Indian Journal of Drugs, 2018, 6(3), 152-164 ISSN: 2348-1684

Review Article

SOLUBILITY ENHANCEMENT OF POORLY WATER SOLUBLE DRUGS USING LIQUISOLID TECHNIQUE

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Received: 28.02.2018
Accepted: 22.09.2018

Access this article online

Website:
www.drugresearch.in

Quick Response Code:

ABSTRACT

Poor dissolution rate is the major challenge for formulation and development of solid oral dosage form of poorly water soluble drugs. Enhancement of aqueous solubility and improve dissolution rate of BCS class II and class IV drugs have been explored extensively. There are many approaches for solubility enhancement, liquisolid compact thechnology also known as powder solution technology is the novel and commonly use for solubility enhancement of poorly water soluble drugs. The liquisolid technique introduced by spireas is a non volatile liquid vehicle is transformed into a free flowing, non adherent and readily compressible dry powder formed by the physical mixing of excipients like carrier and coating material. The drug in non volatile liquid or suspension of drug which is poured into porous carrier material. The water soluble organic solvent system is use with high boiling point like tween, polyethylene glycol, propylene glycol are suitable vehicle. The dissolution rate is enhanced due to increased surface area, wetting properties and bioavailability.

KEY WORDS: Liquisolid compact, Dissolution, Carrier, Coating, Bioavailability.

INTRODUCTION

Concept of solubility

Solubility is the property of a solid, liquid, or gaseous substance called solute to dissolve in a solid, liquid, or gaseous solvent to form a homogeneous solution of the solute in the solvent. The solubility of a substance is depending on the solvent used as well as on temperature and pressure. The solubility of a substance in a specific solvent is measured as the saturation concentration where adding more solute does not increase its concentration in the solution (Alfred martin 3rd edition)**.** Solubility is one of the major factors to achieve desired concentration of drug in systemic circulation (spireas et.al. 2002). The solubility of a substance becomes especially important in the pharmaceutical field because it often represents a major factor that controls the bioavailability of a drug substance. (Harry G. Brittan pg 10). About 40% of drug substances developed in pharmaceutical industry have low aqueous solubility and this is the major problem for the formulation & development of such drugs. (Ketan T. et.al.2012) According to the Biopharmaceutics Classification System (BCS) the class II (low solubility & high permeability) & IV (low solubility & low permeability) drugs are poorly water soluble. Poorly water-soluble drugs will be inherently released at slow rate owing to their limited dissolution rate within the gastrointestinal tract (GIT) contents (Darwish and EI-Kamel). Therefore, this is the major challenges of the pharmaceutical industry is to improve the apparent solubility & dissolution of poorly soluble drugs to develop such poorly soluble compounds into orally bioavailable and therapeutic effective drugs. (Le-Ngoc Vo C. et.al.2013).

Table 1: BCS Classification (Brahmnakar D.M)

Class	Solubility	Permeability
I.	High	High
II.	Low	High
III.	High	Low
IV.	Low	Low

Solubility definition

It is defined as the concentration of solute in a saturated solution at a certain temperature, or it may be defined as the spontaneous interaction of two or more substances to form a homogeneous molecular dispersion. (Alfred martin). Or, it is defined as the maximum amount of solute dissolved in a given solvent under standard conditions of temperature, pressure and pH. (Brahmankar D.M). Or, Solubility is defined as the maximum quantity of a substance that can be completely dissolved in a given amount of solvent (Brittan G.H). Or, the solubility of a solute is the maximum quantity of solute that can dissolve in a certain quantity of solvent or quantity of solution at a specified temperature. (Amit C. et.al 2012)

Table 2: USP and BP solubility criteria (Industrial pharmacy 2014)

Descriptive Term	**Gram of solute/ liter of solvent**
Freely soluble	Less than 1
Very soluble	1-10
Soluble	10-30
Sparingly soluble	30-100
Slightly soluble	100-1000
Very slightly soluble	1000-10000
Practically insoluble	>10000

TECHNIQUES FOR SOLUBILITY ENHANCEMENT

Solubility improvement techniques can be categorized in to physical modification, chemical modifications of the drug substance, and other techniques. (Savjani K.T. et.al.2012and Bindu M.B. et.al.2010)

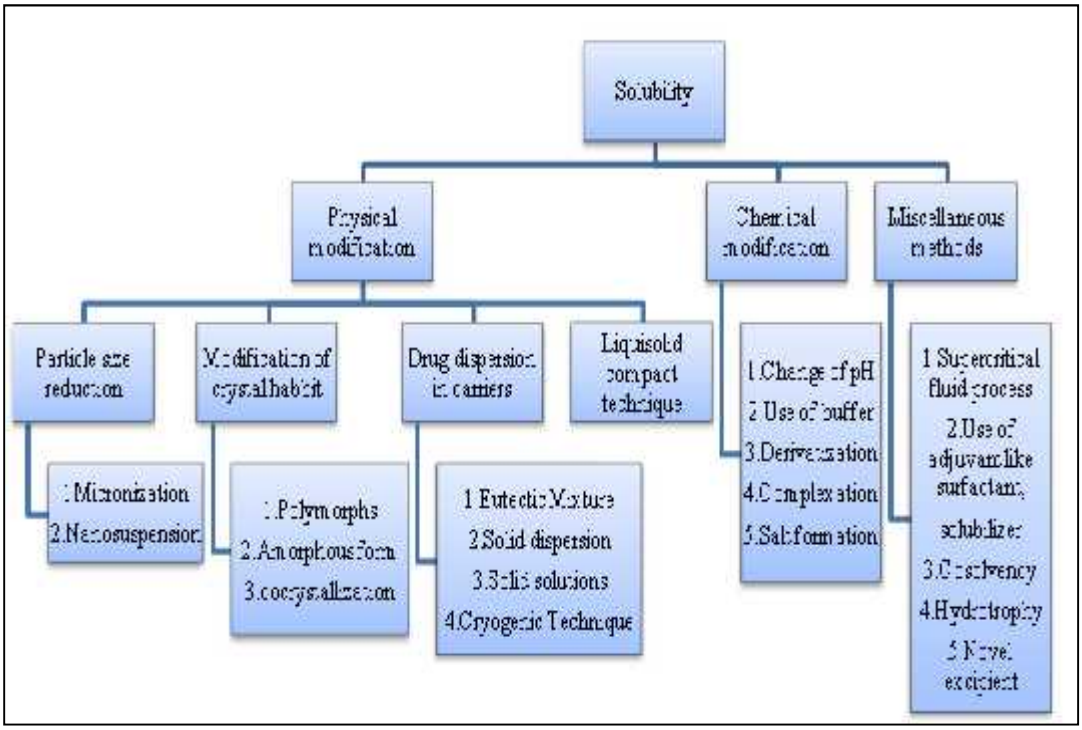

Fig.1. Technique of Solubility Enhancement.

1) Micronisation: The process involves reduction of size of solid drug particles to 1-10 microns by using spray drying or fluid energy mill. The solubility of Griseofulvin and sulph drugs increased by micronization method.

2) **Nanonisation:** In this method the drug powder is converted to Nanocrystal (size-200-600 nm) currently the pearl milling, Homogenization with water and Homogenization in non-aqueous media these technologies are used for preparation of nanoparticle. Eg. Amphotericin-B

3) Supercritical fluid recrystallization: This is novel and nanosizing and solubilisation technology Its application in particle size reduction via supercriticle fluid process.at criticle temperature the drug gets solubilized within the SCF they may recrystallized at reduced particle size.

4) Lyophilization: In this method aqueous organic co-solvent solution containing drug and excipients are directly converted into a compressed gas. Then frozen particles are lyophilized to obtain dry, free flowing , micronized powder. Acetonitrile used as a solvent to increased drug loading and minimize drying time for lyophilization.

5) Use of Salt forms: Salt form of drug increased its solubility and dissolution parameter compared to original drug. eg. Metformin – Metformin HCL.

6) Change in P^H & Buffer addition: The solubility has improved by two methods –*in-situ* salt formation and addition of buffers into formulation. Eg. Buffered Aspirin tablets.

7) Solid solutions: Use of solid solution, Use of solid dispersion and Use of eutectic mixture by using these methods the particle size of drug can be reduced.

8) Solid dispersion: The solid dispersion is prepared by two methods – by use of solvent or co-precipitation method. drug is dissolved in the volatile liquid solvent and then liquid solvent is removed out by evaporation under reduced pressure or lyophilized. Eg. dissolution enhancement of griseofulvin by solid dispersion. (Brahmankar D.M)

9) Cosolvency: Weak electrolytes and nonpolar molecules have a low aqueous solubility for such a drugs the drug is solubilized In the water –miscible solvents in which drug has good solubility. Eg- PG, Various grades of PEG , Glycerin etc. (pharmaceutical codex 12^{th} edition)

10) Complexation: The drug solubility is increased by the formation of drug complex.the cyclodextrin used to increase solubility of the hydrophobic drugs. Eg. thiazide diuretics, NSAIDs.(Khar & vyas)

11) Solubilisers: The use of water soluble organic solvents to enhance the solubility of drug.

Table 3: Advantages and limitations of liquisolid systems (Sibel Uslu.et.al)

Advantages	Limitations
Poorly water soluble or water insoluble drugs can be formulated into LS systems.	This technique is only for slightly*/very slightly water soluble** and practically water insoluble*** drugs.
Better availability of an orally administered poorly water soluble drug is achieved when the drug is in solution form. Also Omit the process approaches like nanonisation, micronization techniques	In order to achieve acceptable flowability and compactability for LS powder formulation, high levels of carrier and coating materials should be added. This will increase the weight of tablets to above one gram which makes them difficult to swallow.
Optimized rapid release LS tablets or capsules of poorly water soluble drugs exhibit enhanced in vitro and in vivo drug release as compared to their commercial counterparts.	The LS systems have drug loading capacities and they require high solubility of drug in non-volatile liquid vehicles.
Can be applied to formulate liquid medications such as oily liquid drugs.	Liquisolid system have low dose drug loading capacities

Enhanced bioavailability can be obtained as compared to conventional tablets.	Carrier to coating ratio should be optimized if not then liquid drug may be squeezed out during compression resulting in tablet compression problem. (Kavitha B. et.al 2014)
Drug release can be modified using suitable formulation ingredients.	
Can be used in controlled drug delivery and zero-order release can be obtained.	
Drug can be molecularly dispersed in the formulation.	

LIQUISOLID TECHNIQUE

A novel **"**Liquisolid or Powder Solution Technology**"** is the novel and promising technique for solubility enhancement of BCS class II & IV drugs which has poor aqueous solubility. In liquisolid systems the drug is already in solution form present in liquid vehicle and it is carried by the powder particles (microcrystalline cellulose and silica). Thus, due to significantly increased wetting properties and surface area of drug available for dissolution ,so liquisolid compacts of water-insoluble drug may be expected to improve the solubility and the bioavailability.(Ajit S.et.al.2010). By using the liquisolid technique, sustained release drug delivery system were developed for the water soluble drugs in which hydrophobic non-volatile solvents are used as a vehicle. (Shashidher B.et.al.2011).and Immediate release (IR) formulation also possible by using the hydrophilic non volatile solvents in which drug solubility is high. (Kharwade M. et.al.2015)

Requirements and components of liquisolid compact

1) **Drug candidates:**
   Mainly poor water soluble (BCS class II or IV) and low dose drugs can be the good candidate for this technique include Carmabazepine, naproxen, furosemide, Ketoprofen etc.
2) **Non-volatile solvents:**
   These solvents should be inert, high boiling point, preferably water-miscible less viscous organic solvent systems, compatible with the drugs and must have high or low drug solubility according to formulation of Sustained or immediate release tablet. These solvents act as binding agents in the liquisolid formulations(Mei Lu.et.al 2016).Nonvolatile solvent present in the liquisolid system increase wetting of drug particles by decreasing interfacial tension between dissolution medium and tablet surface. Eg. PG, Glycerin and Various grades of tween, PEG (Ajit.S.et.al.2010)
3) **Carrier materials:**
   The carrier should be fine and highly porous solid which must hold certain amounts of liquid by maintaining acceptable flow and compression properties.
   Eg. Avicel ph-101 & 102 most commonly used carrier.
4) **Coating materials:**
   These materials should be fine (10 nm to 5000 nm in diameter), porous, flow enhancing and have high absorption which contributes in covering the wet carrier particles and displaying a dry looking powder by absorbing any excess liquid. Coating material is required to cover the surface and maintain the powder flowability.
   Eg. Colloidal silicon dioxide, cab-o-sil M5.(Chandel.p.et.al 2013)

Table 4: Example of solubility enhancement by liquisolid technique compared to pure drug

Class II Drugs	**Class IV Drugs**
Telmiartan- Improved solubility upto 91.37% compared to pure drug. (Monali K.et.al.2017)	**Furosemide-** Improved solubility 89.50% with PEG-400,SynperonicPE/L81 & MCC/silica as coating material.(Elkordy et.al.2010)
Raloxifen HCL- Improved dissolution and intestinal permeation rate upto 88.50%(Komal D. et.al 2015)	**Hydrochlorothiazide-** improved solubility 96.50% with PEG-200 as vehicle,& MCC/silica coating material.(Khaled

Diacerine- improved solubility with PEG-400 as vehicle and MCC/silica as a coating material (J.Padmapreetha et.al.2016)	et.al.2001)
Loperamide – improved solubility upto 86.81% with PG & Avicel ph-102,Aerosil200. (kambham V.et.al.2016)	
Gliclazide- improved solubility with Neusilin/Silica and crosspovidone as disintegrant.(patel.D.et.al.2015)	
Valsartan– improved 90.% drug release with PG, PEG, Glycerin as vehicle & MCC/silica as coating material (Lakshmi, shrinivas et.al.2011)	
Piroxicam- improved solubility upto 94.33% with PG as vehicle & MCC/silica as coating material(shariati et.al.2009)	

MECHANISM OF LIQUISOLID SYSTEM

Commonly water-miscible organic solvent systems with high boiling point such as propylene glycol, liquid polyethylene glycols, or glycerin are best suitable as liquid vehicles. The addition of liquid containing drug or drug suspension to the selected carrier material.Once the carrier is saturated with liquid, 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. Usually, microcrystalline cellulose is used as carrier material and amorphous silicon dioxide (colloidal silica) as coating material. Various excipients such as lubricants and disintegrants may be added to the liquisolid system to produce liquisolid compacts.

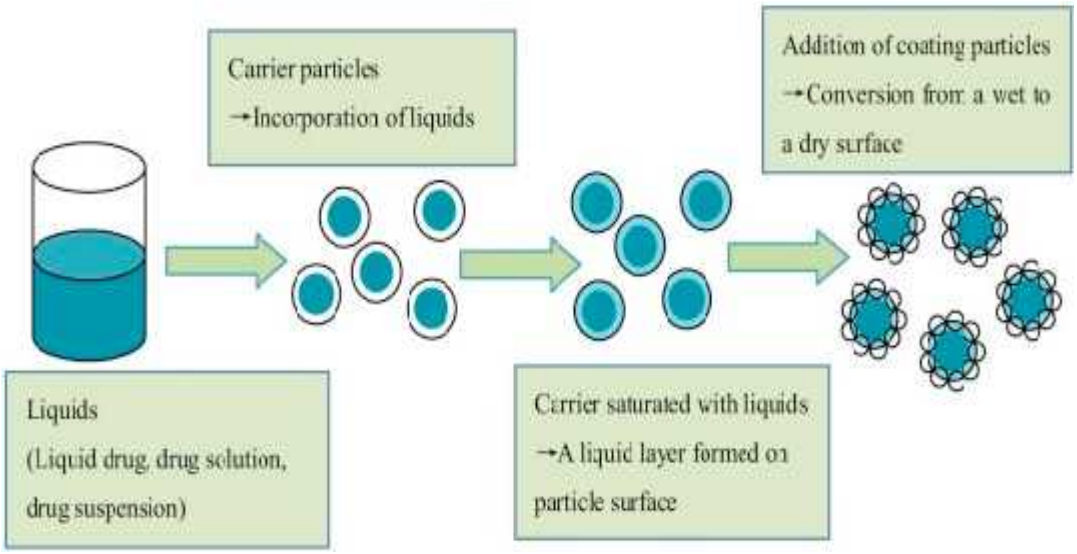

Fig 2: Schematic representation of liquisolid system (Kavitha B. et.al.2012)

Mechanisms of improvement of drug release includes

1. An increase in effective drug surface area
2. An increase in aqueous solubility
3. An increase in wetting properties

I. Enhancement of surface area:

When 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. Hence, the available surface area for drug release is much higher than that of drug particles within directly compressed tablets.

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.(Lohithasu D. et.al.2016)

THEORY OF LIQUISOLID SYSTEMS

The Liquisolid powder can retain only certain limited amount of liquid while maintaining the flowability& compressibility. To calculate the quantities of powder excipients required for the formulation of liquisolid system, a mathematical approach is required and it has been developed by Spireas et. al. This approach is based on flowable (Ø-value) and compressible (Ψ-number) liquid retention potential.(Kavitha B. et.al.2014.)

Flowable liquid retention potential (φ-value) is defined as the maximum weight of liquid that can be retained per unit weight of powder material. This value is important to produce an acceptably flowing liquid/powder admixture

Compressible liquid retention potential (ψ-value)

The Ψ-number of a powder is defined as the maximum amount of liquid that a powder can retain inside its bulk (w/w) while maintaining acceptable compactability, namely, producing cylindrical compacts of adequate crushing strengths and acceptable levels of friability without presenting any 'liquid-squeezing-out' phenomena during compression

Liquid loading capacity of powders

A powder can retain only limited amounts of liquid while maintaining acceptable flow and compression properties. To calculate the required amounts of powder excipients (carrier and coating materials) a mathematical approach for the formulation of liquisolid systems has been developed by Spireas (Spireas and Sadu 1998; Spireas 2002). This approach is based on the flowable (Φ-value) and compressible (Ψ-number) liquid retention potential introducing constants for each powder/liquid combination. The flowability may be determined from the powder flow or by measurement of the angle of repose.

The compactability may be determined by the so-called "pactisity" which describes the maximum (plateau) crushing strength of a one gram tablet compacted at sufficiently high compression forces. The terms "acceptable flow and compression properties" comply the desired chracteristics and thus pre-selected flow and compaction properties which must be meet 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)" and is defined as the ratio between the weights of 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 L_f that ensures acceptable flowability ((ΦL_f) can be determine by : $\Phi Lf = \Phi + {}_{\Phi}$. (1/R),

Where Φ and ${}_{\Phi}$ are the Φ- values of the career and coating material , respectively (Spireas and Sadu 1998; Spireas 2002) . similarly ,the L_f for production of LS system with acceptable compatibility (ΨL_f) can be determined by : $\Psi L_f = \Psi + \psi \cdot (1/R)$, Where Ψ and ψ are the Ψ-numbers of the carrier and coating materials, respectively. The optimum liquid load factor (L_0) required to obtain acceptably flowing and compressible LS system (spireas 2002)

Steps involved in liquisolid compacts

With the liquisolid technology, a liquid may be transformed into a free flowing, readily compressible and apparently dry powder by simple physical blending with selected excipients named the 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.

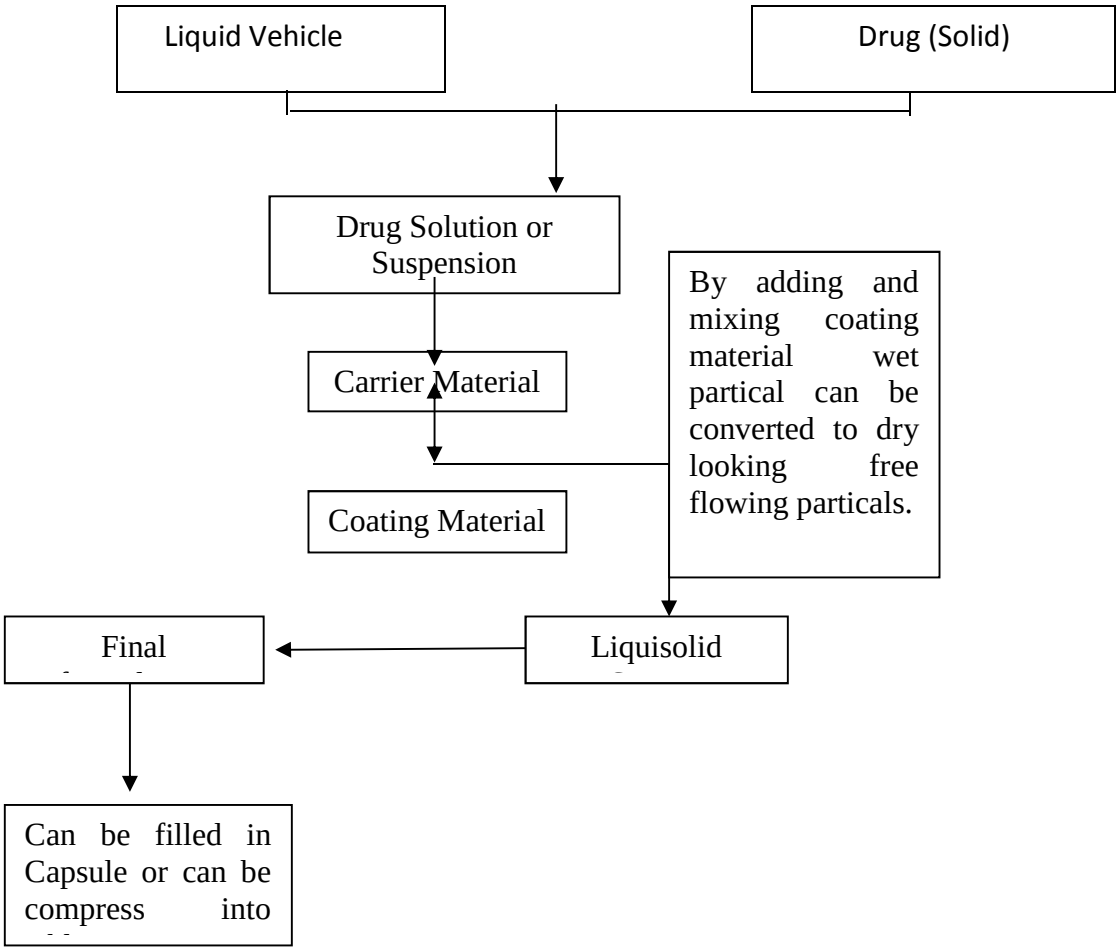

Fig.3. Steps involved in liquisolid technique (UsluSibel 2014)

CLASSIFICATION OF LIQUISOLID SYSTEMS

1) Based on the type of liquid medication, liquisolid systems may be classified into three sub-groups

1) Powdered drug solutions (e.g. prednisolone solution in propylene glycol)
2) Powdered drug suspensions (e.g., gemfibrozil suspension in polysorbate 80)
3) Powdered liquid drugs (e.g. clofibrate, vitamins, etc.)(Kavitha B. et.al 2014.)

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

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

1) Liquisolid compacts
2) Liquisolid microsystems

The term "liquisolid compacts" refers to immediate or sustained release tablets or capsules prepared and combined with the inclusion of appropriate adjuvants required for tabletting or encapsulation, such as lubricants, and for rapid or sustained release action, such as disintegrants or binders. The term "liquisolid Microsystems" refers to capsules prepared by combining the drug with carrier and coating materials with inclusion of an additive e.g. PVP in the liquid medication wherein the resulting unit size may be as much as five times that of liquisolid compacts.(Chandel P.et.al.2013)

EVALUATION OF LIQUISOLID SYSTEMS

1. Determination saturation 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)

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

   Solubility studies were conducted for the selection of high solubility of the pure drug form in the nonvolatile solvents, this involves pure drug dissolved in different non-volatile solvents. Excess amounts of pure drug were added to the non-volatile solvents, followed by saturation solution transfer to a rotatory shaker for 48 hours at 25 ^{0}C under constant vibration. After a 48-hour period the saturated solution was filtered through a 0.45 µm Millipore filter and analyzed.

2. **Determination of angle of slide:**

   Several uniform liquid vehicle/powder admixtures which contain 10 g of the carrier or coating materials with increasing amounts of liquid vehicle were prepared. To measure the angle of slide, the prepared liquid/powder admixtures were placed on polished metal plates, the plate was then tilted gradually until the liquid/powder admixture was about to slide. The angle formed between the plate and the horizontal surface was defined as the angle of slide (h). (Tiong N.et.al 2009)

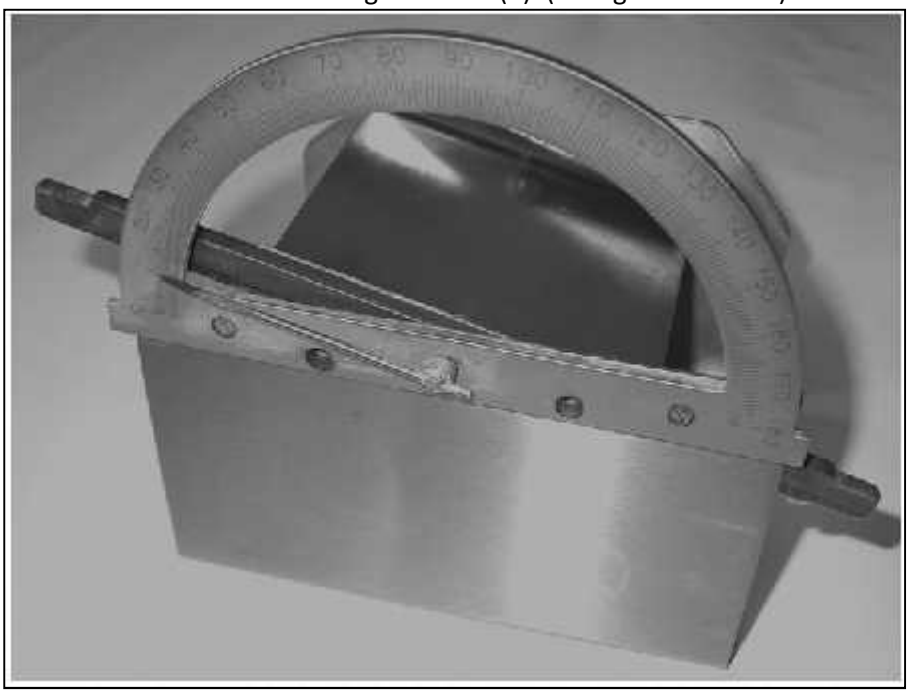

Fig.4: Angle of slide instrument

3. **Determination of Flowable Liquid Retention Potential (Φ value):**

   The flowable liquid-retention 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, (W_{liquid}) that can be retained per unit weight of the sorbent, (W_{solid}), yielding a mixture with acceptable flowability. The flowable liquid-retention potential (Φ-value) of each liquid/powder admixture was calculated using the following equation:

   Φ –value= weight of liquid/weight of solid …..(09)

   The Φ -values were plotted against the corresponding h. An angle of slide (for optimal flow properties) corresponding to 33^{0}of a liquid/powder admixture represented the flowable liquid-retention potential, Φ -value, of its powder which is required for preparation of iquisolid tablets.

Table 5: Liquisolid formulation parameters of various powder Excipients with commonly used liquid vehicles (Kavitha B.et.al.2014)

Powder Excipients Or System	Φ-values		Ψ-numbers	
	Tween-80	PEG 400	Tween-80	PEG 400
Avicel PH102	0.16	0.005	0.224	0.242

Avicel PH 200	0.26	0.02	3.33	0.232
Cab-O SilM5(silica)*with Avicel PH102	3.26	3.26	0.560	0.653
Cab-O-Sil M5(silica)*with Avicel PH200	2.57	2.44	0.712	0.717

Spireas S. and Bolton S. had determined standard Φ value for Avicel PH102 and cab-o-sil M-5 with PEG400, which are used in present research work.(Spireas S. and Bolton S.1999)

In research paper, effects of liquisolid formulations on dissolution of naproxen (2009) by Tiong N. and ElkordyA., elaborate the method for determination of Φ value.

a) The Φ value determined for avicelPH102 and Cab-o-sil with Cremophor EL.(Fig 7)
b) The value determined for avicelPH102 and Cab-o-sil with Synperonic PE/L61.(fig.8)

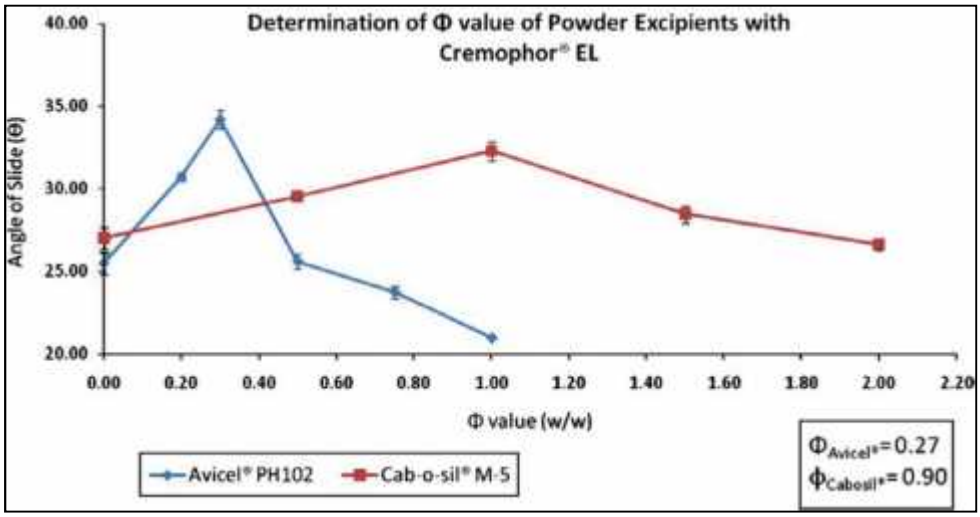

Fig.5: **The angle of slide of various mixtures of powder excipients(i.e. Avicel_ PH102 and Cab-o-sil_ M-5) with Cremophor EL**.

The intersection of each curve with horizontal dashed line at 33^0 represents the Φ -value of the respective powder excipients.(TiongN.,et.al 2009)

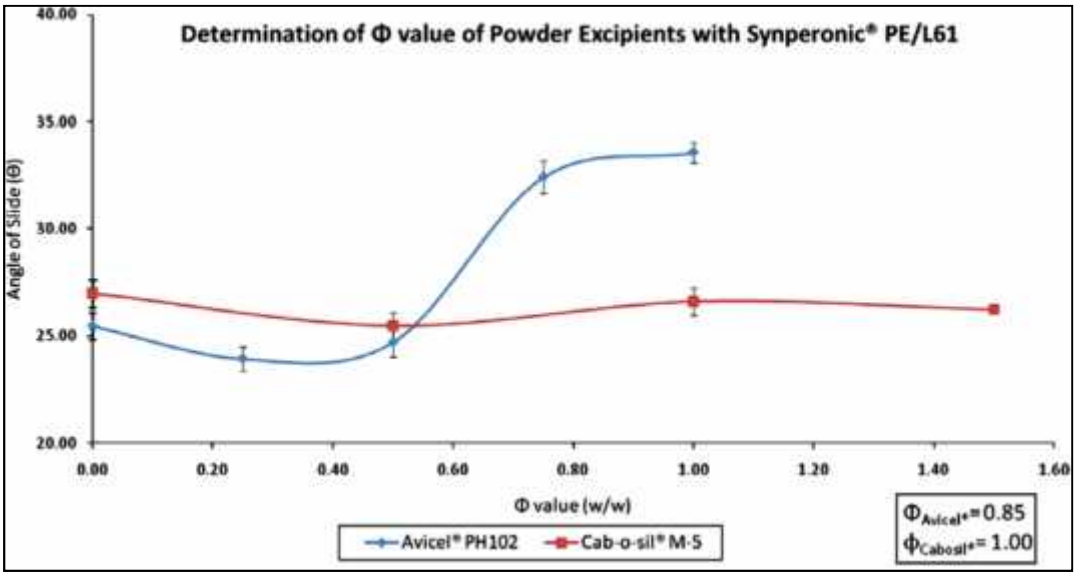

Fig.6:The angle of slide of various mixtures of powder excipients (i.e. Avicel_ PH102 and Cab-o-sil_ M-5) with Synperonic_ PE/L61.

The intersection of each curve with horizontal dashed line at 33^0 represents the Φ -value of the respective powder excipients.(TiongN.,et.al 2009)

4. Liquid Load Factor (Lf):

It is defined as the ratio of weight of liquid medication (W) to weight of carrier material (Q). It is determined by dissolving or dispersing the drug in nonvolatile solvent and to this, carrier-coating material admixture is added and blended. The amount of carrier coating admixture used to convert it into free flowing powder is determined by using the following formula.

Lf = W/Q ……2

OR

Lf = Φ CA + Φ CO (1/R) … 3

W = weight of liquid medication, Q = weight of carrier material

It is used to calculate the amount of carrier and coating material in each formulation. The excipients ratio R of powders is defined as ratio of weight of carrier and coating material present in the formulation. R is suitably selected for successful formulation.

R = Q/ q …… 1

Where q = coating material(Wankhede N.B.et.al.2014)

Pre-compression study

The flow property of all liquisolid formulation were studied such as bulk density, tapped density, carr's index, hausnars ratio and angle of repose.

1) Bulk density: Bulk density refers to the measure used to describe a packing of particles or granules. Bulk density is defined as the mass of powder divided by the bulk volume and is expressed in grams per milliliter (g/mL). The equation for determining bulk density (ρb) is

ρb = M / Vb

where, ρb = Bulk density

M = Mass of sample in g

Vb = Total volume of packing in mL

2) Tapped density:

Tapped density can be defined as mass of blend in the measuring cylinder divided by its tapped volume.

ρt = M / Vt

Where ρt = Tapped density

M = Mass of blend in g

Vt = Tapped volume of blend in cm^3

3) Angle of Repose

Angle of repose for blend of each formulation was determined by fixed funnel method. The funnel is secured with its tip with height 'h' above a plane of paper kept on a flat horizontal surface. The powders were carefully poured through the funnel until the apex of the conical pile so formed just reaches the tip of funnel. Angle of repose was determined by substituting the values of the base radius 'r' and height of the pile 'h' in the given equation below.

$\tan\theta = h/r$

Table 6: Angle of repose as an indication of powder flow properties (Industrial pharmacy 2014)

Sr.No.	Angle of repose (degrees)	Flow property
1	25 – 30	Excellent
2	31 – 35	Good
3	36 – 40	Fair-aid not needed
4	41 – 45	Passable – may hang up

5	46 – 55	Poor – must agitate, vibrate
6	56 – 65	Very poor
7	>66	Very, very poor

4) % Compressibility (Carr's index)

It is used to evaluate flowability of powder by comparing the bulk density and tapped density of a powder. The percentage compressibility of a powder is direct measure of the potential of powder arch or bridge strength is calculated according to the equation given below:

$$\% \text{ Compressibility (Carr's index)} = \frac{\text{Tapped density - Bulk density}}{\text{Tapped density}} \times 100$$

Table 7: Carr's index as an indication of powder flow

Sr.No.	Carr's index (%)	Type of Flow
1	5-15	Excellent
2	12 – 16	Good
3	18 – 21	Fair
4	21 – 25	Passable
5	23 – 35	Poor
6	33 – 38	Very poor
7	>40	Very, very poor

5) Hausner's ratio

Hausner found that the ratio tapped density/bulk density was related to inter particle friction as such, could be used to predict powder flow properties. He showed that the powder with low inter particle friction had ratio of approximately 1.2, whereas more cohesive less free flowing powders have Hausner's ratio greater than 1.6. Hausner's ratio less than 1.25 indicate good flow.(table 5)

$$\text{Hausner's Ratio} = \frac{\text{Tapped density}}{\textit{Bulk Density}}$$

Table 8: Hausner's ratio as an indication of powder flow(Lachman *leon*)

Sr.No.	Hausner's ratio	Type of Flow
1	1.05 – 1.18	Excellent
2	1.14 – 1.20	Good
3	1.22 – 1.26	Fair
4	1.26 – 1.29	Passable
5	1.30 – 1.54	Poor
6	1.50 – 1.61	Very poor
7	>1.67	Very, very poor

Differential scanning calorimetry (DSC)

Differential scanning calorimetry (DSC) is performed in order to assess the thermotropic properties and the thermal behaviors of the drug, excipients used in the formulation, as well as the liquisolid system prepared. Complete 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 (Fahmy RH et al., 2008).

X-ray diffraction (XRD)

For characterization of the crystalline state, the X-ray diffraction (XRD) patterns are determined for drug, excipients used in formulation, physical mixture of drug and excipients, finally for the prepared liquisolid system (Javadzadeh Y et al., 2007). Absence of constructive specific peaks of the drug in the liquisolid X-ray diffractogram indicate 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 system may contribute to the consequent improvement in the apparent solubility and therefore the dissolution rate of the drug (Fahmy RH et al., 2008).

Scanning electron microscopy (SEM)

Scanning electron microscopy (SEM) is utilized to assess the morphological characteristics of the raw materials and the drug–carrier systems (Fahmy RH et al., 2008).

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(Javadzadeh Y et al., 2007).

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 (Spireas S et al., 1998), prednisolone (Spireas S et al., 1998), carbamazepine (Javadzadeh Yet al 2007; Tayel SA et al., 2008), piroxicam (Javadzadeh Y et al., 2008; Javadzadeh Y et al., 2005; Rakshit P, 2007), etc. Also several water insoluble drugs, namely, nifedipine, gemfibrozil, and ibuprofen, have exhibited higher bioavailability in rats as compared to their commercial counterparts.

APPLICATION OF LIQUISOLID COMPACT

1) Enhancement of solubility and dissolution rate in drugs like Indomethacin, Famotidine, Furosemide, Naproxen, Prednisolone, Bromhexine Hydrochloride, Carbamazapine, Rofecoxib, Piroxicam etc.

2) Enhancement of bioavailability of drugs like Atorvastatin Calcium, Hydrochlorthiazide, Repaglinide, Famotidine etc.

3) Formulation of sustained release tablets by the use of hydrophobic carriers like Propanolol Hydrochloride, Tramadol Hydrochloride, and Theophylline etc.

4) It is also applicable in probiotics.

5) Controlled release formulations are also prepared by the use of different carriers that may show the zero order release similar to osmotic pumps.

6) This technique is widely employed for liquid lipophilic drugs / oily drugs. (Chandel P.et.al2013)

CONCLUSION

Liquisolid technique is a promising alternative method for formulation of poorly water soluble or water insoluble solid and liquid lipophilic drugs. Liquisolid compacts refer to formulations formed by conversion of solid state to liquid state, drug suspensions or drug solution in non-volatile solvents into dry, non-adherent, free flowing and radially compressible powder mixture by blending the suspension or solution with selected carrier and coating materials. When the drug within the liquisolid system is completely dissolved in the liquid vehicle, it is located in the powder substrate still in a solubilized state. Already the dissolved drug only needs to diffuse out of the formulation and the liquid components of the formulation acts as a solubilizing aid to facilitate the wetting and dissolution of the undissolved particles. Thus, this shows improved release rate and greater bioavailability. This technique is also used to design immediate release and sustained release system by using hydrophilic and hydrophobic carrier in liquisolid system.

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