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Review Article

LIQUISOLID TECHNOLOGY: A REVIEW

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ABSTRACT

Poor bioavailability which is only caused by poor water solubility is a technological challenge represented by poorly soluble, highly permeable active pharmaceutical ingredients (BCS Class II drugs) resulting in low drug absorption. Various techniques are used for the improvement of the aqueous solubility, dissolution rate, and bioavailability of poorly water soluble drugs include micronization, chemical modification, pH adjustment, solid dispersion, complexation, co-solvency, micellar solubilization, hydrotropy etc. A more recent technique, **"**powdered solution technology" or "Liquisolid technology", has been applied to prepare water-insoluble drugs into rapid-release solid dosage forms. In this case, even though the drug is in a solid dosage form, it is held within the powder substrate in solution or, in a solubilized, almost molecularly dispersed state, which contributes to the enhanced drug dissolution properties. With Liquisolid technique liquid formulations such as solutions or suspensions of poorly soluble drugs in a non-volatile liquid vehicle are converted into acceptably flowing and compressible powders by simple physical blending with selected excipients named the carrier and the coating material. The liquisolid approach has been successfully applied in release enhancement of low dose poorly soluble drugs.

Keywords: Liquisolid, Poor water solubility, Carrier material, Coating material, powdered solution technology

INTRODUCTION

Bioavailability is affected by the dissolution properties of a drug and its release from a dosage form. The rate of dissolution of a drug is a function of its intrinsic solubility and its particle size. Studies have demonstrated that particle size reduction to the sub-micron range of poorly soluble drugs can lead to an increase in dissolution rate and higher bioavailability.[1]

The process by which a solid substance goes into solution is termed as dissolution. The extent to which the dissolution proceeds, under a given set of conditions are referred to as the solubility of the substance in the solvent i.e. rate of solution (dissolution) and amount that can be dissolved (solubility) are not same. As per Noyes-Whitney equation the rate of dissolution of a drug is directly proportional to its solubility and therefore solubility of a drug substance is a major factor that determines its dissolution rate and hence its absorption and bioavailability eventually. The various properties of drug like solubility, particle size, polymorphism, salt form, complexation, wettability affect drug dissolution and its rate and can be targeted to enhance dissolution of poorly water soluble drugs.[2]

Spireas described the method for promoting dissolution i.e. the formation of liquisolid compacts. A liquid may be transformed into a free flowing, readily compressible and apparently dry powder with the liquisolid technology 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.[3] 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. Figure 1 represents the schematic representation of a liquisolid system.[4]

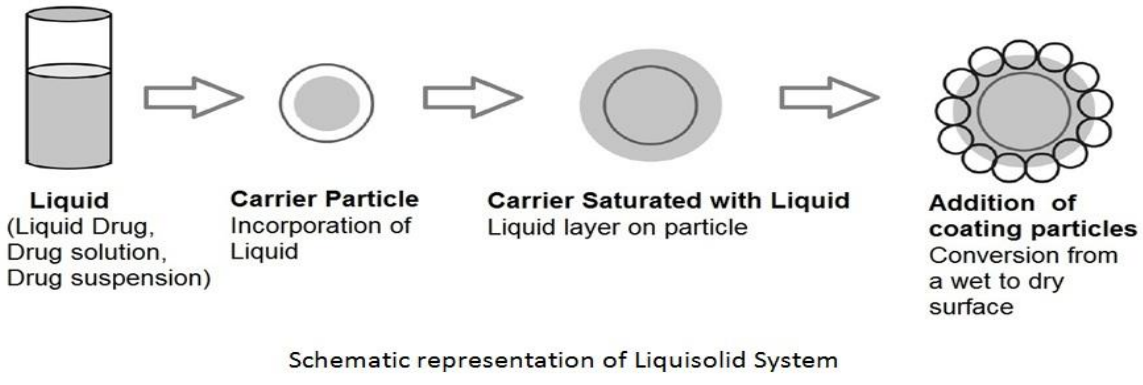


Fig.1.Schematic Representation of LiquiSolid System

ADVANTAGES

1. Drugs such as Digitoxin, Prednisolone and Hydrocortisone etc. i.e. practically water-insoluble liquid and solid drugs can be formulated into liquisolid systems using the new formulation-mathematical model.
2. Better availability of an orally administered water-insoluble drug is achieved when the drug is in solution form.
3. Though the drug is in a tabletted or encapsulated dosage form it is held in a solubilised liquid state, which consequently contributes to increased drug wetting properties, thereby enhancing drug dissolution.
4. Production cost is lower than that of soft gelatin capsules.
5. Advantage of liquisolid systems, particularly for powdered liquid drugs, during dissolution of a liquisolid tablet, after the disintegration process is completed, the drug solution or liquid drug, carried on the suspended and thoroughly agitated primary particles, is dispersed throughout the volume of the dissolution medium; such a phenomenon does not extensively occur during the dissolution process of soft gelatin capsule preparations. Therefore, since more drug surface is exposed to the dissolving medium, liquisolid systems exhibit enhanced drug release.
6. Optimized rapid-release liquisolid tablets or capsules of water-insoluble drugs exhibit enhanced *in-vitro* and *in-vivo* drug release as compared to their commercial counterparts.
7. Can be used for the formulation of liquid oily drugs.
8. Can be used in controlled drug delivery
9. Optimized sustained-release liquisolid tablets or capsules of water-insoluble drugs exhibit surprisingly constant dissolution rates (zero-order-release) comparable only to expensive commercial preparations that combine osmotic pump technology and laser-drilled tablets.[5]

DISADVANTAGES

1. The liquisolid systems have low drug loading capacities and they require high solubility of drug in non-volatile liquid vehicles.
2. More efficient excipients having higher adsorption capacities are required which provide faster drug release with a smaller tablet size to improve liquisolid formulations.
3. High levels of carrier and coating materials are required to maintain acceptable flowability and compatibility for liquisolid powder formulation and that in turn will increases the weight of each tablet above 1 gm which is very difficult to swallow.[6]

CLASSIFICATION OF LIQUISOLID SYSTEMS

A. Based on the type of liquid medication

1. Powdered drug solutions
2. Powdered drug suspensions
3. Powdered liquid drugs

Powdered drug solutions & powdered drug suspensions may be produced from the

conversion of drug solutions or (e.g. prednisolone solution in propylene glycol drug suspensions (e.g. gemfibrozil suspension in polysorbate 80) and the latter from the formulation of liquid drugs (e.g. clofibrate, liquid vitamins, etc.) into liquisolid systems.

B. Based on the formulation technique used

1. Liquisolid compacts
2. Liquisolid Microsystems [7]

COMPONENTS OF LIQUISOLID COMPACT FORMULATION

Liquisolid compact formulation mainly includes

1. Non volatile solvent
2. Disintegrant
3. Drug candidate
4. Carrier material
5. Coating material [8]

Non volatile Solvent

Non volatile Solvent should be Inert, having high boiling point, preferably water-miscible and not highly viscous organic solvent systems and compatible with having ability to solubilise the drug. The non volatile solvent acts as a binding agent in the liquisolid formulation. E.g. Polyethylene glycol 200 and 400, glycerine, polysorbate 80 and propylene glycol. [9]

Disintegrant

Superdisintigrants increases the rate of drug release, water solubility and wettability of liquisolid granules. Mostly superdisintigrants like sodium starch glycolate and crosspovidone are used. [10]

Drug candidates

Liquisolid technique was successfully applied for low dose BCS class II and class IV drugs which are poorly water soluble and have slow dissolution rate. E.g. carbamazepine, famotidine, piroxicam, indomethacin, hydrocortisone, naproxen and prednisolone, digoxin, digitoxin, prednisolone, hydrocortisone, spironolactone, hydrochlorothiazide, polythiazide, and other liquid medications such as chlorpheniramine, water insoluble vitamins, fish oil etc.[11]

Carrier Materials

Carrier material should be porous material possessing sufficient absorption properties which contributes in liquid absorption. The carrier and coating materials can retain only certain amounts of liquid and at the same time maintain acceptable flow and compression properties hence, increasing moisture content of carrier's results in decreased powder flowability. E.g. Grades of microcrystalline cellulose such as Avicel PH 102 and avicel PH 200, lactose, eudragit Rl and eudragit RS12 (to sustain drug delivery) etc. [12]

Coating Materials

Coating material should be a material possessing fine and highly adsorptive particles which contributes in covering the wet carrier particles and displaying a dry-looking powder by adsorbing any excess liquid. Coating material is required to cover the surface and so maintain the powder flowability. E.g. silica (Cab-O-Sil) M5, Aerosil 200, Syloid, 244FP etc. [13.]

THEORY OF LIQUISOLID SYSTEMS

A powder can retain only limited amounts of liquid while maintaining acceptable flow and compression properties. To calculate the required amounts of powder excipients a mathematical approach for the formulation of

liquisolid systems has been developed by Spireas. This approach is based on the flowable (Φ-value) and compressible (Ψ-number) liquid retention potential introducing constants for each powder/liquid combination. [14]

The Φ-value of a powder is defined as the maximum amount of a given non-volatile liquid that can be retained inside its bulk while maintaining an acceptable flowability. The flowability may be determined from the powder flow or by measurement of the angle of repose or angle of slide.

The Ψ-number of a powder is defined as the maximum amount of liquid the powder can retain inside its bulk while maintaining acceptable compactability resulting in compacts of sufficient hardness with no liquid leaking out during compression. It can be measured as the maximum crushing strength of a one-gram tablet compacted at sufficiently high compression forces. [15]

Table 1 represents different Φ-values and Ψ-values of different carrier and coat materials

The liquid load factor that ensures acceptable flowability ($^{\Phi}Lf$) can be determined by:

$$Lf = \Phi + \varphi.(1/R)$$

where Φ and φ are the Φ-values of the carrier and coating material, respectively.

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.

$$R = Q/q$$

R=represents the ratio between the weights of the carrier (Q) and the coating (q) material present in the formulation.

As soon as the optimum liquid load factor is determined, the appropriate quantities of carrier (Qo) and coating (qo) material required to convert a given amount of liquid formulation (W) into an acceptably flowing and compressible liquisolid system may be calculated as follows:

$$Qo = W/Lo$$

and

$$qo = Qo/R$$ [16-17]

Table.1.Examples of liquisolid formulation parameters of various powder excipients with commonly used liquid vehicles are listed. [18]

Powder excipient or system	Φ Values		Ψ values	
	Propylene Glycol	PEG 400	Propylene Glycol	PEG 400
Avicel PH102	0.16	0.005	0.224	0.242
Avicel PH200	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 200	2.56	2.44	0.712	0.717

Φ Value = Flowability index

Ψ value = Compressibility index

Table.2.Formulations of liquisolid systems with enhanced drug release

Drug	Liquid vehicle	Carrier material	Coating material	Ref.
Aceclofenac	PEG 400, PG Tween 80	MCC	Colloidal silica	19
Aceclofenac	PEG 400	MCC	Colloidal silica	20
Aceclofenac	PEG 400	DCP, MCC	HPMC	21
Atorvastatin	PEG 400, PG	Avicel PH 102	Aerosil 200	22
Bromohexine HCl	PG	Avicel PH 102	Aerosil 200	23
Carbamezepine	PEG 200	Avicel PH 102	Aerosil 200	24
Carbamezepine	PEG 400	Avicel PH 102	Aerosil 200	25
Carvedilol	PEG 200, PEG 400	Avicel PH 102	Aerosil 200	26
Cyclosporine	PEG 400	Avicel PH 101 Avicel PH 102	Neusilin S1	27
Diclofenac Sodium	PG	Avicel	Aerosil	28
Ezetimibe	PEG 400, PG	Avicel PH 102	Aerosil 200	29
Famotidine	PG	Avicel PH 102	Aerosil 200	30
Fenofibrate	PEG 400	MCC	Colloidal silica	31
Fenofibrate	PG	Avicel PH 102	Aerosil 200	32
Furosemide	Synperonic® PE/L 81	Avicel PH 101	Cab-O-Sil M5	33
Glipizide	PEG 400	Avicel PH 102	Aerosil 200	34
Griesofulvin	PEG 400	Avicel PH 102	Cab-O-Sil M5	35
Griesofulvin	PEG 300	Avicel & Neusilin	Aerosil & Neusilin	36
Hydrocholothiazide	PEG 200	Avicel PH 101 Avicel PH 102	Magnesium carbonate + Colloidal silica	37
Ibuprofen	PEG 300	Avicel PH 101	Aerosil	38
Indomethacin	Tween 80	MCC	Amorphous Silicon Dioxide	39

Indomethacin	PEG 400	Avicel PH 102, DCP	HPMC	40
Ketoprofen	PEG 400	Avicel PH 101	Silica gel	41
Lansoprazole	PEG 400	Avicel PH 102	Aerosil 200	42
Meloxicam	PEG 200, PEG 400	Avicel PH 102	Aerosil 200	43
Naproxen	Cremophor® EL	Avicel PH 102	Cab-o-sil M5	44
Nimesulide	PEG 400	MCC, HPMC E15& Starch	Silica gel	45
Piroxicam	Polysorbate 80	MCC	Colloidal silica	46
Propanolol	Polysorbate 80	Eudragit RL/RS	Silica	47
Repaglinide	Polysorbate 80	Avicel PH 101	Calcium silicate	48
Rofecoxib	PG, Glycerol	Cab-O-Sil M5P	Amorphous fumed silica	49
Simvastatin	PG	Avicel PH 101	Aerosil 200	50
Tramadol	PG	Avicel PH 102	Aerosil 200	51
Valsartan	PG	Avicel PH 102	Aerosil 200	52
Valsartan	PG, PEG, Glycerine	PVP K 30, PEG 6000	Colloidal Silica	53

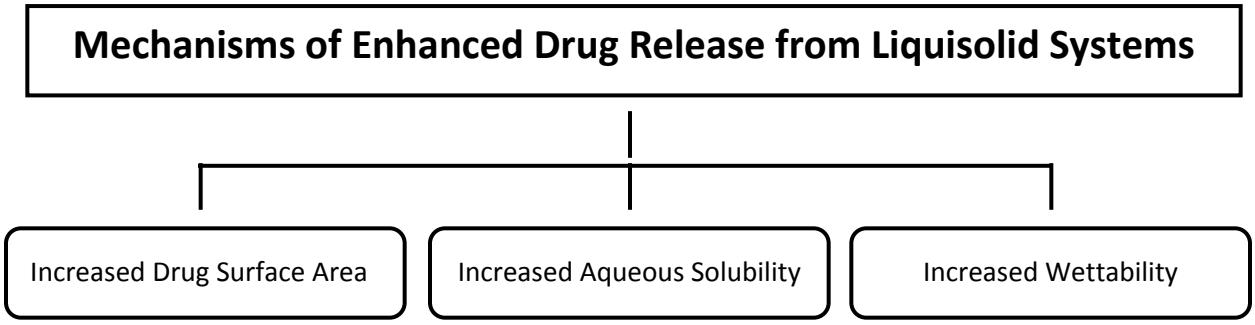


Fig.2.Different mechanisms for enhancement of drug release from a liquisolid system

Figure 2 represents the different types of mechanism that supposedly take place to enhance the release rate of a drug and hence dissolution from a liquisolid system. The mechanisms are described as :

INCREASED DRUG SURFACE AREA

If 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. Therefore, the surface area of drug available for release is much greater than that of drug particles within directly compressed tablets.

Accordingly, with increasing drug content exceeding the solubility limit and thus, increasing fraction of undissolved drug in the liquid vehicle the release rate decreases. [54]

INCREASED AQUEOUS SOLUBILITY OF THE DRUG

In addition to the first mechanism of drug release enhancement it is expected that the solubility of the drug, might be increased with liquisolid systems. In fact, the relatively small amount of liquid vehicle in a liquisolid compact is not sufficient to increase the overall solubility of the drug in the aqueous dissolution medium. However, at the solid/liquid interface between an individual liquisolid primary particle and the release medium it is possible that in this microenvironment the amount of liquid vehicle diffusing out of a single liquisolid particle together with the drug molecules might be sufficient to increase the aqueous solubility of the drug if the liquid vehicle acts as a cosolvent. [55]

IMPROVED WETTING PROPERTIES

Due to the fact that the liquid vehicle can either act as surface active agent or has a low surface tension, wetting of the liquisolid primary particles is improved. Wettability of these systems has been demonstrated by measurement of contact angles and water rising times.

Nonvolatile solvent present in the liquisolid system facilitates wetting of drug particles by decreasing interfacial tension between dissolution medium and tablet surface. shows lower contact angle of liquisolid compacts than the conventional tablets and thus improved wettability. Figure 3 represents the comparison of wettability between a conventional tablet and a liquisolid tablet. [56]

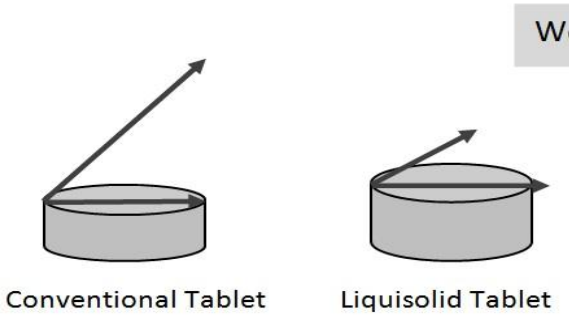


Fig.3. Comparison of Wettability between a Conventional tablet and a Liquisolid tablet

FORMULATION OF LIQUISOLID COMPACT

The formulation part of liquisolid compact mainly includes Pre-formulation studies and Formulation of liquisolid compact system.

PRE-FORMULATION STUDIES

Pre-formulation Studies includes

1. Determination 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) [57]

Solubility studies

Solubility studies are carried out by preparing saturated solutions of drug in non-volatile solvent and analyzing them spectrophotometrically. Saturated solutions are prepared by adding excess of drug to non volatile solvent and shaking them on shaker for specific time period under constant vibration. After this, the solutions are filtered and analyzed spectrophotometrically.

Determination of angle of slide

Angle of slide is used as a measure of the flow properties of powders. Determination of angle of slide is done by weighing the required amount of carrier material and placed at one end of a metal plate with a polished surface. The end is gradually raised till the plate becomes angular to the horizontal at which powder is about to slide. This angle is known as angle of slide. Angle of **33°** is regarded as optimum.

Determination of flowable liquid retention potential (Φ value)

The term "flowable liquid-retential 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 that can be retained per unit weight of the powder material in order to produce an acceptably flowing liquid/powder admixture. The Φ values are calculated according to equation.

Φ value = weight of liquid / weight of solid

Calculation of liquid load factor (Lf)

Different concentrations of non-volatile solvents are taken and the drug is dissolved. Such liquid medication is added to the carrier-coating material admixture and blended. Using equation (2) drug loading factors are determined and used for calculating the amounts of carrier and coating materials in each formulation.

Lf = weight of liquid medication / weight of carrier material

Liquisolid compressibility test (LSC)

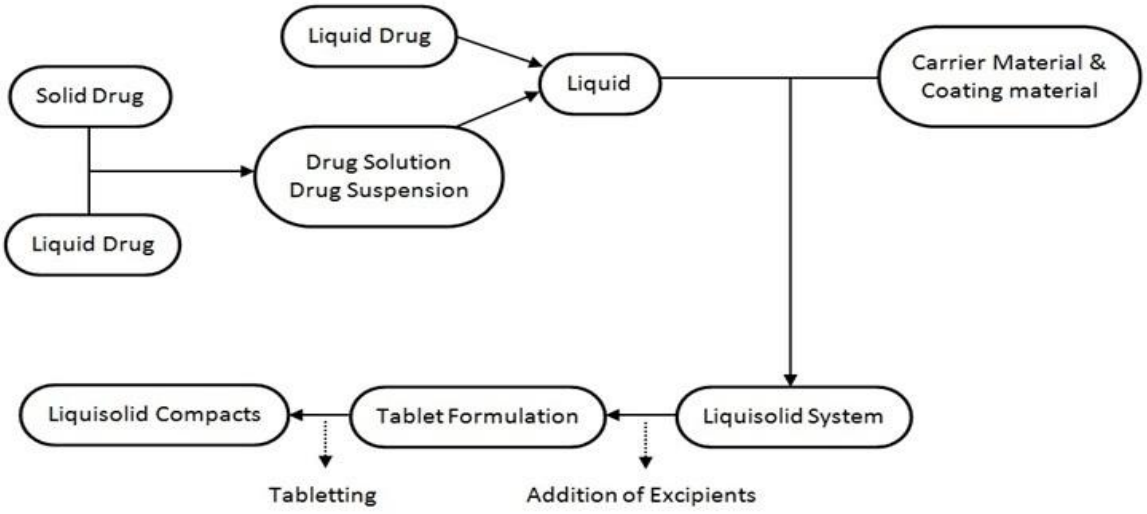
Liquisolid compressibility test is used to determine Φ values and involves steps such as preparing carrier coating material admixture systems, preparing several uniform liquid or powder admixtures, compressing each liquid or powder admixtures to tablets, assessing average hardness, determination of average liquid content of crushed tablets, as well as determining plasticity, sponge index and Φ value and L_f . [58-61]

PREPARATION OF LIQUISOLID TABLETS

1. A drug substance was initially dispersed in the nonvolatile solvent systems (Polysorbate 80, Polyethylene glycol-200) termed as liquid vehicles with different drug: vehicle ratio.

2. Then a mixture of carrier or different polymers and excipients were added to the above liquid medication under continuous mixing in a mortar. These amounts of the carrier and excipients are enough to maintain acceptable flow and compression properties.
3. To the above binary mixture disintegrant like sodium starch glycolate and other reaming additives were added according to their tion and mixed for a period of 10 to 20 min. in a mortar.
4. The final mixture was compressed using the manual tableting machine to achieve tablet hardness.
5. Characterize the final liquisolid granules for solubility, dissolution, flowability, compressibility and other physicochemical properties.

Figure 4 represents schematic diagram of preparation of liquisolid compacts [62-64]



Schematic Diagram Representing Preparation of Liquisolid Compacts

Fig.4.Schematic Diagram Representing Preparation of LiquiSolid Compacts

EVALUATION OF LIQUISOLID SYSTEMS

Precompression Studies Of Prepared Liquisolid Powders

In order to ensure the suitability of selected excipients Differential Scanning Calorimetry (DSC), X-ray diffraction (XRD) & Scanning Electron Microscopy (SEM) studies are performed. In addition flowablity studies are also carried out to select the optimal formulae for compression prior to compression of the formulation to tablets.

Flow behavior

Flow properties are the important concern in the formulation and industrial production of tablet dosage form. Angle of repose is characteristic to the flow rate of powder. In general, values of angle of repose ≥ **40°** indicate powders with poor flowability. [65]

Differential Scanning Calorimetry (DSC)

It is necessary to determine any possible interaction between excipients used in the formulation. This will also indicate success of stability studies41. 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. [66]

X-ray diffraction (XRD)

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 solubilised form in the liquisolid formulation. [67]

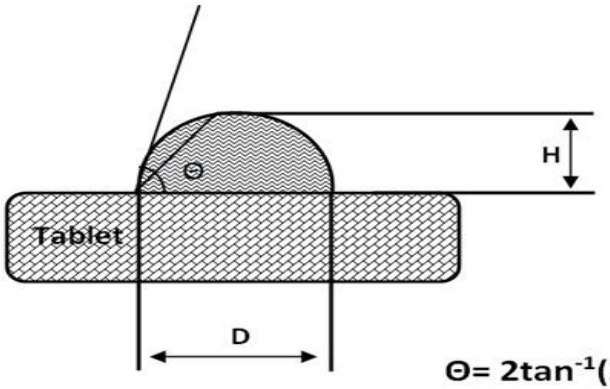
Scanning Electron Microscopy (SEM)

After SEM study, complete disappearance of crystals of drug which confirms that drug is totally solubilized in liquisolid system and this ensures the complete solubility. After complete formulation, Tablets are evaluated by carrying out tests for weight variation, uniformity of tablet thickness and diameter, humidity content using karl fisher method, friability, hardness, disintegration, dissolution, and content uniformity. All these tests are carried out in triplicate and according to the compendial specifications.

For content uniformity test tablets should contain not less than 95% and not more than 105% of the labelled potency. The disintegration test was carried out on six tablets in distilled water at 37 ± 2 °C using the SP disintegration apparatus. [68]

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 solid, the so called imaging method. A saturated solution of 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 the diameter of sphere drop on the tablet. Figure 5 represents the measurement of contact angle using imaging method. [69]



Schematic Representation of Contact Angle Measurement Using Imaging Method

Fig.5.Schematic Representation of Contact Angle Measurement Using Imaging Method

Dissolution studies of Liquisolid tablet

Generally Dissolution studies of liquisolid tablet are carried out using dissolution apparatus USP II at 37°C ± 2°C. Many researchers revealed that at low drug concentrations in liquid medication, more rapid release rates are observed. The consistent and higher dissolution rate displayed by liquisolid compacts will improve the absorption of drug from gastrointestinal tract.

***In vivo* evaluation of Liquisolid tablets**

The improvement in oral bioavailability was confirmed by estimating the pharmacokinetic parameters in various animals such as rabbit, beagle dog. Results show that absolute bioavailability of drug from liquisolid tablets was much higher than marketed tablets. [70]

APPLICATIONS

1. Liquisolid compact technology is a powerful tool to improve bioavailability of water insoluble drugs. Several water insoluble drugs on dissolving in different non-volatile solvents have been formulated into liquisolid compacts.
2. Literature cites different drugs successfully incorporated into liquisolid compacts.
3. Rapid release rates are obtained in liquisolid formulations.
4. These can be efficiently used for water insoluble solid drugs or liquid lipophilic drugs.
5. Sustained Release of drugs which are water soluble drugs such as propranolol hydrochloride has been obtained by the use of this technique.
6. Solubility and dissolution improvement
7. Flowability and compressibility
8. Designing of Controlled Release Tablets
9. Bioavailability Enhancement.[71]

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