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Review Article

LIQUISOLID TECHNIQUE: AN APPROACH FOR ENHANCEMENT OF SOLUBILITY

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ABSTRACT

Slow dissolution rate of poorly water soluble drugs faces major challenge in the drug development and delivery processes. Improving aqueous solubility and slow dissolution of BCS Class II and Class IV drugs have been explored extensively. Of the available approaches, liquisolid compact technology is the most latest and novel approach for overcoming the trouble of inadequate solubility of the poorly soluble drugs. The liquisolid technology as described by Spireas is a liquid which is transformed into a free flowing, readily compressible and apparently dry powder by simple physical blending with selected excipients like the carrier and coating material. The liquid portion, which is a liquid drug, a drug suspension or a drug solution in suitable non-volatile liquid vehicles, is incorporated into the porous carrier material. Water-miscible organic solvent systems with high boiling point like propylene glycol, polyethylene glycols, or glycerine are the suitable liquid vehicles. The drug is present in the liquid medicament as solubilized or molecularly dispersed state, so the dissolution is enhanced due to increased surface area, wetting area and also increases bioavailability.

KEY WORDS: Liquisolid compact, dissolution, bioavailability, surface area, carrier material.

INTRODUCTION

The oral Route is the most preferred route of drug administration because of high patient compliance (or) acceptance and drug development. Due to some problems occurring through this oral route the plasma drug concentration may not be reached. The solubility of the drug is major concern. Solubility is one of the major factors to achieve desired concentration of drug in systemic circulation. (Kavitha B. et.al.2014) Drug substances are considered highly soluble when the largest dose of compound is soluble in < 250ml of water over a range of pH from 1.0 to 7.5. In contrast, compounds with solubilities below 0.1mg/mL face significant solubilization obstacles, and often even compounds with solubilities below 10mg/mL present difficulties related to solubilization during formulation.(Nagabandi V.et.al.2011) The poorly water soluble drugs may have poor dissolution rate and incomplete bioavailability. The challenge for poorly water soluble drugs is to enhance the dissolution.There are different types of techniques are available to increase the solubility of poorly water soluble drugs i.e., Micronization, Lyophilisation, Solid dispersions, use of complexing agents, co solvency, chemical modification, pH adjustment, solubilisation by surfactants, solid solutions, inclusion of liquid drug into the soft gelatin capsules, salt formation etc. These techniques have been introduced to increase the dissolution rate, there by absorption and bioavailability. But there are some practical limitations in this type of technique. Micronization is the

process of size reduction, due to the reduction in particle size the expected dissolution & absorption rates may not be achieved because the fine particles tend to form aggregates (or) agglomerates due to increased surface energy & Vander Waals attraction. Solid dispersions are important for improving solubility, wettability, dissolution rate and further bioavailability of drugs. However, only few products are available commercially, because of their poor physical characteristics for dosage form formulation. Solid dispersions prepared by melting technique may leads to stability problems. Salt formation leads to hygroscopicity and May causes stability problems. By the use of co solvents precipitation may occurs upon dilution. To overcome all these types of problems the "Liquisolid Technique" was introduced liquisolid technology also called as "Powder Solution Technology"(Kavitha B. et.al 2014).

The term liquisolid technique refers to immediate release or sustained release tablets or capsules, combined with the inclusion of appropriate adjuvant required for tabletting or encapsulating. Liquisolid compacts are acceptably free flowing and compressible powder forms of liquid medications. The liquid portion, which can be an oily liquid drug, suspension or solution of water insoluble solid drugs in suitable non-volatile liquid vehicles, is incorporated into the porous 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. The concentrations of the carriers, coating materials, disintegrants, lubricants and glidants are optimized to get a non-sticky easily compressible blend.(Kharwade M.et.al.2015)

DEFINITIONS:

Liquid medication:

Liquid medication includes liquid lipophilic drugs and drug suspensions or solutions of solid water insoluble drugs in suitable non-volatile solvent systems.

Liquisolid systems:

Liquisolid system refers to powdered forms of liquid medications formulated by converting liquid lipophilic drugs, or drug suspensions or solutions of water insoluble solid drugs in suitable non-volatile solvent systems, into dry, non-adherent, free-flowing and readily compressible powder admixtures by blending with selected carrier and coating materials.

Non-volatile solvent:

Non-volatile solvent may be hydrophilic or lipophillic in nature depending upon the type of formulation like immediate release or sustained release. Non solvent should be inert, high boiling point, water miscible.

Carrier material:

Carrier material refers to a preferably porous material possessing sufficient absorption properties, such as microcrystalline and amorphous cellulose, which contributes in liquid absorption.

Coating material:

Coating material refers to a material possessing fine and highly adsorptive particles, such as various types of silica, which contributes in covering the wet carrier particles and displaying a dry looking powder by adsorbing any excess liquid. Furthermore replacement of commonly used carrier and coating materials like Avicel and Aerosil respectively with Fujicalin and Neusilin led to considerably higher liquid adsorption capacity because of large specific surface area and good flow property.

Disintegrant:

5 % of disintegrant is used in formulation, mainly Sodium Starch glycolate is used as disintegrant.(Chandel P. et.al 2013.)

PRINCIPLE OF 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 carrier material (Fig. 1).(Nagabandi V.et.al.2011).

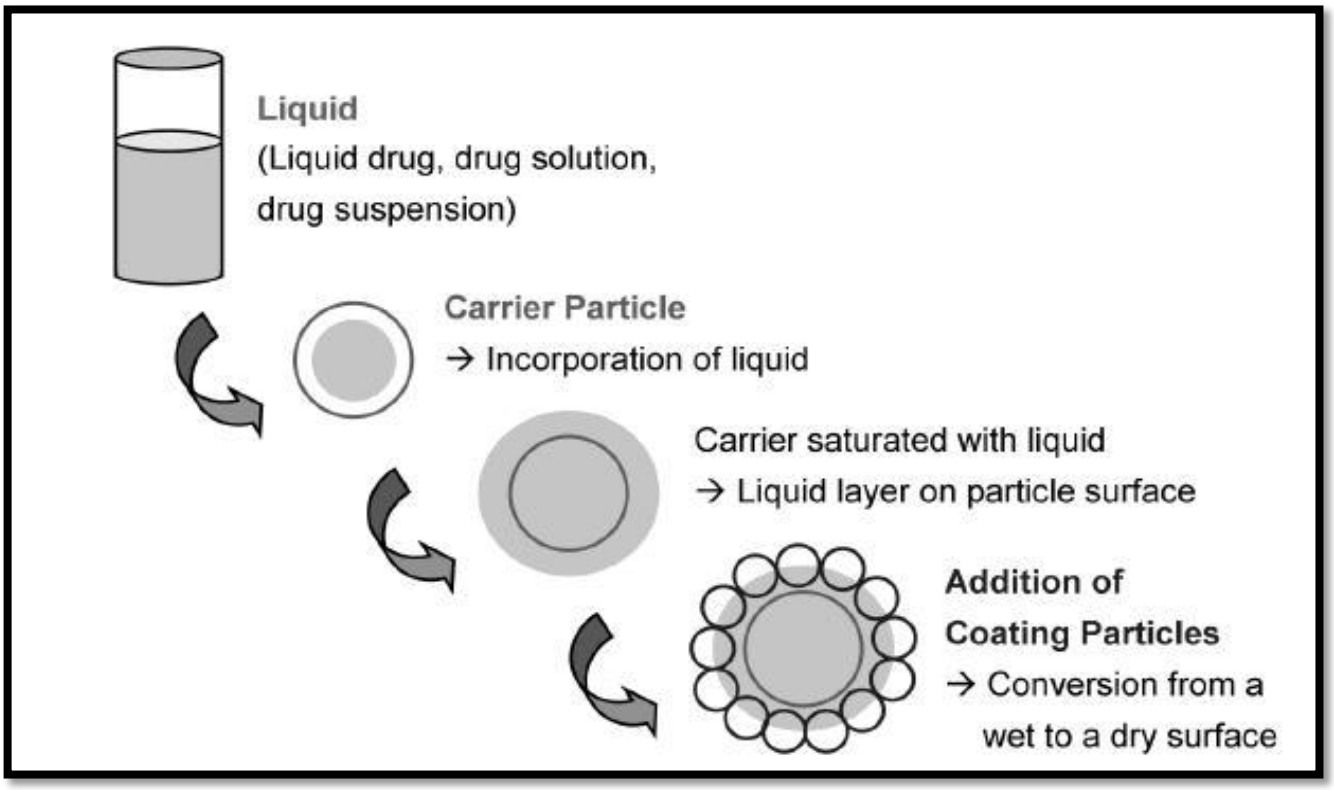

Fig 1: Schematic representation of liquisolid systems (Kavitha et.al. 2014)

Inert, preferably water-miscible organic solvent systems with high boiling point such as propylene glycol, liquid polyethylene glycols, or glycerine are best suitable as liquid vehicles. 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).

Liquisolid compacts of poorly soluble drugs containing a drug solution or drug suspension in a solubilising vehicle show enhanced drug release due to an increased surface area of drug available for release, an increased aqueous solubility of the drug, and an improved wettability of the drug particles. Accordingly, this improved drug release may result in a higher drug absorption in the gastrointestinal tract and thus, an improved oral bioavailability.

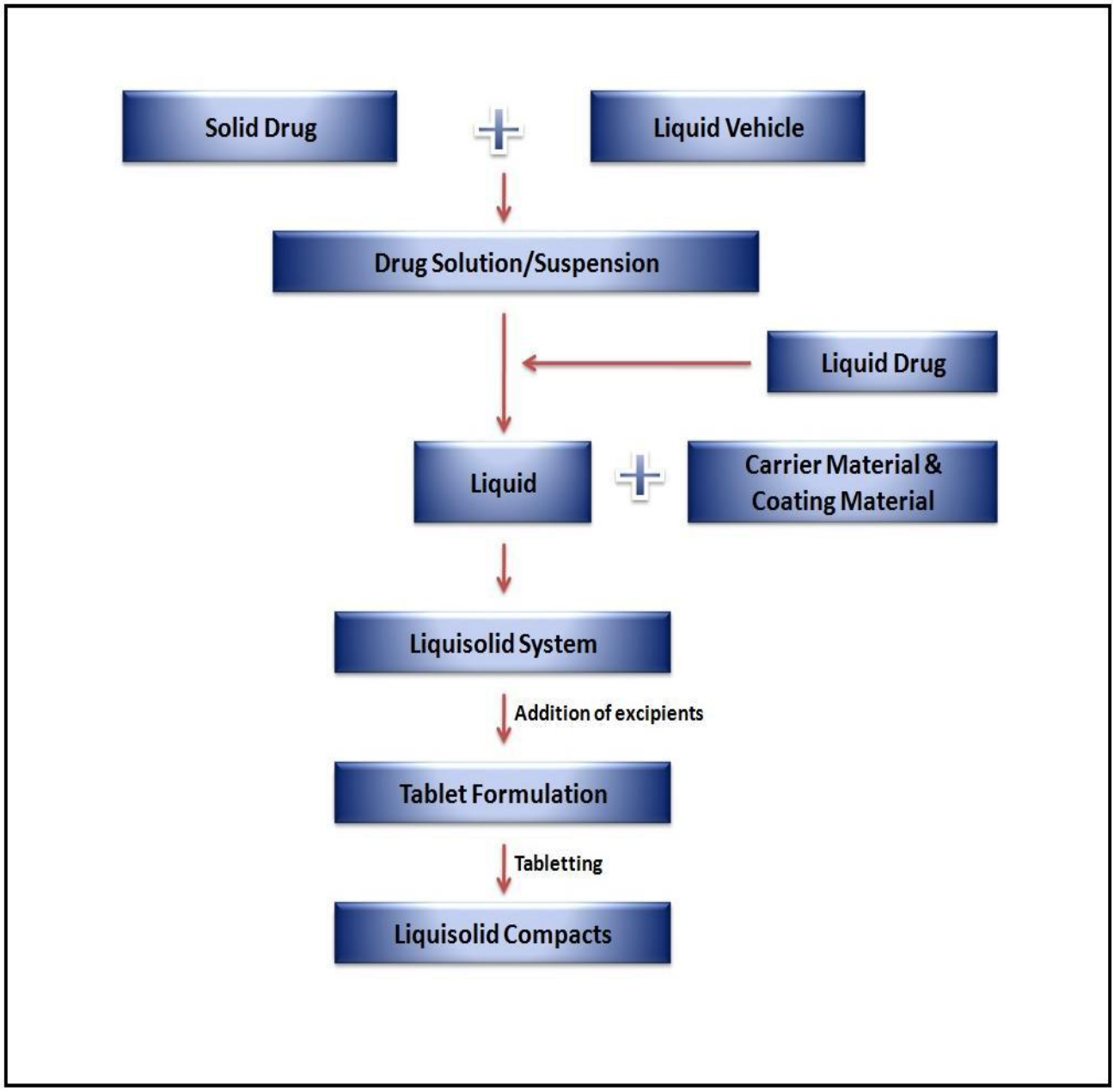

Fig. 2: Schematic outline of the steps involved in the preparation of liquisolid compacts (Kavitha B. et.al.2014)

ADVANTAGES:

1. Huge number of Bio-Pharmaceutical classification class II drugs with high permeability, slightly or very slightly water soluble and practically insoluble liquids and solid drugs can be formulated into liquisolid systems.
2. Improvement of bioavailability of an orally administered water insoluble drugs is achieved.
3. This principle governs or administers the mechanism of drug delivery from liquisolid systems of powdered drug solutions and it is mainly responsible for the improved dissolution profiles exhibited by this preparations.
4. In this technique, production cost is low compared to soft gelatin capsules.

5. Drug is formulated in a tablet form or encapsulated dosage form and is held in solubilized liquid state, which confers developed or improved drug wetting properties thereby improving drug dissolution profiles.
6. Greater drug surface area is exposed to the dissolution medium.
7. This liquisolid system is specifically for powdered liquid medications.
8. These liquisolid systems formulate into immediate release or sustained release dosage forms.
9. Optimized sustained release, liquisolid tablets or capsules of water insoluble drugs demonstrate constant dissolution rates (zero order release).
10. It is used in controlled drug delivery systems.
11. Drug can be molecularly dispersed in the formulation.
12. Drug release can be modified using suitable formulation ingredients.
13. Capability of industrial production is also possible.
14. Enhanced bioavailability can be obtained as compared to conventional tablets.
15. Differentiate the dosage form by admixture of colour into liquid vehicle.
16. To minimize excipients in formulation compare with other formulations like solid dispersions.
17. Omit the process approaches like nanonisation, micronization techniques.
18. Greater drug surface area is exposed to the dissolution medium. (Wankhede N.B.et.al.2014),

DISADVANTAGES:

1. Liquisolid system requires low drug loading capacities.
2. Requires more efficient excipients and it should provide faster drug release with smaller tablet size.
3. Higher amounts of carrier and coating materials are required
4. Requirement of high solubility of drug in non-volatile liquid vehicles.(Nagabandi V.et.al 2011)

LIMITATIONS:

1. Not suitable for formulation of high dose water insoluble drugs.
2. If more amounts of carrier is added it increase the flow properties of powder, it may increases the tablet weight too, hence it is difficult to swallow.
3. It does not require chemical modification of drugs.
4. Acceptable compression may not be achieved because the liquid drug may be squeezed out during compression resulting in unsatisfactory tablet weight.(Kavitha B. et.al 2014.)

CLASSIFICATION OF LIQUISOLID SYSTEMS:

1. **Based on the type of liquid medication, liquisolid systems may be classified into three sub-groups.**
    a) Powdered drug solutions (e.g. prednisolone solution in propylene glycol)
    b) Powdered drug suspensions (e.g., gemfibrozil suspension in polysorbate 80)
    c) Powdered liquid drugs (e.g. clofibrate, vitamins, etc.)(Kavitha B.et.al2014)

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 systems.

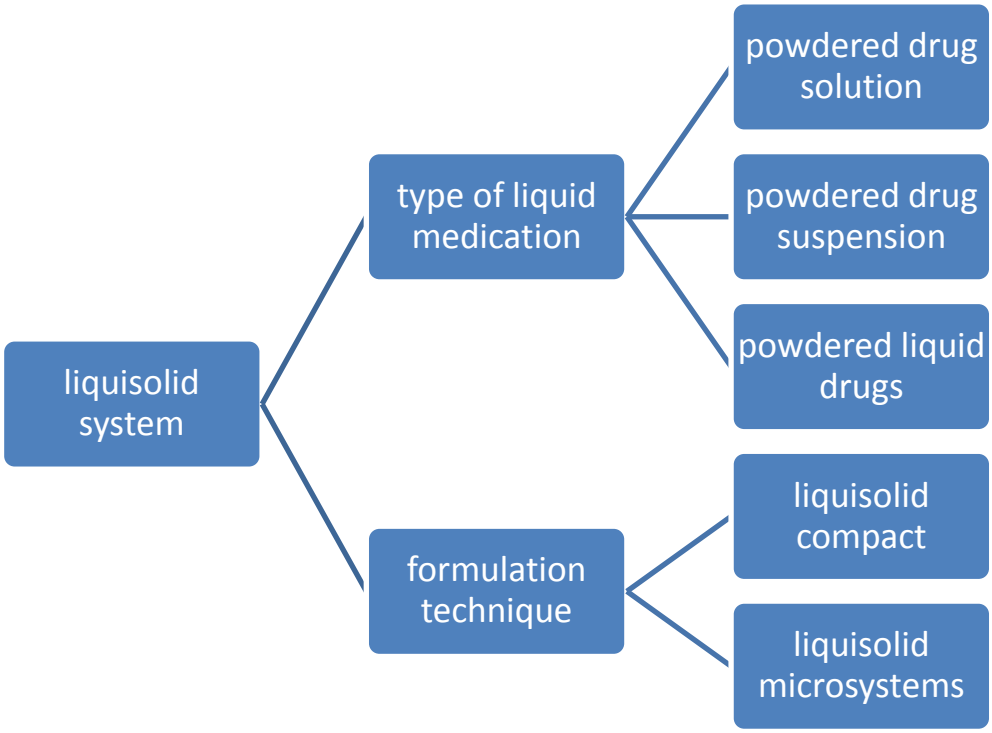

Fig.3 schematic representation for classification of liquisolid system

2. **Based on the formulation technique used, liquisolid systems may be classified into two categories**
   - **a)** Liquisolid compacts
   - **b)** 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)

THEORY OF LIQUISOLID SYSTEMS

The 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 in order 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.

According to the new theories, the carrier and coating powder materials can retain only certain amounts of liquid while maintaining acceptable flow and compression properties. Depending on the excipient ratio (*R*) of the powder substrate, where:

$$R=Q/q \quad \ldots\ldots\ldots\ldots (1)$$

which is the fraction of the weights of the carrier (*Q*) and coating (*q*) materials present in the formulation, an acceptably flowing and compressible liquisolid system can be prepared only if a maximum liquid load on the carrier material is not exceeded. Such a characteristic amount of liquid is termed the liquid load factor (L_f) and defined as the weight ratio of the liquid medication (*W*) and carrier powder (*Q*) in the system, i.e.:

$$Lf=W/Q \quad \ldots\ldots\ldots\ldots (2)$$

It has been established (Spireas, 1993) that, for a given powder substrate consisting of a certain carrier and coating powders mixed at various powder excipient ratios (*R*), there are specific maximum liquid load factors (L_f) which must be employed in order to produce acceptably flowing liquisolid systems. Such flowable L_f values, denoted as ${}^{\Phi}L_f$, are related to the *R*-values of their powder blends by:

$${}^{\Phi}L_f=\Phi+\phi(1/R) \quad \ldots\ldots\ldots(3)$$

where, as mentioned earlier, Φ and ϕ are the Φ -values of the carrier and coating powder materials ,respectively.

Similarly, the compressible liquid load factors, ${}^{\Psi}L_f$, required to produce liquisolid compacts with acceptable compaction properties, are related to the excipient ratios (*R*) of their powder substrates as follows:

$${}^{\Psi}L_f=\Psi+\psi\,(1/R) \quad \ldots\ldots\ldots\ldots (4)$$

where Ψ and ψ are the C-numbers of the carrier and coating powders, respectively.

Therefore, for any liquid medication incorporated onto a given powder substrate consisting of certain carrier and coating materials (e.g. microcrystalline cellulose and silica) blended at a specific excipient ratio (*R*), there exists an optimum liquid load factor, L_O, required to produce acceptably flowing and, simultaneously, acceptably compressible liquisolid preparations. In essence, the L_O value required at a given powder excipient ratio for any system is equal to either its ${}^{\Phi}L_f$ or ${}^{\Psi}L_f$ value, whichever is less; thus:

$$L_O={}^{\Phi}L_f \quad \text{when: } {}^{\Phi}L_f<{}^{\Psi}L_f \ldots\ldots\ldots(5)$$

or

$$L_O={}^{\Psi}L_f \quad \text{when: } {}^{\Phi}L_f>{}^{\Psi}L_f \ldots\ldots\ldots\ldots(6)$$

Based on Eqs. (1) and (2), as soon as the optimum liquid load factor of a given excipient ratio system is established, the appropriate quantities of carrier (Q_O) and coating (q_O) powder materials required to convert a given amount of liquid medication (*W*) into an acceptably flowing and compressible liquisolid system, may be calculated as follows:

$$Q_O=W/L_O \quad \ldots\ldots\ldots(7)$$

and

$$q_O=Q_O/R \quad \ldots\ldots\ldots\ldots(8)$$

The validity of the preceding principles has been repeatedly tested and verified by producing liquisolid compacts possessing acceptable (or anticipated at a desired level) flow and compaction properties.(Spireas S.et.al.1998)

MECHANISMS OF IMPROVEMENT OF DRUG RELEASE

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.(Lohithasu D. et.al.2016)

COMPONENTS OF LIQUISOLID COMPACT FORMULATION

Drug candidates

Mainly poorly water soluble (BCS class II or IV), low dose drugs can be the good candidate for this technique include Carmabazepine, Naproxen, Furosamide, Ketoprofen etc.

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 drug solubiliy. These solvents act as binding agents in the liquisolid formulations.

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.

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.

Disintegrants

These materials increase the rate of drug release, water solubility and wettability of liquisolid granules. Mostly superdisintegrants like sodium starch glycolate, crosspovidone, croscarmellose sodium are used.(Kharwade M.et.al.2015)

Drug Candidates	Hydrochlorothiazide, Digitoxin, Prednisolone Hydrocortisone, Spironolactone, Digoxin etc.
Nonvolatile liquids	Poly Ethylene Glycol 200, Poly Ethylene Glycol 300, Poly Ethylene Glycol 400, Glycerine, Propylene Glycol, fixed oils.
Carrier Materials	Microcrystalline Cellulose PH 101, Microcrystalline Cellulose PH 200, Lactose, Methyl Cellulose, Ethyl Cellulose, Starch1500, Ethocel, Eudragit RL, Eudragit RS 12, Hydroxy Propyl Methyl Cellulose K4M, Hydroxy Propyl Methyl Cellulose K100M, Xanthum Gum, Guargum.
Coating Materials	Aerosil 200, Silica (Cab-O-Sil M5), Syloid 244FP, and Colloidal Silicon Dioxide.
Disintegrants	Sodium Starch Glycolate (Explotab, Primogel), Croscarmellose Sodium, Cross Polyvinyl Pyrrolidine, Pregelatized Starch.
Glidant	Talc
Lubricant	Magnesium Stearate
Release retardant	Eudragit RS, RL, Hydroxy Propyl Methyl Cellulose K100M, K15M, K4M.

Table 1: Components of Liquisolid Technique (Chandel P. et.al. 2013)

OPTIMIZATION OF LIQUISOLID FORMULATIONS WITH ENHANCED DRUG RELEASE

The liquisolid technology has been successfully applied to low dose, poorly water soluble drugs. The formulation of a high dose, poorly soluble drug is one of the limitations of the liquisolid technology. As the release rates are directly proportional to the fraction of molecularly dispersed drug (FM) in the liquid formulation, a higher drug dose requires higher liquid amounts for a desired release profile. Also, to obtain liquisolid systems with acceptable flowability and compactability high levels of carrier and coating materials are needed. However, this results in an increase in tablet weight ultimately leading to tablet sizes which are difficult to swallow. Therefore, to overcome this and various other problems of the liquisolid technology several formulation parameters may be optimized (Table 2). In various studies the effect of different types of non-volatile liquid vehicles has been investigated. The results suggest that the selection of a liquid vehicle with a high solubilizing capacity for the drug and thus, an increased FM, leads to enhanced release profiles . That means that by selection of a liquid vehicle with optimum solubilizing properties the amount of liquid and thus, the weight and size of the liquisolid compacts can be reduced. However, in addition to the drug solubility in the liquid vehicle other physicochemical characteristics of the liquid vehicles such as polarity, viscosity, molecular weight, chemical structure, and lipophilicity may also have an effect on drug release. A further approach to minimize tablet weight is to increase the liquid load factor by using carrier and coating materials with a high specific surface area or by adding PVP to the liquid formulation. It was found that the higher the specific surface area of an excipient the higher the liquid load factor . For instance, the liquid adsorption capacity of microcrystalline cellulose (1.18 m^2/g) is higher than that of lactose (0.35 m^2/g), starch (0.6 m^2/g), and sorbitol (0.37 m^2/g) . Fujicalin® (30 m^2/g), a spherically granulated dicalcium phosphate anhydrous, and Neusilin® US2 (300 m^2/g), a magnesium aluminometasilicate, turned out to be very effective excipients for liquid adsorption while maintaining acceptable flow and

compaction properties. Khaled noticed precipitation and consequently retention of the drug in the cavities of porous excipients upon contact of the liquid formulation with the release medium. This retention could be minimized by using either a diluted drug solution or PVP as crystallization inhibitor. Moreover, PVP may also act as binder during compaction leading to an increase of the liquid load factor. The release rate of a drug from a dosage form is dependent on its disintegration and the dissolution rate of the drug. Therefore, it is very important for liquisolid systems with enhanced drug release to ensure that disintegration is not the rate-limiting step and drug dissolution is not hindered by a slow disintegration of the dosage form. It was found that the release rate increases by addition of superdisintegrants such as sodium starch glycolate or croscarmellose sodium to the liquisolid formulation.

Another formulation parameter that may be optimized is the ratio of carrier to coating material (R). An increase in the R-value results in an enhanced release rate if microcrystalline cellulose and colloidal silica are used as carrier and coating materials, respectively. Liquisolid compacts with high R-values contain high amounts of microcrystalline cellulose, low quantities of colloidal silica, and low liquid/powder ratios. This is associated with enhanced wicking, disintegration and thus, enhanced drug release. In contrast, if high amounts of colloidal silica are used, which means that the R-value is low, the liquisolid compact is overloaded with liquid formulation due to a high liquid load factor. In such cases, even though drug diffusion out of the primary particles may be rapid, oversaturation might occur resulting in local precipitation/ recrystallization of the drug and thus decreased release rates. Moreover, as colloidal silica is a hydrophobic material high amounts of it can cause retardation of drug release. Therefore, Spireas et al. recommend a minimum R-value of 20. In the case of liquisolid sustained release compacts lower R-values may be used. (Kala et. al. 2014)

Formulation parameter	Optimization	Effect
liquid vehicle	high drug solubility in the vehicle	increased fraction of the molecularly dispersed drug (FM)
carrier and coating materials	high specific surface area	increased liquid load factor (Lf)
addition of excipients	Polyvinylpyrrolidone (PVP)	increased liquid load factor (Lf), increased viscosity of liquid vehicle,inhibition of precipitation
	Superdisintegrant	fast disintegration
Excipient ratio (R)	high R-value	fast disintegration, inhibition of precipitation

TABLE2: Optimization of formulation parameters for liquisolid systems with immediate drug release (kala et.al.2014)

EVALUATION OF LIQUISOLID SYSTEMS

I. Pre-formulation studies

Pre-formulation Studies includes

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)
5. Liquisolid compressibility test (LSC)

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 non-volatile 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)

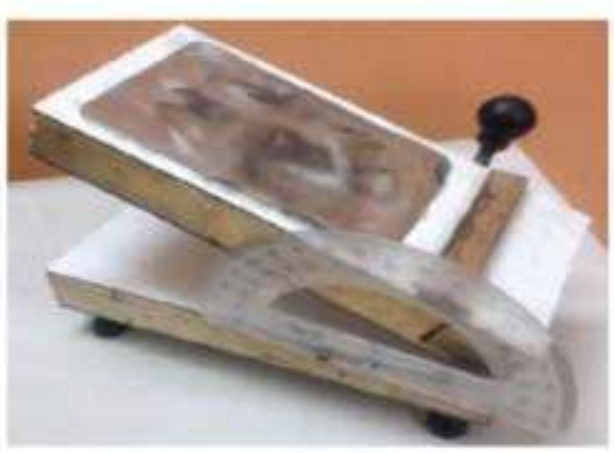

Fig. No. 4: Angle of slide instrument (Wankhede N.et.al.2014)

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 (Figs. 5and 6). 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 liquisolid tablets. All measurements were carried out in triplicate.

Powder Excipients Or System	Φ-values		Ψ-numbers	
	Propylene glycol	PEG 400	Propylene glycol	PEG 400
Avicel PH102	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 PH102	3.31	3.26	0.560	0.653
Cab-O-Sil M5(silica)*with Avicel PH200	2.57	2.44	0.712	0.717

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

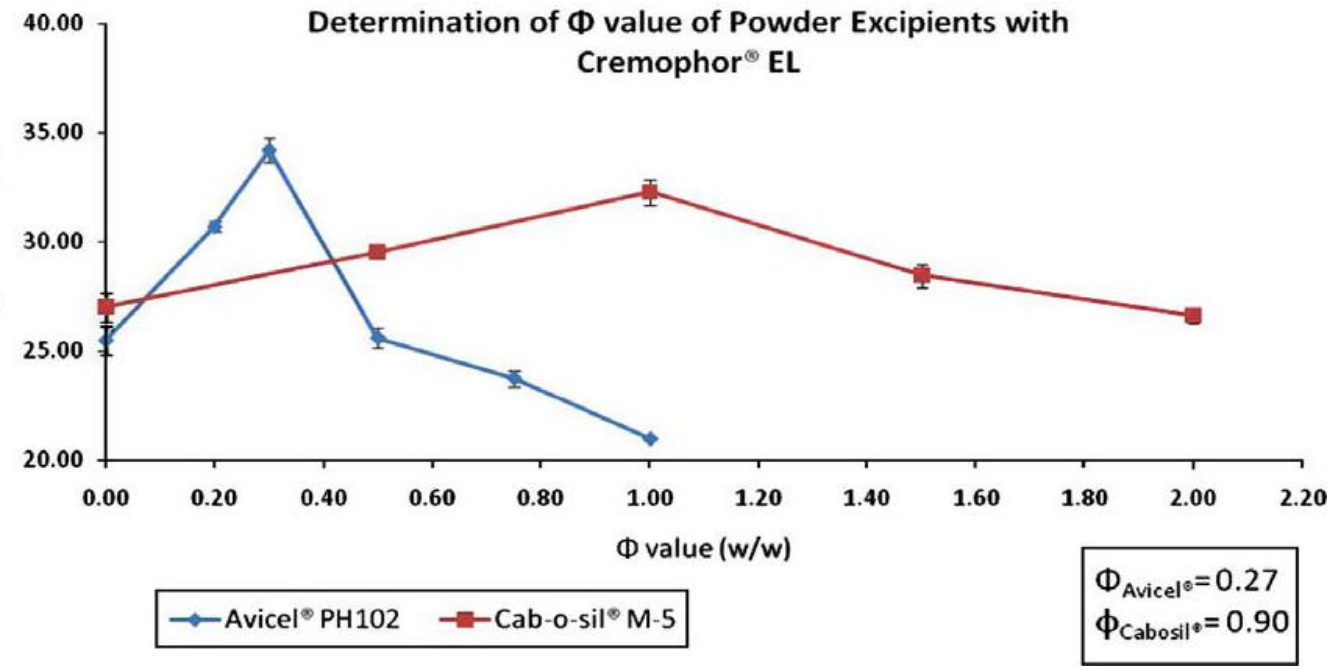

Fig. 5. The angle of slide of various mixtures of powder excipients (i.e. Avicel_ PH102 and Cab-o-sil_ M-5) with Cremophor EL. The intersection of each curve with horizontal dashed line at 33^0 represents the Φ -value of the respective powder excipients.(Tiong N.,et.al 2009)

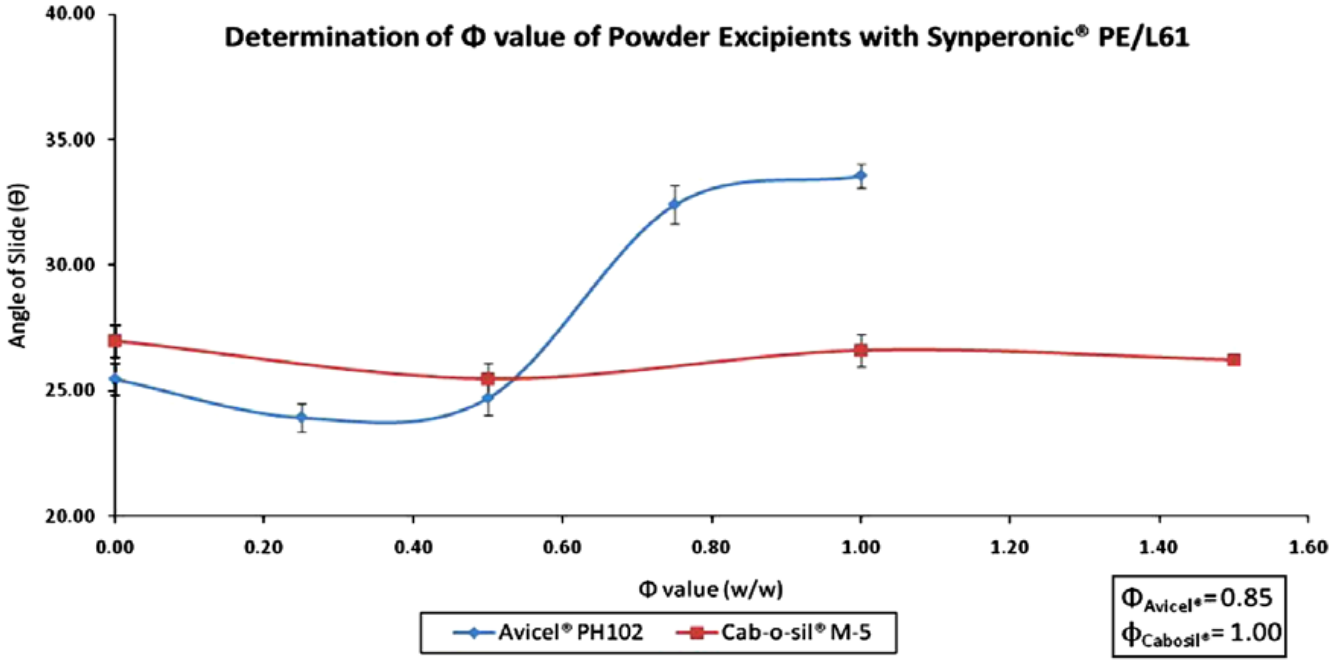

Fig. 6. The angle of slide of various mixtures of powder excipients (i.e. Avicel_ PH102 and Cab-o-sil_ M-5) with Synperonic_ PE/L61. The intersection of each curve with horizontal dashed line at 33^0 represents the Φ -value of the respective powder excipients.(Tiong N.,et.al 2009)

4. Liquid Load Factor (L_f)

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.

$$L_f = W/Q \quad \ldots\ldots\ldots\ldots 2$$

OR

$$Lf = \Phi CA + \Phi CO (1/R) \ldots 3$$

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.

$$R = Q/ q \quad \ldots\ldots\ldots\ldots 1$$

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

5. Liquisolid Compressibility Test (LSC)

It was 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 value and L_f. . (Wankhede N.B.et.al.2014)

II. Pre-compression studies of the liquid solid system

1. **Flow properties of the liqui-solid system**
2. **Differential Scanning Calorimetry (DSC)**
3. **Powder X-ray diffraction (PXRD)**
4. **Scanning Electron Microscopy (SEM)**

5. **Fourier Transform Infrared Spectroscopy (FTIR)**

1.Flow Properties of the liquisolid system

1) Angle of repose: Angle of repose can be measured by fixed funnel method. The frictional forces in loose powder or granules can be measurement by the angle of repose. This is the maximum angle possible between the surface of a pile of powder or granules and the horizontal plane. Thus, r being the radius of the base of the conical pile. This is shown in table.

$$\text{Tan } \theta = h/r$$

Flow property	**Angle of repose (degrees)**
Excellent	25 – 30
Good	31 – 35
Fair-aid not needed	36 – 40
Passable – may hang up	41 – 45
Poor – must agitate, vibrate	46 – 55
Very poor	56 – 65
Very, very poor	>66

2) 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) although the international unit is kilogram per cubic meter (1 g/mL = 1000 kg/m^3) because the measurements are made using cylinders. It may also be expressed in grams per cubic centimeter (g/cm^3). The equation for determining bulk density (ρb) is

$$\rho b = M / Vb$$

where ρb = Bulk density

M = Mass of sample in g

Vb = Total volume of packing

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

$$\rho t = M / Vt$$

Where ρt = Tapped density

M = Mass of blend in g

Vt = Tapped volume of blend in cm^3

4) Carr's index: The compressibility index (Carr's Index) is a measure of the propensity of a powder to be compressed. It is determined from the bulk and tapped densities and is calculated using the following formulas and is shown in table.

$$\text{Carr's Index} = \rho t - \rho b/\rho t * 100$$

ρb = bulk density

ρt = tapped density

property	**C.I (%)**
Excellent	≤10
Good	11 – 15
Fair	16 – 20
Passable	21 – 25

Poor	26 – 31
Very poor	32 – 37
Very, very poor	>38

5) Hausner's ratio: A flow property of powder mixture can be determined by Hauser's ratio. It is calculated by following formula and is shown in table

Hausner's ratio = Tapped density/ Bulk density

A Hausner ratio greater than 1.25 is considered of poor flow ability.

Flow property	**Hausner ratio**
Excellent	1.00 – 1.11
Good	1.12 – 1.18
Fair	1.19 – 1.25
Passable	1.26 – 1.34
Poor	1.35 – 1.45
Very poor	1.46 – 1.59
Very, very poor	>1.60

2.Differential Scanning Calorimetry (DSC)

Differential scanning colorimetry measures the heat loss or gain resulting from physical or chemical changes within a sample as a function of temperature. This will also indicates the success of stability studies, if the characteristic peak is absent in the thermogram, it indicates that the drug is in the form of solution and it is molecularly dispersed within the system.

3.Powder X-ray Diffraction (PXRD)

The disappearance of characteristic peaks and retaining of extra peaks of carriers in the liquisolid formulation is observed. It indicates that drug converted to amorphous form or to stabilized form.

4. **Scanning Electron Microscopy (SEM):**

Scanning electron microscopy (SEM) is utilized to assess the morphological characteristics of the raw materials and the drug–carrier systems. This study confirms if there are any crystals present, or else drug is present in completely solubilised form by absence of crystals of drug.

5.Fourier Transform Infrared Spectroscopy (FTIR)

These studies are performed to estimate the chemical interactions between excipients and drug. If there is the presence of characteristic peaks and absence of extra peaks in formulation indicates that there are no chemical interactions

III. Post compression evaluation of liquisolid formulation

1. Hardness
2. Weight variation
3. Thickness
4. Friability
5. Disintegration
6. Drug content/Content uniformity
7. *In vitro* dissolution studies
8. Contact angle measurement
9. *In-vivo* studies
10. Stability studies

1. Hardness

The hardness of the tablets was determined by using Monsanto hardness tester. Five individual tablets from each batch were and results averaged.

2. Weight Variation

Twenty tablets were randomly selected from each batch and individually weighed. The average weight and standard deviation three batches were calculated. It passes the test for weight variation test if not more than two of the individual tablet weights deviate from the average weight by more than the allowed percentage deviation and none deviate by more than twice the percentage shown. It was calculated on an electronic weighing balance.

3. Thickness

The thickness of liqui-solid tablets was determined by using Digital micrometres. Ten individual tablets from each batch were used and the results averaged.

4. Friability

The friability values of the tablets were determined using a Roche-type friabilator. Accurately weighed six tablets were placed in Roche friabilator and rotated at 25 rpm for 4 min.

Percentage friability was calculated using the following equation.

$$\text{Friability} = ([W_O - W] / W_O) \times 100$$

Where,

W_O = Weight of the tablet at time zero before revolution.

W = Weight of the tablet after 100 revolutions.

5. Disintegration Test

Six tablets were taken randomly from each batch and placed in USP disintegration apparatus baskets Apparatus was run for 10 minutes and the basket was lift from the fluid, observe whether all of the tablets have disintegrated.

6. Drug content/Content uniformity

Drug content in different liquisolid tablet formulation was determined by accurately weighing 10 tablets of each batch formula individually. Each tablet was then crushed and a quantity equivalent to 10 mg was dissolved in a specific solvent, then this solution was filtered, properly diluted and then analyzed spectrophotometrically using Uv- spectrophotometer**.**

7. In-vitro Release

Drug release from liqui-solid tablets was determined by using USP dissolution test apparatus type II(paddle). 5ml aliquots of dissolution media were withdrawn each time at suitable time intervals (5,10, 15, 20, 25, 30, 45 and 60 minutes.) and replaced with fresh medium. After withdrawing, samples were filtered and analyzed after appropriate dilution by appropriate analytical method. The concentration was calculated using standard calibration curve.

8. 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.(Lohithasu D. et.al.2016)

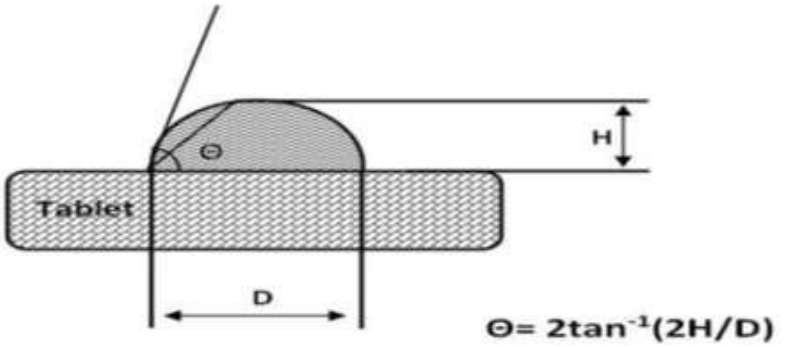

Fig.7.Schematic Representation of Contact Angle Measurement Using Imaging Method (Wankhede N.B.et.al.2014)

9.*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 hydroclorothiazide liquisolid compacts in comparison with commercial tablets were studied in beagle dogs and rabbits. 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.(Lohithasu D. et.al.2016)

10.Stability studies

The stability studies are conducted to know the shelf life of the products. Shelf life is defined as the time required reducing the concentration of the reactant to 90 percent of its initial concentration. To know 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^{o}C/76% R.H., 4 weeks), carbamazepine (24^{o}C/76% R.H., 6 months), Indomethacin (24^{o}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 (Lohithasu D. et.al.2016).

APPLICATION

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)

LIQUISOLID COMPACT AS SUSTAINED RELEASE OF DRUG FROM ITS DOSAGE UNIT

Liquisolid technique can be an emerging technique used for sustained release formulation with zero order kinetics. In sustained release liquisolid formulation hydrophobic carriers such as Eudragit R L and RS etc are used leading to poor wetting of formulation with slow disintegration and prolonged release. Use of liquid vehicles which acts as plasticizer e.g. polysorbate 80 lowers the glass transition temperature of polymer, resulting matrix of low porosity and high tortuesity formation due to coalescence of polymer particle with liquisolid compact. Addition of polymer like HPMC increases the retardation effect due to swelling of polymer in contact with water with zero order release kinetics (Kharwade M.et.al. 2015).

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.

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