



LIQUISOLID SYSTEMS - AN EMERGING STRATEGY FOR SOLUBILIZATION & DISSOLUTION RATE ENHANCEMENT OF BCS CLASS-II DRUGS

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ABSTRACT

Now-a day's efforts are ongoing to enhance the oral bioavailability of lipophilic drugs/water insoluble drugs in order to increase their clinical efficacy. One of the most popular approaches includes Liquisolid technique, which is a new and most promising method that can change the solubility of more insoluble drugs. Liquisolid systems are acceptably flowing and compressible powdered forms of liquid medications. Formulation and manufacture of liquisolid tablets is quite simple method according to new mathematical model described by Spireas et al. According to this concept, liquid lipophilic drugs, or water-insoluble solid drugs dissolved in suitable nonvolatile solvents have been converted into free-flowing and readily compressible powders by a simple admixture with selected powder excipients, which in turn acts as a self-emulsifying system *in-vivo*. Liquisolid compacts enhances the oral bioavailability enabling reduction in dose, shows more consistent drug absorption through temporal profiles, Selective targeting of drug(s) toward specific absorption window in GIT and protection of drug(s) from the hostile environment in gut.

Key words: liquisolid compact, Dissolution rate enhancement, BCS class II drugs, Liquid retention potential (\emptyset).

INTRODUCTION

The oral route is the preferred route for the chronic drug therapy. Numerous potent lipophilic drugs exhibit low oral bioavailability due to their poor aqueous solubility properties. The most popular approach is the incorporation of the active lipophilic component into inert lipid vehicles such as oils, surfactant dispersions, self-emulsifying formulations, emulsions and liposome's with every formulation approach having its special advantages and limitations. To compensate for the poor absorption displayed by many drugs, a pharmaceutical formulation may utilize or take advantage of one or more mechanisms to increase the rate and/or the extent to which the drug is absorbed.

The emulsion/drug dissolved in lipophilic vehicle was generally delivered only in the form of soft or hard gelatin capsules or as a liquid dispensed directly into the patient's mouth. However, gelatin capsule shells contain water, which can migrate into water-in-oil ("w/o") emulsions. This can change the relative proportions of the

different phases of the emulsion and/or cause the gelatin shell to become dry and susceptible to cracking. Alternatively, a w/o emulsion can lose water to the gelatin shell, again changing the proportions of the different emulsion phases or causing the shell to swell and become soft. The latter effect makes it difficult for a patient or caregiver to handle the capsule. Moreover, surfactants and co-surfactants within the emulsion, often used as emulsifying agents, can react with the capsule shell. Hence, liquid drug medicaments generally cannot be incorporated in such capsules because the liquid phase may react or dissolve the capsule shell. In addition, gelatin capsules which contain liquids present handling problems to both the patient and the manufacturers. Capsule leakage is a common problem and sophisticated detection systems are sometimes employed to monitor such leakage. Upon physical handling by the patient, the capsule may also soften or leak. With prolonged storage at temperatures and humidity, levels that are not as closely controlled as the

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environment in the pharmaceutical factory, the capsule may also swell, shrink or leak [1].

More recently, powdered solution (liquisolid) technology has been proposed as a technique for the delivery of water-soluble drugs. The concept of powdered solutions involves converting drug solutions or liquid drugs into a dry, non-adherent, free-flowing compressible powder by admixturing the liquid drugs or drug solutions with a selected carrier. Although the dosage form is a solid, the drug was held in a solubilized liquid state, which enhances diffusion directly into cells. Alternatively, improves the wetting properties of the drug and therefore enhanced dissolution [2].

BCS class II drugs

BCS class II drugs pose challenging problems in their pharmaceutical product development process because of their low solubility and dissolution rates. They require enhancement in solubility and dissolution rate in their formulation development especially solid dosage forms such as tablets and capsules.

Therapeutic effectiveness of a drug depends up on the bioavailability and ultimately upon the solubility and dissolution rate of drug molecules. Solubility and dissolution rate are the important parameters to achieve desired concentration of drug in systemic circulation for pharmaceutical response to be shown.

LIQUISOLID SYSTEMS

“The term liquisolid compact refers to immediate release or sustained release tablets or capsules, combined with the inclusion of appropriate adjuvant required for tableting or encapsulating [3-5].”

Oral delivery of poorly water-soluble compounds is to pre-dissolve the compound in a suitable solvent and fill the formulation into capsules or compressed into a tablet form. The main benefit of this approach is that pre-dissolving the compound overcomes the initial rate-limiting step of particulate dissolution in the aqueous environment within the GI track. However, a potential problem is that the drug may precipitate out of solution when the formulation disappears in the GI tract, particularly if a hydrophilic solvent is used (e.g. Polyethylene glycol). If the drug can be dissolved in a lipid vehicle there is less potential for precipitation on dilution in the GI tract, as partitioning kinetics will favor the drug remaining in the lipid droplets.

A drug substance is considered highly soluble when the highest dose strength is soluble in <250ml water over a pH range of 1 to 7.5 and it is considered highly permeable when the extent of absorption in humans is determined to be >90% of an administered dose, based on mass-balance or in comparison to an IV reference dose. A drug product is considered to be rapidly dissolving when >85% of the labeled amount of drug substance dissolves within 30 minutes using USP apparatus I or II in a volume of <900ml buffer solutions.

The rate limiting process for drug absorption and bioavailability (rate and extent of absorption) is either the release (or dissolution) of drug substances from the dosage

form or its permeation through the intestinal membrane. If permeation through intestinal membrane is rate limiting, dissolution properties may of negligible importance. Drugs having high permeability and low solubility (class II), dissolution or release from the dosage form occurs slowly and the dissolution rate will become the rate limiting factor for drug absorption [6].

Historical development

Historically, liquisolid compacts are descendants of ‘powder solutions’, an older technique which was based on the conversion of a solution of a drug in a non volatile solvent into a dry looking, non adherent powder by mainly adsorbing the liquid onto silicas of large specific surfaces. Such preparations, however, have been investigated for their dissolution profiles while being in a powder dispersion form and not as compressed entities, simply because they could not be compressed into tablets. In later studies on powder solutions, compression enhancers such as microcrystalline cellulose were added in such dispersions in order to increase the compressibility of the systems.

Liquisolid compacts, on the other hand, are acceptably flowing and compressible powdered forms of liquid medications, and have industrial application. In addition, the term ‘liquid medication’ does not only imply drug solutions, as in powdered solutions, but also drug suspensions, emulsions or liquid oily drugs. Therefore, in contrast to ‘powder solutions’, the term ‘liquisolid compacts’ is more general and it may encompass four different formulation systems namely,

- Powder drug solutions
- Powder drug suspensions
- Powder drug emulsions
- Powder liquid drugs [7]

The new liquisolid technique may be applied to formulate liquid medications (i.e., oily liquid drugs and solutions, suspensions or emulsions of water insoluble solid drugs carried in non-volatile liquid vehicles) into powders suitable for tableting or encapsulation. Simple blending of such liquid medications with calculated quantities of a powder substrate consisting of certain excipients referred to as the carrier and coating powder materials, can yield dry looking, nonadherent, free-flowing and readily compressible powders.

Advantages

- Huge number of BCS 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.
- Simplicity
- Viability of industrial production
- Improvement of bioavailability of an orally administered water insoluble drugs achieved.
- 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.

- In this technique, production cost is low compared to soft gelatin capsules.
- 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.
- Greater drug surface area is exposed to dissolution medium.
- The liquisolid system is specifically for powdered liquid medications.
- These liquisolid systems may further formulated into immediate release or sustained release dosage forms.
- Optimized sustain release, liquisolid tablets or capsules of water insoluble drugs demonstrate constant dissolution rates.
- Drug can be molecularly dispersed in the formulation.
- Drug release can be modified using suitable formulation ingredients.
- Enhanced bioavailability can be obtained as compared to conventional tablets.
- To minimize excipients in formulation compare with other formulations like solid dispersions.
- Omit the process approaches like nanonisation, micronization techniques [8].

Disadvantages

- Formulation of high dose lipophilic drugs the liquisolid tablet is one of the limitations of this technique [9].
- In order to achieve acceptable flowability and compactability for liquisolid powder formulations, high levels of carrier material and coating materials should be added. This will increase the weight of tablet to above 1 gm which makes them difficult to swallow.

Concept

When the drug dissolved in the liquid vehicle is incorporated into a carrier material which has a porous surface and closely matted fibers in its interior as cellulose, both absorption and adsorption takes place; i.e., the liquid initially absorbed in the interior of the particles is captured by its internal structure, and after the saturation of this process, adsorption of the liquid onto the internal and external surfaces of the porous carrier particles occur. Then, the coating material having high adsorptive properties and large specific surface area gives the liquisolid system the desirable flow characteristics.

In liquisolid systems the drug is already in solution in liquid vehicle, while at the same time, 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, liquisolid compacts of water insoluble substances may be expected to display enhanced drug release characteristics and consequently, improved oral bioavailability. Since, dissolution of a non polar drug is often the rate limiting step in GI absorption, better bioavailability of an orally administered water-insoluble drug is achieved when the drug is already in solution,

thereby displacing enhanced dissolution rates. That is why soft gelatin elastic capsules containing solutions of such medications demonstrate higher bioavailability when compared to conventional oral solid dosage forms. A similar principle underlies the mechanism of drug delivery from liquisolid compacts and is chiefly responsible for the improved dissolution profiles exhibited by these preparations.

The wettability of the compacts by the dissolution media is one of the proposed mechanisms for explaining the enhanced dissolution rate at the time of burst release from the liquisolid compacts. Nonvolatile solvent present in the liquisolid system facilitates wetting of drug particles by decreasing interfacial tension between dissolution medium and tablet surface. Fig shows lower contact angle of liquisolid compacts than the conventional tablets and thus improved wettability.

Designing of Liquisolid Systems

Before designing the liquisolid system, the preformulation studies should be performed first, which includes, Determination of drug solubility in different non-volatile solvents

Determination of angle of slide

Carrier-Coating material ratio (R)

Determination of flowable liquid retention potential (\emptyset value)

Calculation of liquid load factor (L_f)

Liquid solid compressibility test (LSC)

The flowability and compressibility of liquisolid compacts are addressed concurrently in the new formulation mathematical model of liquisolid systems, which was used to calculate the appropriate quantities of the carrier and coating materials required to produce acceptably flowing and compressible powders based on new fundamental powder properties called the flowable liquid retention potential (\emptyset value) and compressible liquid retention potential (Ψ value) of the consistent powders [10, 11].

Determination of drug solubility in different non-volatile solvents

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

Determination of angle of slide

The required amount of carrier is weighed and placed at one of a metal plate with a polished surface and it is gradually raised till the plate becomes angular to the horizontal at which powder is about to slide. It was used to measure the flow properties of powders. The angle of 33^0 is optimum for flow of powders.

Carrier-Coating material ratio (R)

It is the ratio between the quantities of carrier (Q)

and coating (q) present in the formulation. It is represented as

$$R=Q/q$$

Determination of flowable liquid retention potential (\emptyset)

It is defined as maximum weight of liquid that can be retained per unit powder material in order to produce an acceptably flowing liquid/powder admixture. This \emptyset -value of powders may be determined using a new procedure, the liquisolid flowability (LSF) test. This test is basically a titration-like procedure in which 25-30 grams of mixtures of the powders under investigation, with increasing amounts of a non-volatile solvent (i.e., liquid/solid weight composition), such as, for example, poly ethylene glycol, light mineral oil and clofibrate, are prepared using a standard mixing process which ensures uniformity, and their flow rate and consistency are assessed using a recording powder flow meter (RPF) [3-5].

$$L_f = \emptyset + \emptyset (1/R)$$

Where, \emptyset and \emptyset are the constant liquid retention potential values of carrier and coating materials, respectively. By calculating L_f and W , we can calculate the Q and q required for liquisolid systems [12].

Calculation of liquid load factor (L_f)

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

$$L_f = W/Q$$

Where W is ratio of weight of liquid medication and Q is weight of carrier material [13].

Liquid solid compressibility test (LSC)

It was developed to determine Ψ values and involves steps such as preparing carrier coating material admixture systems [14], 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 .

COMPONENTS

The major formulation components of liquisolid compacts are

Carrier material

These are compression enhancing, relatively large, preferably porous particles possessing a sufficient absorption property which contributes in liquid absorption. Various grades of microcrystalline cellulose (MCC) such as pH101, and 200 Avicel RTM 105, Avicel pH 102 granular microcrystalline cellulose grades, Avicel pH 200 coarse granular MCC grade, experimental grade of granular amorphous cellulose, starch, lactose used as carrier materials. Starch 1500, silica possessing large surface areas and MCC of fine particle size granular grades produced good flow properties and compression

properties resulting in good tablets [3, 15].

Coating material

These are flow-enhancing, very fine (10nm to 5,000nm in diameter), highly adsorptive coating particles. Silica of various grades like Cab-O-Sil M5, Aerosil 200, Syloid 244FP etc., contributes in covering the wet carrier particles and displaying a dry-looking powder by adsorbing any excess liquid [3, 7, 15-18].

Non-volatile solvents

Inert, high boiling point, preferably water-miscible and not highly viscous organic solvent systems like propylene glycol, liquid polyethylene glycols, polysorbates, glycerin, N, N-dimethylacetamide, fixed oils, etc. are most suitable as vehicles.

Hydrophobic carriers

Eudragit RL and RS [18], HPMC K4M [19] etc, were used for sustained release.

Super disintegrants

Sodium starch glycolate (Explotab, Pumogel) [20], Crosspovidone [21], sodium crosscarmellose [22, 23], Pre gelatinized starch [24].

GENERAL METHOD OF PREPARATION

Liquid lipophilic drug (e.g., chlorphenamine, clofibrate, etc.) can be converted into a liquisolid system without being further modified. On the other hand, if a solid water-insoluble drug (e.g., hydrochlorothiazide, mefenamic acid, prednisone, etc.) is formulated, it should be initially dissolved or suspended in a suitable non-volatile solvent system to produce a drug solution or drug suspension of desired concentration.

Next, a certain amount of the prepared drug solution or suspension, or the liquid drug itself, is incorporated into a specific quantity of carrier material which should be preferably of a porous nature and possessing sufficient absorption properties, such as powder and granular grades of microcrystalline and amorphous cellulose are most preferred as carriers. The resulting wet mixture is then converted into a dry looking, non adherent, free flowing and readily compressible powder by the simple addition and mixing of a calculated amount of coating material. Excipients possessing fine and highly adsorptive particles such as various types of amorphous silicon dioxide are most suitable for this step. Before compression or encapsulation, various adjuncts such as lubricants and disintegrants (immediate) or binders (sustained-release) may be mixed with the finished liquisolid systems to produce liquisolid compacts i.e. tablets or capsules [3, 4, 5].

The liquisolid tablet preparation method involves, first a mathematically calculated amount of pure drug weighed and dissolved in the suitable amount of solvent in a molecularly dispersed state. For attaining good flow properties trial and error methods were used i.e. changing the carrier: coating material ratio from 50:1 to 5:1 ratios according to new mathematical model expressions

proposed by Liao [25]. This liquid medication is poured on the suitable amount of carrier material. The liquid medication is absorbed into the carrier material internally and externally and then a suitable carrier or disintegrant was added to this material. Finally, coating material was added for dry looking, adherent to the carrier material for achieving good compression properties. Liquid medication is incorporated into carrier material which has a porous surface and closely matted fibers in its interior as cellulose [26]. Both absorption and adsorption takes place, i.e. the liquid absorbed into the interior of the particles is captured by its internal structure and after saturation of this process, adsorption of the liquid onto the internal and external surface of the porous carrier particles occurs [25].

Liquisolid system for Controlled Drug Delivery

Development of sustained release oral dosage form is beneficial for optimal therapy in terms of efficacy, safety and patient compliance. There are several techniques for preparation of sustained release formulations, among which control of drug dissolution is one of the best and most successful methods due to its viability. Several methods have been developed to this end or to achieve this aim. It is suggested that liquisolid technique has the potential to be optimized for the reduction of drug dissolution rate and thereby production of sustained release systems. If hydrophobic carriers such as Eudragit RL and RS are used instead of hydrophilic carriers in liquisolid systems, sustained release can be obtained. The mechanism of release prolongation is likely to be a more efficient encapsulation of drug particles by the hydrophobic polymers. The presence of nonvolatile solvent reduces the glass transition temperature (T_g) of polymers and imparts flexibility. Therefore, reduction of T_g of the polymer might be the reason for the release prolongation of liquisolid tablets. In the temperature above the T_g , a better coalescence of the polymer particles occurs that forms a fine network and a matrix with lower porosity and higher tortuosity. In this way, the drug is surrounded and entangled by the polymer network, resulting in the restricted leaching of the drug thus, sustaining the drug from liquisolid matrices [27].

EVALUATION OF LIQUISOLID SYSTEMS

Flow behavior

The flowability of a powder is of critical importance in the production of pharmaceutical dosage forms in order to reduce high dose variations [28, 29]. Angle of repose, Carr's index and Hausner's ratio were used in order to ensure the flow properties of the liquisolid systems.

Precompression studies

In order to ensure the suitability of the selected excipients, Differential Scanning Calorimetry, X-ray Diffraction, Fourier Transform Infrared Spectroscopy, and Scanning Electron Microscope studies are to be performed.

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 of the liquisolid system. Complete disappearance of characteristic peaks of drug indicates the formulation of the drug solution in the liquisolid powder system, i.e., the drug is molecularly dispersed within the liquid matrix [10, 15, 30-36].

X-Ray Diffraction (XRD)

For the characterization of crystalline state, X-ray diffraction patterns are determined for physical mixture of drug and excipients used in formulation and for the prepared liquisolid compacts.³² Absence of constructive specific peaks of the drug in the liquisolid compacts in the x-ray diffractogram specify 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 [37].

Scanning Electron Microscopy (SEM)

Scanning electron microscopy is utilized to assess the morphological characteristics of the raw materials and the drug-carrier systems [38].

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 by placing 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 angle is calculated by measuring the height and diameter of sphere drop on the tablet [15].

In-vitro dissolution studies

The liquisolid technology is a promising tool for the enhancement of drug release of poorly soluble drugs. 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. The absolute bioavailability of drug from liquisolid tablets was 15% higher than that from the commercial formulation [39].

The enhanced dissolution rates of liquisolid compacts compared to pure drug may be attributed to the fact that the drug is already in solution in liquid vehicle, while at the same time, it is carried by the powder particles (MCC and Silica). Thus, its release is accelerated due to its markedly increased wettability and surface area availability to the dissolution medium [7, 38].

Liquisolid compacts with lower R-values (carrier: coating ratio) contain relatively smaller amounts of carrier powder (microcrystalline cellulose), and larger quantities of fine drug loaded silica particles, and the ratios of the amounts of their liquid medication per powder substrate are relatively higher. On the other hand, liquisolid

compacts with higher R-values contain low liquid/powder ratios, high presence of cellulose and low presence of silica. This could be directly associated with enhanced wicking, disintegration and disaggregation properties. Therefore, the liquid tablets with low R-values showed relatively poor dissolution [7].

Mathematical modeling for drug release profile

The cumulative amount of Mefenamic acid released from the formulated tablets at different time intervals were fitted in to several kinetic models such as Zero order kinetics, First order kinetics, Higuchi model and Korsmeyer-peppas model to characterize mechanism of drug release.

Zero order kinetics

It describes the system in which the drug release rate is independent of its concentration.

$$Q_t = Q_0 + K_0 t$$

Where, Q_t = amount of drug dissolved in time “t”

Q_0 = initial amount of drug in the solution

K_0 = Zero order release constant

If the zero order release kinetic is obeyed, then a plot of Q_t vs. t will give a straight line with a slope of K_0 and an intercept at zero.

To study the release kinetics, data obtained from *in vitro* drug release studies were plotted as *cumulative amount of drug released vs. time*.

First order kinetics

It describes the drug release from the systems in which the release rate is concentration dependent.

$$\text{Log } Q_t = \text{Log } Q_0 + K_1 t / 2.303$$

Where, Q_t = amount of drug release in time “t”

Q_0 = initial amount of drug in the solution

K_1 = first order release constant

If the release pattern of drug follows first order kinetics, then a plot of $\log(Q_0/Q_t)$ versus t will be a straight line with a slope of $K_1/2.303$ and an intercept at $t=0$ of $\log Q_0$.

The data obtained are plotted as *log cumulative percentage of drug remaining vs. time*.

Higuchi model

It describes the fraction of drug release from a matrix is proportional to square root of time.

$$Mt/M\infty = K_H t^{1/2}$$

Where, Mt & $M\infty$ = cumulative amounts of drug release at time “t” and infinite time

K_H = Higuchi dissolution constant reflection formulation characteristics.

If the Higuchi model of drug release (*i.e.*, Fickian diffusion) is obeyed, then a plot of $Mt/M\infty$ vs. $t^{1/2}$ will be a straight line with a slope of K_H .

The data obtained were plotted as *cumulative percentage drug release vs. square root of time*.

Korsmeyer-Peppas model (Power law)

The power law describes that the fractional amount of drug release is exponentially related to the release time and adequately describes the release of drug from slabs, cylinders and spheres.

$$Mt/M\infty = K t^n$$

$$\text{Log } [Mt/M\infty] = \text{Log } K + n \text{ log } t$$

Where, Mt & $M\infty$ = cumulative amounts of drug release at time “t” and infinite time

K = constant incorporating structural and geometrical characteristics of CR device

n = diffusional release exponent indicative of the mechanism of drug release for drug dissolution.

A plot of \log (drug release) versus $\log t$ will be linear with slope of n and intercept gives the value of $\log k$.

To study the release kinetics, data obtained from *in vitro* drug release studies were plotted as *log cumulative percentage drug release vs. log time*.

- $n = 0.5$, indicates pure Fickian diffusion.
- $n = 0.5-1$ or $0.45-0.89$ indicates anomalous non-Fickian diffusion *i.e.*, the rate of solvent penetration and drug release are in the same range. This deviation is due to increased drug diffusivity from the matrix by the solvent-induced relaxation of the polymers.
- $n = 0.89$ or 1 indicates zero-order release which can be achieved when drug diffusion is rapid compared to the constant rate of solvent induced relaxation and swelling in the polymer (case 2 transport for swellable polymer).

Ø and Ψ values of various powder materials when used with various liquid vehicles are listed [4]

Powder excipients	Ø Values		Ψ Values	
	PEG 400	Propylene glycol	PEG 400	Propylene glycol
Avicel PH102	0.005	0.16	0.242	0.224
Avicel PH200	0.02	0.26	0.232	0.209
Cab-O-Sil M5 (Silica) with Avicel PH102	3.26	3.31	0.653	0.560
Cab-O-Sil M5 (Silica) with Avicel PH200	2.44	2.56	0.717	0.712

Diffusional exponent n and mechanism of diffusional release from swellable controlled release systems of different geometrics

Slab	Cylinder	Sphere	Drug release mechanism
0.5	0.45	0.43	Fickian diffusion
0.5-1.0	0.45-0.89	0.43-0.85	Anomalous transport (Non-Fickian)
1.0	0.89	0.85	Zero order
1.0	0.89	0.85	Case 2 transport
1.0	1.0	1.0	Super case 2 transport

Examples of drugs which were successfully formulated and incorporated into liquisolid compacts so far includes

Reference number	Drug	Carrier material	Coating material	Liquid vehicle
40	Atorvastatin	Avicel PH 102	Aerosil 200	PEG 400, PG
41	Bromohexine HCl	Avicel PH 102	Aerosil 200	PG
42	Diclofenac sodium	Avicel	Aerosil	PG
43, 44	Aceclofenac	MCC	Colloidal silica	PEG 400, PG, Tween 80
45		DCP, MCC	HPMC	
46	Carbamazepine	Avicel PH 102	Aerosil 200	PEG 200
47	Griseofulvin	Avicel PH 102	Cab-O-Sil M5	PEG 400
48	Ezetimibe	Avicel PH 102	Aerosil 200	PEG 400, PG
49	Famotidine	Avicel PH 102	Aerosil 200	PG
50	Valsartan	PVP K 30	Colloidal silica	PG, PEG,
51	Piroxicam	MCC	Colloidal silica	Polysorbate 80
52	Repaglinide	Avicel PH 101	Calcium silicate	Polysorbate 80
53	Rofecoxib	Cab-O-Sil M5P	Amorphous fumed silica	PG, Glycerol
54	Tramadol	Avicel PH 102	Aerosil 200	PG
55	Lansoprazole	Avicel PH 102	Aerosil 200	PEG 400
56	Propranolol	Eudragit RL/RS	Silica	Polysorbates 80
57	Nimesulide	MCC, HPMC E15, Starch	Silica gel	PEG 400
58	Naproxen	Avicel PH 102	Cab-O-Sil M5	Cremophor EL
59	Meloxicam	Avicel PH 102	Aerosil 200	PEG 200, PEG 400
60	Ibuprofen	Avicel PH 101	Aerosil	PEG 300
61	Indomethacin	MCC	Amorphous silicon dioxide	Tween 80
62		Avicel PH 102, DCP	HPMC	PEG 400

Fig 1. Different methods to enhance the solubility of BCS class II drugs

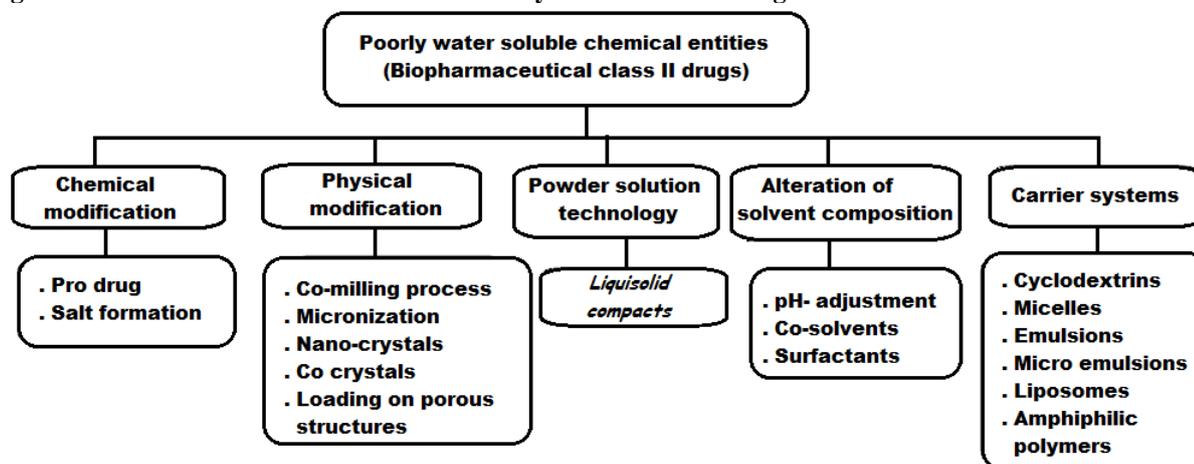


Fig 2. Comparison of wettability between Conventional tablet (A) and Liquisolid tablet (B)

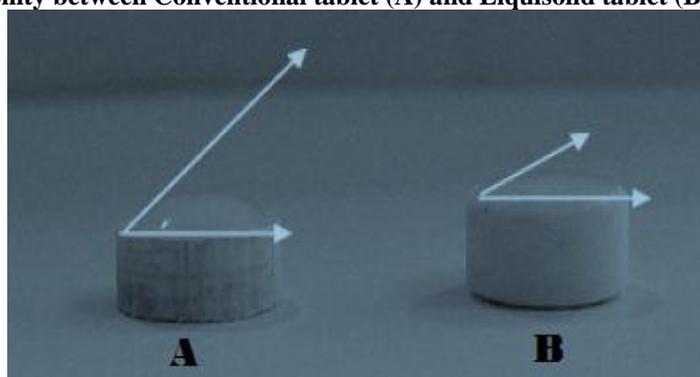


Fig 3. General procedure for formulation of Liquisolid tablets

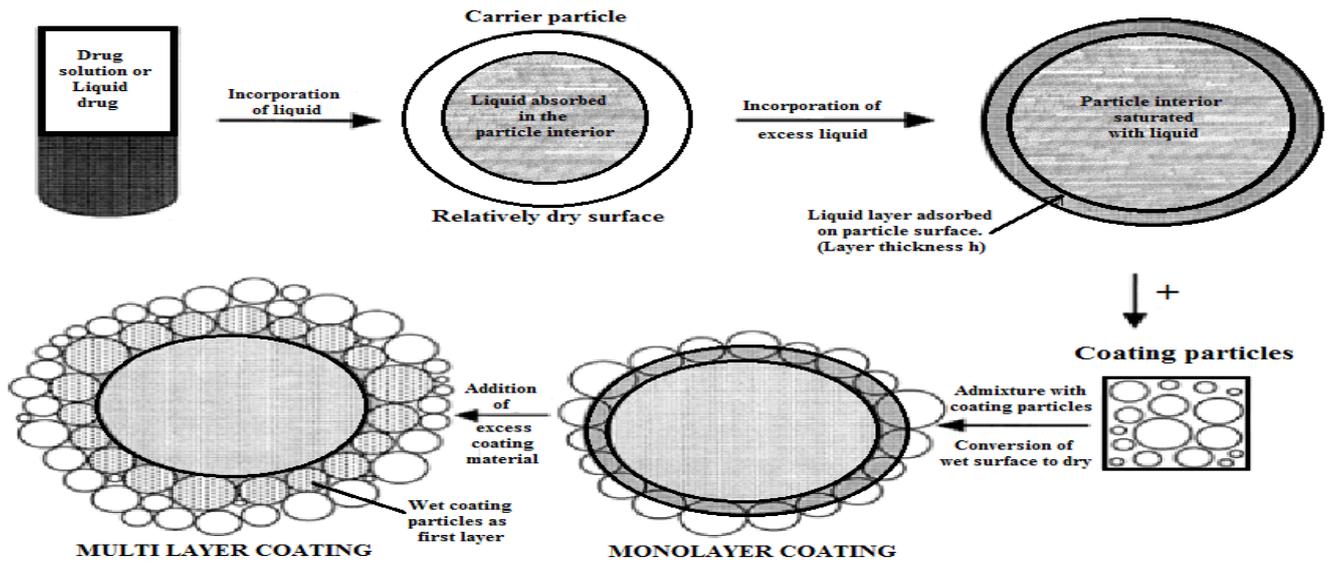


Fig 4. Schematic representation of formulation of Liquisolid tablets

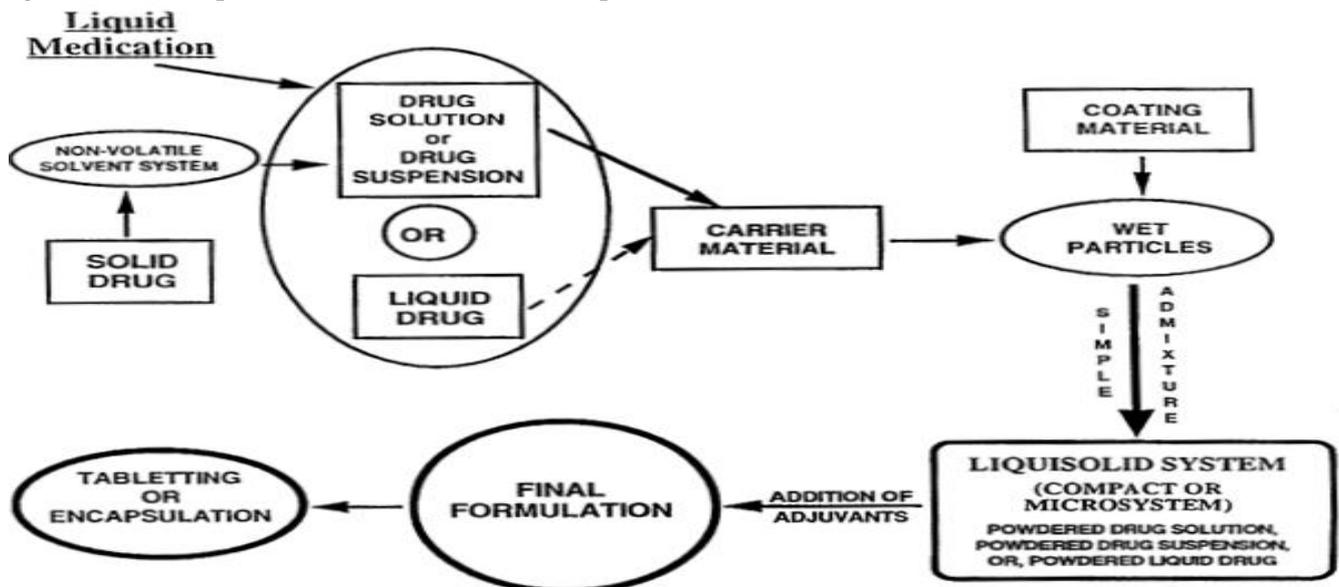
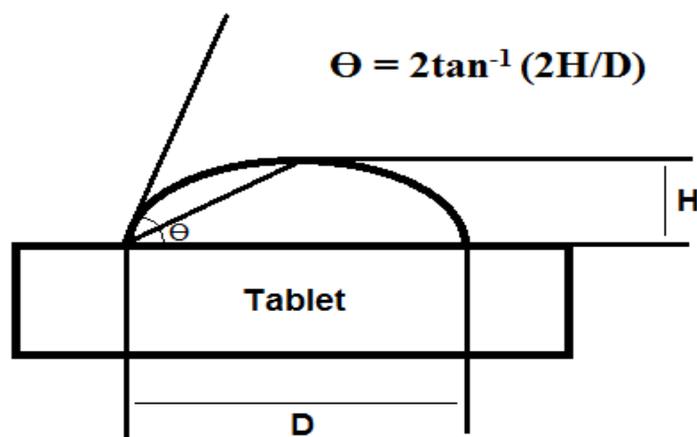


Fig 5. Schematic representation of contact angle measurement using imaging method



CONCLUSION

This technique is a promising alternative for formulation of BCS class-II (water insoluble solid drugs and liquid lipophilic drugs). The enhanced rate of drug dissolution from liquisolid tablets is probably due to an increase in wetting properties and surface area of drug

particles available for dissolution. Rapid disintegration rates are observed compared to conventional tablets and therefore, they showed improved release rates and hence greater bioavailability. Modification of formulation by use of certain agents cause sustained release of drugs from the liquisolid tablets.

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