free flowing and compressible powder properties.

**Keywords:** BCS-Class II drug, Liquisolid Compact, Non-Volatile Liquid, Carrier, Coating material.

**Article Info:** Received 19 Aug, 2018; Review Completed 02 Sep 2018; Accepted 05 Sep 2018; Available online 15 Sep 2018

**Cite this article as:**

Naik NG, Shaym Sunder R, Sateesh Kumar M, A promising technique to improve the solubility by liquisolid compaction technology, Journal of Drug Delivery and Therapeutics. 2018; 8(5):56-61

**DOI:** http://dx.doi.org/10.22270/jddt.v8i5.1919

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## INTRODUCTION

Numerous potent lipophilic drugs show low oral bioavailability due to their poor aqueous solubility properties that falls under BCS- II- low solubility and high permeability[1]. However low solubility and dissolution rate are main rate limiting factors[2]. As per bioavailability is concerned, a drug is poor bioavailability is one with

1. Poor aqueous solubility or slow dissolution rate in the biological fluid.

2. No proper partition coefficient and thus poor permeation through the biomembrane.

3. Less stability of the dissolved drug at the physiological $P^H$.

**There are few approaches to overcome the bioavailability problem as listed below**

A. Modification of formulation, manufacturing process/ changing the Physiochemical properties of drug according to pharmaceutical approach.

B. Alteration of chemical structure according to pharmacokinetic approach.

C. Route of drug administration may be changed from oral to parenteral route according to biological approach.

As per the pharmacokinetic approach, chemical structure modification having number of draw backs. It is expensive and time consuming and also requires clinical study for longer time and the new chemical entity suffer from another pharmacokinetic disorders.

Finally the pharmaceutical approach will be dealt here with.

The attempts whether optimizing the formulation, manufacturing process or drug physico- chemical properties that are mainly aimed at enhancement of dissolution rate as it is the major rate limiting step in the absorption of most drugs[3]. When the largest dose of a drug substance is soluble in lesser than 250 ml water such drugs are consider as highly soluble. Drug with solubility below 0.1 mg / ml or 10 mg/ml faces significant obstacles[4].

The drug dissolution rate is directly proportional to solubility as per Noyes whitney equation and therefore solubility of a drug substance is a major factor. They are several methods to enhance the solubility, surface area and dissolution rate of poorly soluble drugs[5]. They are as follows:

1. Complexation with cyclodextrins
2. Solid dispersion
3. Eutectic mixture
4. Solvent deposition
5. Hydrotrophy
6. Use of surfactants
7. Micronization technique
8. Solvent evaporation
9. Lyophilization technique
10. Solid solution
11. Co solvency

Micronization is a common method to increase surface area but alter the flow property when drugs are encapsulated or tableted[6]. In complexation with cyclodextrins maximum drug loaded is relatively low and also depends upon the cavity of the dextrin[7,8]. Solid dispersion preparation requires special equipments likes spray dryer or fluid bed dryer[9]. Each and every technique has advantages and disadvantages. So to overcome the solution a novel technique-liquisolid compaction technology is developed to increase the solubility and dissolution rate of poorly soluble drugs.

## Liquisolid system:

Liquid solid systems are powdered forms of liquid medication that exhibit acceptable or desirable flowability and compressibility properties. That term liquid medication refers to a solution or a suspension of a water insoluble drug in non-volatile solvent.

Based on the type of liquid medication, liquisolid systems may be classified into three subgroups:

1) Powdered drug solutions

2) Powdered drug suspensions

3) Powdered liquid drugs

The first two may be produced from the conversion of drug solutions (e.g. Prednisolone solution in propylene glycol) or drug suspensions (e.g. gemfibrozil suspension in Polysorbate 80) and the latter from the formulation of liquid drugs (e.g. clofibrate, valproic acid, liquid vitamins, etc.) into liquisolid systems[10].

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

1) Liquisolid compacts

2) Liquisolid Microsystems.

Liquisolid compacts are prepared by using the below method to produce tablets or capsules, whereas the liquisolid Microsystems are based on a new concept which employs similar methodology combined with the inclusion of an additive, e.g., polyvinylpyrrolidone (PVP) in the liquid medication which is incorporated into the carrier and coating materials to produce an acceptably flowing admixture for encapsulation[11]. The technique of liquisolid compaction has been used successfully to improve the invitro release of poorly soluble drugs such as piroxicam[12], progesterone[13], repaglinide[14], furesomide[15].

## Components of liquisolid compaction formulation

**1. Poorly insoluble drugs:**

**Examples:** Bromohexine hydrochloride, Indomethacin, Prednisolone & Aceclofenac.

This technique is successfully applied for low dose BCS class II and class IV drugs which are poorly water soluble and have slow dissolution rate[16].

**2. Non volatile solvents**

**Examples:** Polyethylene glycol 400, Polyethylene glycol 200,Tween 20,Tween 80,Synperonic PE, Cremophore EL, Captex 200,captex 355 & Polysorbate.

Principle of Non volatile solvent:

Non volatile solvents improve wetting properties where liquid vehicle acts as wetting agent or surface active agent. Therefore interfacial tension decreases between media and surface of the drug or decreases the contact angle and increases the surface area in turn increases the solubility[17].

**3. Carrier:**

**Examples:** starch, lactose, sorbitol, microcrystalline cellulose.

Principle of carrier: Carrier involves in the sorption process of liquid medication that improves surface area due to adsorption of porous particle and also having adsorption property and matted fibers in interior contribute in liquid medication[18].

**4. Coating material:**

**Examples:** Colloidal silica of various grades such as cab-o-sil –M5, aerosil 200, syloid 244FP, Principle of coating material: A coating material forms a uniform film around the particles of carrier and prevents the aggregation of particles as well as reduces inter particulate friction and improves flowability[19].

**5. Disintegrants:**

**Examples:** sodium starch glycollate, crosspovidone & crosscarmellose etc.

Principle of Disintegrants: Disintegrants are the agents added to tablet formulation to promote the breakup of the tablet in to smaller fragments in an aqueous environment thereby increasing the available surface area and promoting rapid release of the drug substance[20].

## Pre formulation studies of liquisolid compacts

1. Determination of drug solubility in different non volatile solvents

2. Angle of slide determination

3. Flowable liquid retention potential determination

4. Calculation of liquid loading factor

5. Liquisolid compressibility (LSC)

In the liquid solid compact formulation, flowability and compressibility are calculated by mathematical model of liquid solid system to know the quantities of carrier and coating material that gives flowable liquid retention potential(Ø value) and compressible liquid retention potential (Ψ-number ) of powder[21].

1. Determination of drug solubility in different non volatile solvents:

Saturated solutions are prepared by adding excess of drug to non volatile solvents and shaking them on a shaker for 48 hours and the solutions are filtered by whatman filter paper and analyzed by spectrophotometer and the best solubility solvent is selected[22].

2. Angle of slide determination:

Weighed amount of carrier is placed at one end of metal plate with a polished surface and gradually raised till the plate becomes angular to the horizontal at which powder is about to slide. It is used to measure the flow properties of powders. The angle of 33° is optimum for flow of powder.

3. Flowable liquid retention potential (Φ value) determination:

It is defined as the maximum weight of liquid that can be retained per unit powder material in order to produce and acceptably flowing liquid/powder admixture. This Φ –value of powders may be determined using a new procedure- liquisolid flowability (LSF) test. The Ø value is used to calculate excipient quantities. Equation for this is as follows:

$Lf = Ø + Ø (1 / R)$

Where

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

4. Calculation of liquid loading factor (Lf)):

It is defined as the ratio of weight of liquid medication (w) to weight of carrier material (Q). Different concentrations of nonvolatile solvents are taken and the drug is dissolved and the carrier coating material is added and blended[23].

$Lf=W/Q$

W=ratio of weight of liquid medication

Q= weight of carrier material

The liquid load factor that ensures acceptable flowability (Lf), and can be measured by:

$Lf= (1/R)$

5. Liquisolid compressibility test (LSC):

It is developed to determine Ψ values and involves steps such as preparing carrier coating material admixture systems, preparing several uniform liquid/powder admixtures to tablets, determining average hardness, measuring of average liquid content of crushed tablets, as well as determining plasticity, sponge index and Ψ[24].

**Table 1: Liquisolid formulation parameters of various excipients with commonly used non volatile liquids**

| Powder excipients | Ø-Values | | Ψ- Numbers | |
|---|---|---|---|---|
| | Propylene glycol | PEG 400 | Propylene glycol | PEG 400 |
| Avicel PH 102 | 0.16 | 0.005 | 0.224 | 0.242 |
| Avicel PH 200 | 0.26 | 0.02 | 0.209 | 0.232 |
| Cab-O-Sil M5(silica) With Avicel PH 102 | 3.31 | 3.26 | 0.560 | 0.653 |
| Cab-O-Sil M5(silica) With Avicel PH 102 | 2.57 | 2.44 | 0.712 | 0.717 |

## Preparation of Liquid Solid Compacts

This method involves first a mathematically calculated amount of pure drug weighed and dissolved in the solvent in a molecularly dispersed state. For attaining good flow properties trial and error methods were used i.e. changing the carrier: coating material ratio from 50:1 to 5:1 ratios according to new mathematical model expressions proposed by *Liao*. This liquid medication is poured on the suitable amount of carrier material. The liquid medication is absorbed into the carrier material internally and externally and then a suitable disintegrant is added to this material. Finally, coating material is

added for dry looking, adherent to the carrier material for achieving good compression properties.

Excipients possessing fine and highly adsorptive particles such as various types of amorphous silicon dioxide (silica) are most suitable for this step. Before compression or encapsulation, various ingredients such as lubricants, disintegrants or polymers, and binders, may be mixed with the finished liquid-solid systems to produce liquid-solid compacts in the dosage form of tablets or capsules[25]

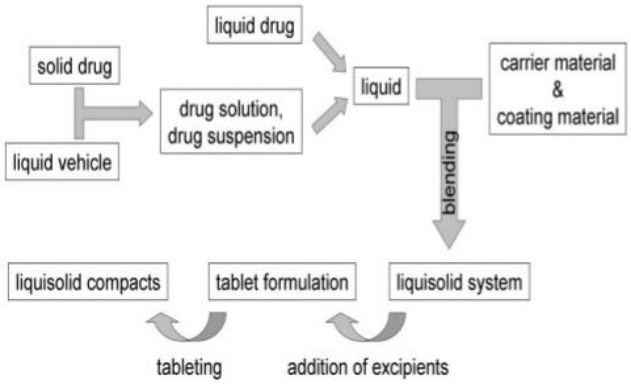


Figure 1: Preparation of Liquisolid Compacts

**Table 2: Examples of liquisolid compacts drugs**

| Poorly soluble drugs | Non volatile solvents | Carrier and Coating material |
|---|---|---|
| Piroxicam[26] | Tween 80 | MCC and colloidal silica |
| Ibuprofen[27] | PEG 400 | MCC and colloidal silica |
| Ketoprofen[28] | PEG 400 | lactose and silica gel |
| Naproxen[29] | Cremophor EL, Synperonic PE/L61 and PEG-200 | MCC and colloidal silica |
| Valsartan[30] | Propylene glycol | MCC and colloidal silica |
| Etoricoxib[31] | PEG 400 | MCC and colloidal silica |
| Famotidine[32] | Propylene glycol | MCC and colloidal silica |
| Fenofibrate[33] | Propylene glycol | MCC and colloidal silica |
| Fenofibrate[34] | PEG 400 | MCC and colloidal silica |
| diclofenac sodium[35] | PEG 400 | MCC and colloidal silica |

## Evaluation

**Pre-compression parameters**

**1. Flow properties of the liquid solid system:**

The flow properties of the liquid solid system are determined by angle of repose, carr's index and hausner ratio.

**2. Scanning electron microscopy:**

Scanning electron microscopy is used to assess the morphological characteristics of the poorly soluble drugs - carrier system and liquid solid compact. The sample is mounted on double sided adhesive carbon tape on brass stubs and analyzed and also confirms the drug is totally solubilized in liquid solid system and this ensures the complete solubility.

**3. X-Ray Powder diffraction (XRD) studies:**

X-ray powder diffraction studies conducted to pure drug, liquisolid physical mixture. These samples are exposed to Cu-Kα radiation at a scan rate of 1.50 / min over the 2θ range of 4-400 $^0$C. Generally, disappearance of characteristic peaks of drug in the liquisolid formulation and retaining peaks of carrier material is observed. This indicates that drug gets converted to amorphous form or in solubilized form in the liquisolid formulation.

4. **Differential Scanning Calorimetry (DSC)**:

To determine the interaction between excipients used in the formulation. This will also indicate success of stability studies. If the characteristic peak for the drug is absent in the DSC thermogram, there is an indication that the drug is in the form of solution in liquisolid formulation and hence it is molecularly dispersed within the system[36].

**Post compression evaluation**:

**Hardness:** hardness of the tablet is determined by Monsanto hardness tester and Pfizer tester. It is expressed in Kg/cm².

**Friability:** In friability test, samples are counted and weighted then tumbled in rotating drums with baffles, when the process is stopped; samples are moved out from the instrument, wiped-off dust and weighted again. The difference between the weight before and after the process is determined as Friability and should not exceed 1%, which is considered an ideal percentage.

***In-vitro* dissolution studies:**

Generally dissolution studies are carried out using dissolution test apparatus USP -II at 37°±5°C. Many researches reveal that at low drug concentration in liquid medication, more rapid release rates are observed[37].

**Invivo evaluation of liquisolid powder or tablets:** The improvement in oral bioavailability is confirmed by estimating the pharmacokinetic parameters in various animals such as rabbit, beagle dog and the results are compared to the pure drug and marketed tablets[38].

## Merits

1. Bio-Pharmaceutical classification class II drugs with high permeability, slightly or very slightly water soluble

and practically insoluble liquids and solid of numerous drugs can be formulated into liquisolid systems.

2. Enhancement of bioavailability of an orally administered water insoluble drugs is achieved.

3. This principle governs the drug delivery from liquisolid systems of powdered drug solutions and it is mainly responsible for the improved dissolution profiles exhibited by this preparations.

4. Liquisolid systems formulate into immediate release or sustained release dosage forms.

5. Optimized sustained release, liquisolid tablets or capsules of water insoluble drugs demonstrate constant dissolution rates (zero order release).

## Demerits

1. This technique is only for water insoluble drugs.

2. However, for formulation of high dose insoluble drugs, the liquisolid tablet is one of the limitations of this technique.

3. In order to achieve acceptable flowability and compactability for liquisolid powder formulation, high levels of carrier material and coating materials should be added. This will increase the weight of tablets to above one gram which makes them difficult to swallow. Therefore, it is impossible with conventional tablet methods to convert high dose to liquisolid tablets with a tablet weight of less than 50 mg.

4. Dissolution profile enhancement occurs in the presence of low levels of hydrophilic carrier, where coating material is not significant.

## Limitations

1. Not applicable for formulation of high dose insoluble drugs.

2. 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.

3. 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.

## CONCLUSION

Liquisolid technique is a promising tool to improve the solubility, wettability of water insoluble drug and ensures the molecular dispersion of a drug in the formulation by blending the pure drug with non-volatile solvent, carrier and coating material modification of formulation. By use of certain agents also causes sustained release of drugs from the liquid solid compacts.

**Conflict of interest:** We have no conflict of Interest.

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