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LIQUISOLID TECHNOLOGY: A NOVEL APPROACH TO ENHANCE BIOAVAILABILITY AND SOLUBILITY OF POORLY SOLUBLE DRUGS

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Keywords:

Liquisolid compact, carrier material, coating material, BCS classification

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ABSTRACT

The Preparation of liquisolid systems is a novel technique for improving solubility, dissolution and bioavailability of such drugs. Liquisolid technique is novel and the aim of this technique is solubility enhancement and dissolution improvement and thereby it increases the bioavailability. This technique is based upon the admixture of drug loaded solutions with appropriate carrier and coating materials. Limited solubility is the major challenge for the development of ideal solid unit dosage form. "Liquisolid compact technique" or "the powder solution technology" is a novel and most promising technology for overcoming this consequence. This is the novel technique of oral drug delivery. This approach is suitable to formulate both immediate release and also sustained release formulations. This liquisolid technique is characterized by flow behaviour, saturation solubility, Fourier transform infra red spectroscopy (FTIR), X- ray diffraction, scanning electron microscopy.

INTRODUCTION [2, 4, 8]

In liquisolid technique the drugs are insoluble or poorly soluble drugs are dissolved or dispersed in non-volatile solvent then converted into free flow powder by using carrier material proposed by Spireas et al. Solubility is the important parameter to achieve desired concentration of drug in systemic circulation for pharmacological response. The liquisolid compacts are acceptably compressible powdered forms of liquid medications. The major challenges of present pharmaceutical research are to enhance dissolution, absorption and bioavailability of water insoluble drugs. There are several methods are available to improve these characteristics that are:

1. Reducing particle size to increase surface area
2. Use of pro-drug and drug derivatization such as strong electrolyte salt forms that usually have higher dissolution rates.

   Solubilisation in surfactant systems.
3. Formation of water-soluble complex.

Liquisolid compacts are acceptably flowing and compressible powdered forms of liquid medications. The term liquid medication implies oily, liquid drugs and solutions or suspensions of water-insoluble solid drugs carried in suitable nonvolatile solvent systems termed the liquid vehicles.

Therapeutic effectiveness of a drug depends upon the bioavailability therefore it ultimately depends upon the solubility and dissolution rate of drug molecules. These solubility and dissolution rate are important parameters to achieve desired concentration of drug in systemic circulation for pharmacological response. The Biopharmaceutical Classification System (BCS) is an experimental model that measures solubility and permeability.

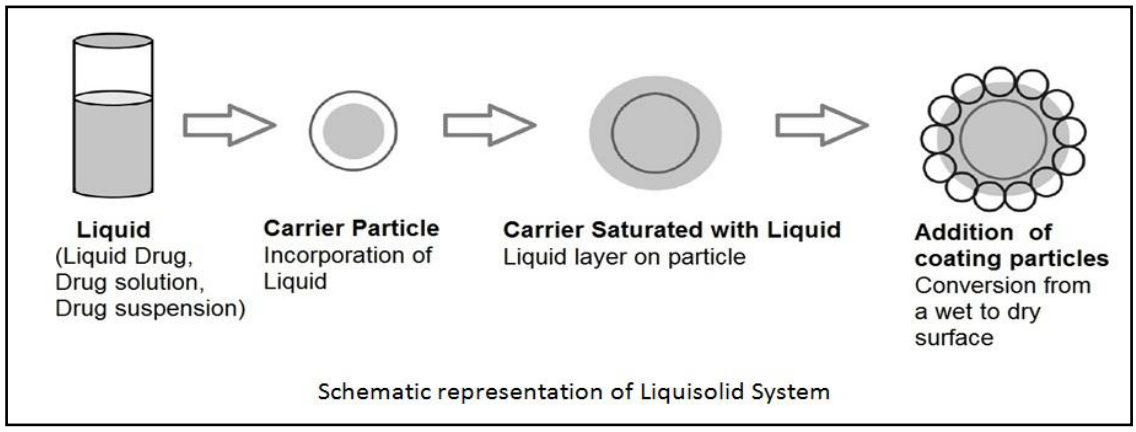

Fig 1. Schematic representation of liquisolid system

BCS CLASSIFICATION

1) Class I: High Permeability and Solubility

The bioavailability of class-I compounds is determined only by delivery of the drug solution to the intestine. Examples: Benzapril, Loxoprofen, Sumatriptan etc.

2) Class II: High Permeability but Low Solubility

The bioavailability of class-II compounds is limited by drug solubility/dissolution. Examples: Albendazole, Aceclofenac, Diazepam, Eprosartan, Erythromycin etc.

3) Class III: low Permeability but High Solubility

The bioavailability of class-III compounds is limited by intestinal permeability. Examples: Gabapentine, Topiramate, Atropine etc.

4) Class IV: Low Permeability and Low Solubility

The bioavailability of class-IV compounds is limited both by solubility or dissolution and intestinal permeability. A drug substance is considered as highly soluble when the highest dose strength is soluble in < 250 ml 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 administered dose. A drug 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 < 900 ml buffer solutions.

Advantages:

1) Better availability of an orally administered water-insoluble drug is achieved when the drug is in solution form.
2) 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.
3) Production cost is lower than that of soft gelatin capsules.
4) 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.
5) Can be used for the formulation of liquid oily drugs.

6) Can be used in controlled drug delivery
7) 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 tablet

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

METHODS OF SOLUBILITY ENHANCEMENT [1,10]

• Particle Size Reduction
 Conventional methods
 Micronization
 Nanosuspension
• Solid Dispersion
• pH adjustment
• High Pressure Homogenization
• Supercritical fluid recrystallization (SCF)
• Sonocrystallisation
• Inclusion Complex Formation-Based Techniques
 Kneading Method
 Lyophilization/Freeze-Drying Technique
 Microwave Irradiation Method
• Liquisolid technique
• Salt formation

Particle size reduction

The solubility of drug is often intrinsically related to drug particle size as a particle becomes smaller, the surface area increases. The larger surface area allows a greater interaction with the solvent which cause increase in solubility. By reducing particle size, increased surface area improves the dissolution properties.

Techniques of Particle Size Reduction

Conventional methods: Conventional methods of particle size reduction, such as spray drying, rely upon mechanical stress to disaggregate the active compound. Particle size reduction is thus permitting an economic, reproducible, and efficient means of solubility improvement. However, the mechanical forces natural to communition, such as milling and grinding, often impart significant amounts of physical stress upon the drug product which may induce degradation. The thermal stress which may occur during communition and spray drying is also a consider when processing of thermo sensitive or unstable active agents. Only by using traditional methods of solubility enhancement it is not possible to increase the solubility of poorly soluble drugs up to desirable level.

Micronization: Micronization is another conventional technique for the particle size reduction. Micronization increases the dissolution rate of drugs through increased surface area; by decreasing particle size, it does not increase equilibrium solubility. Micronization of drugs is done by milling techniques using jet mill, rotor stator colloid mills and so forth micronization is not suitable for drugs having a high dose number because it does not change the saturation solubility of the drug.

Nanosuspension: This technology is applied to poorly soluble drugs that are insoluble in both water and oils. A pharmaceutical nanosuspension is biphasic systems consisting of Nano sized drug particles stabilized by surfactants for either oral and topical use or parenteral and pulmonary administration. The particle size distribution of the solid particles in nanosuspensions is usually less than one micron with an average particle size ranging between 200 and 600 nm.

Hydrotropy: Hydrotropy is a solubilization phenomenon whereby addition of large amount of a second solute results in an increase in the aqueous solubility of existing solute. Concentrated aqueous hydrotropic solutions of sodium benzoate, sodium salicylate, urea, nicotinamide, sodium citrate, and sodium acetate have been observed to enhance the aqueous solubilities of many poorly water-soluble drugs.

Cosolvency: The solubility of poorly soluble drugs in water can be increased by mixing it with some water miscible solvent in which the drug is readily soluble. This process is known as cosolvency and the solvent used in combination are known as cosolvent. Cosolvent system works by reducing the interfacial tension between the aqueous solution and hydrophobic solute. It is also commonly known as solvent blending. There is a dramatic change in the solubility of drugs by addition of organic co-solvent into the water. The co-solvents are

having hydrogen acceptor or donor groups with a small hydrocarbon region. The hydrophobic hydrocarbon region usually interferes with the hydrogen bonding network of water which consequently reduces the intermolecular attraction of water while the hydrophilic hydrogen bonds ensures water solubility.

Solubilisation by Surfactants: Surfactants are molecules with distinct polar and nonpolar regions. Most surfactants consist of a hydrocarbon segment connected to a polar group. The polar group can be anionic, cationic, zwitterionic or nonionic. When small polar molecules are added they can accumulate in the hydrophobic core of the micelles. This process of solubilization is very significant in industrial and natural processes. The addition of surfactants may decrease the surface tension and increase the solubility of the drug within an organic solvent. The use of surfactants to improve the dissolution performance of poorly soluble drug products is possibly the fundamental, chief, and the oldest method. Surfactants are the agent's which reduces surface tension and enhance the dissolution of lipophilic drugs in aqueous medium. The surfactants are also used to stabilize drug suspensions. When the concentration of surfactants more than their critical micelle concentration (CMC, which is in the range of 0.05–0.10% for most surfactants), micelle formation occurs which entrap the drugs within the micelles. This is known as micellization and generally results in enhanced solubility of poorly soluble drugs.

Solid Dispersion: Solid dispersion as group of solid products consisting of at least two different components, generally, a hydrophilic matrix, and a hydrophobic drug. The matrix can be either crystalline or amorphous. The drug can be isolated molecularly, in amorphous particles or in crystalline particles. Solid dispersion can also be referred as the dispersion of one or more active ingredients in an inert matrix at solid state prepared by the melting, solvent, and melting solvent method. The most commonly used hydrophilic carriers for solid dispersions include polyvinylpyrrolidone, polyethylene glycols, Plasdone-S630. Many times surfactants may also used in the formation of solid dispersion. Surfactants like Tween-80, Docusate sodium, Myrj-52, Pluronic-F68 and Sodium Lauryl Sulphate are used.

pH adjustment: Poor water soluble drug may potentially dissolve in water by applying a pH change. To access the solubility of this approach, the buffer capacity and tolerability of the selected pH are important to consider. Solubilized excipients that increase environmental pH within the dosage form to a range higher than pKa of weekly acidic drugs increase the solubility of that drug, those excipients that act as alkalizing agents may increase the solubility of weekly basic drugs.

High Pressure Homogenization: High-pressure homogenization has been used to prepare nanosuspension of many poorly water soluble drugs. In this method, the suspension of a drug and surfactant is forced under pressure through a nanosized aperture valve of a high pressure homogenizer. The principle of this method is based on cavitation in the aqueous phase. The cavitation forces within the particles are sufficiently high to convert the drug micro particles into nanoparticles. The concern with this method is the need for small sample particles before loading and the fact that many cycles of homogenization are required.

Supercritical fluid recrystallization (SCF): Those fluids are referred to as supercritical fluids which are having temperature and pressure greater than its critical temperature and critical pressure so as they are acquire properties of both gas and liquid. The best example of this is carbon dioxide. SCF are highly compressible at critical temperatures and allows alteration in density and mass transport characteristics which determines its solvent power due to moderate changes in pressure. As the drug gets solubilized within SCF they can be recrystallized with reduced particle size of drug.

Sonocrystallisation: Recrystallization of poorly soluble materials using liquid solvents and antisolvents has also been employed successfully to reduce particle size. The novel approach for particle size reduction on the basis of crystallization by using ultrasound is Sonocrystallisation. Sonocrystallisation utilizes ultrasound power characterised by a frequency range of 20–100 kHz for inducing crystallization. It's not only enhances the nucleation rate but also an effective means of size reduction and controlling size distribution of the active pharmaceutical ingredients. Most applications use ultrasound in the range 20 KHz-5 MHz.

Complexation: Complexation of drugs with cyclodextrins has been used to enhance aqueous solubility and drug stability. Cyclodextrins of pharmaceutical relevance contain 6, 7 or 8 dextrose molecules (α, β, γ-cyclodextrin) bound in a 1,4-configuration to form rings of various diameters. The ring has a hydrophilic exterior and lipophilic core in which appropriately sized organic molecules can form noncovalent inclusion complexes resulting in increased aqueous solubility and chemical stability. Complexation relies on relatively weak forces such as London forces, hydrogen bonding and hydrophobic interactions.

Co-precipitate method: Active drug is dissolved in ethanol at room temperature and suitable polymer is dissolved in distilled water. Different molar ratios of active drug and suitable polymers are mixed respectively. The mixture is stirred at room temperature for one hour and

the solvent is evaporated. The resultant mass is pulverized and passed through sieve no. 80 and stored in desiccators.

Spray Drying: The solvent evaporation of drug and polymer solution in different ratio is carried out by using spray dryer. The solutions are prepared by dissolving drug in methanol and polymer in distilled water and mix both solutions, which produces a clear solution. The solvent evaporated by using evaporator. The spray dried mixture of drug with polymer is obtained in 20–30 min.

Inclusion Complex Formation-Based Techniques: Among all the solubility enhancement techniques, inclusion complex formation technique has been employed more precisely to improve the aqueous solubility, dissolution rate, and bioavailability of poorly water soluble drugs. Inclusion complexes are formed by the insertion of the nonpolar molecule or the nonpolar region of one molecule (known as guest) into the cavity of another molecule or group of molecules known as host.

MICRO-EMULSION

A micro emulsion is an optically clear pre-concentrate, isotropic, thermo dynamically stable transparent (or translucent) system, containing a mixture of oil, hydrophilic surfactant andhydrophilic solvent which dissolves a poorly water soluble drug. Upon contact with water, the formulations spontaneously disperse (or 'self emulsifies') to form a very clear emulsion of exceedingly small and uniform oil droplets containing the solubilized poorly soluble drug. Micro-emulsions have been employed to increase the solubility of many drugs that are practically insoluble in water, along with incorporation of proteins for oral, parenteral, as well as percutaneous/transdermal use.

Self-Emulsifying Drug Delivery Systems: Self-emulsifying or self-micro emulsifying systems use the concept of in situ formation of emulsion in the gastrointestinal tract. The mixture of oil, surfactant, co-surfactant, one or more hydrophilic solvents and co- solvent forms a transparent isotropic solution that is known as the self-emulsifying drug delivery system (SEDDS).

Salt formation: Dissolution rate of particular salt is usually different from that of parent compound. Sodium and potassium salt of week acid dissolve more rapidly than that of pure salt. Limitation of salt formation includes epigastric distress due to high alkalinity, reactivity with atmospheric water and carbon dioxide leads to precipitation, patient compliance and commercilation.

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 and 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 polysorbate 80) and 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

Preparation of liquisolid tablets

Calculated quantities of drug and non-volatile solvent is accurately weighed in 20 ml glass beaker and then heated to dissolve the drug in that solvent. The resulting hot medication is incorporated into calculating quantities of carrier and coating materials. The mixing process is carried out in three steps as described by Spireas8 et al. During the first stage, the system is blended at an approximate mixing rate of one rotation per second for approximately one minute in order to evenly distribute liquid medication in the powder. In the second stage, the liquid/powder admixture is evenly spread as a uniform layer on the surfaces of a mortar and left standing for approximately 5 min to allow the drug solution to be absorbed into the interior of powder particles. In the third stage, the powder is scraped off the mortar surfaces by means of aluminium spatula and then blended with sodium starch glycolate for another 30 seconds in a similar way to the first stage. This gives final liquisolid formulation to be compressed.

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

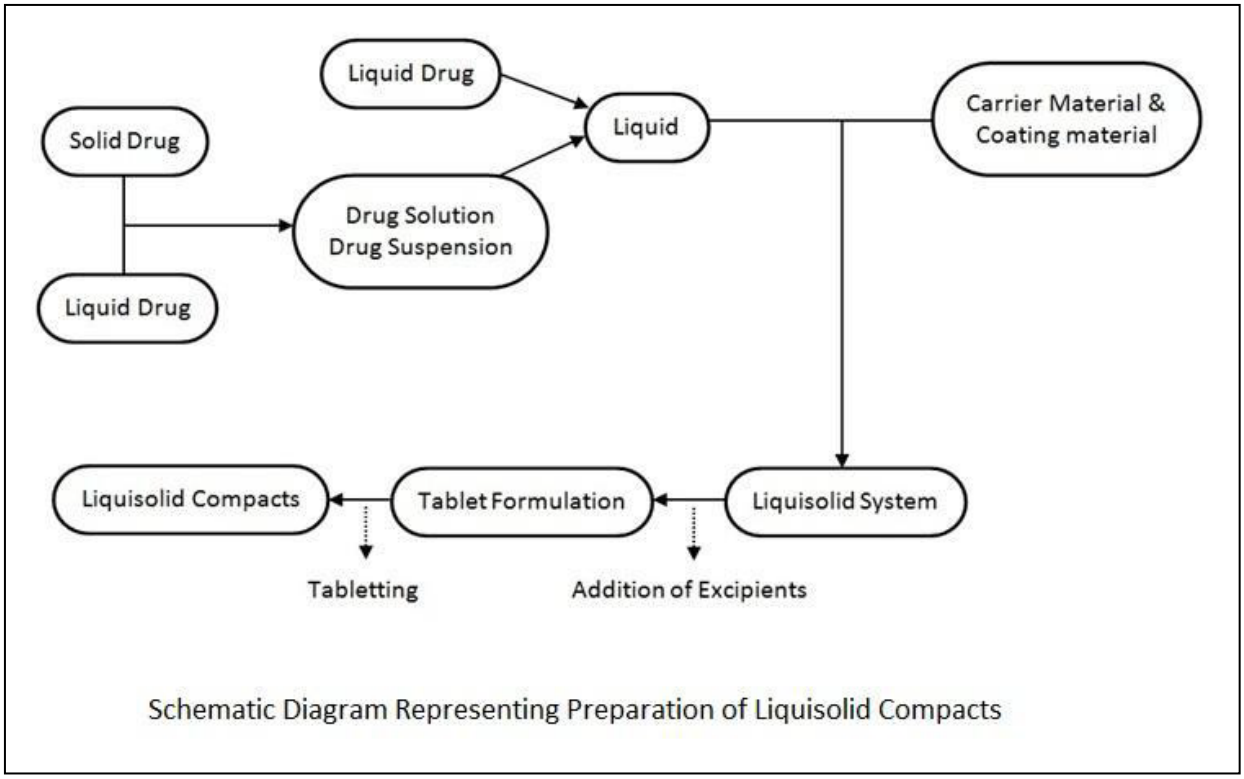

Figure 2: Schematic diagram representing preparation of liquisolid compacts.

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, polysorbate 80 and propylene glycol

Disintegrant

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

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.

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.

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.

MECHANISMS OF ENHANCED DRUG RELEASE FROM LIQUISOLID SYSTEM

- Increased Aqueous Solubility.
- Increased Drug Surface Area.
- Increased Wettability.

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

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.

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.

The Mathematical Model for Designing the Liquisolid Systems

To achieve good flow behaviour and compressibility of liquisolid systems a mathematical model designed by Spireas was used as formulation design model for the liquisolid tablets. Prerequisites for this include suitable drug candidate, suitable non-volatile solvent, carrier and coating materials.

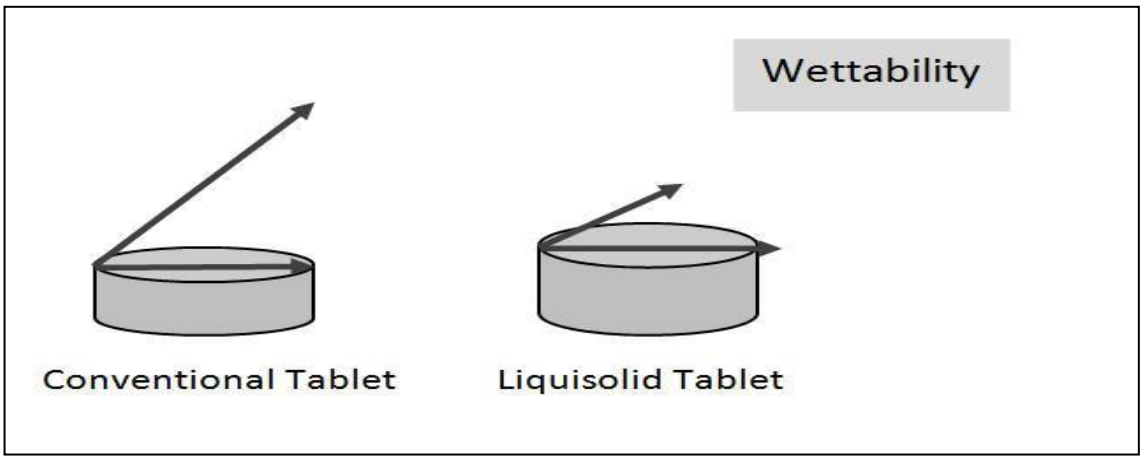

Figure 3: Comparison of wettability between a conventional tablet and a liquisolid Tablet

The Spireas et al model is based on new fundamental properties of powder called "flowable liquid retention potential" (ϕ value) and "compressible liquid retention potential" (ψ value) of powdered excipients used in the formulation. The 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 while the ψ 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 compressible liquid or powder admixture i.e. being able to yield tablets of satisfactory mechanical strength without presenting any liquid squeezing out of liquisolid mass during compression**.** The excipients ratio (*R*) or the carrier: coating material ratio is represented as follows:

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

Where,

R is ratio of carrier (*Q*)

and coating materials (*q*).

For, a successful formulation design, this ratio *R* should be suitably selected. Another term called Liquid load factor (Lf) is defined as ratio of weight of liquid medication (W) to weight of carrier material (*Q*) in system.

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

The ϕ value was used to calculate excipient quantities. Equation derived for this is as follows:

$$Lf = \phi + \phi (1 / R) \quad \ldots\ldots\ldots (3)$$

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

Table no-1 List of several investigated liquisolid systems for enhanced drug release

1	Aceclofenac	13	Loratadine
2	Bromhexine HCl	14	Methyclothiazide
3	Carbamazepine	15	Naproxen
4	Clofibrate	16	Nifedipine
5	Ezetimibe	17	Flutamide
6	Famotidine	18	Piroxicam
7	Fenofibrate	19	Furosemide
8	Felodipine	20	Polythiazide
9	Hydrocortisone	21	Glibenclamide
10	Ibuprofen	22	Repaglinide
11	Indomethacin	23	Glyburide
12	Lamotrigin	24	Griseofulvin

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
10. Application in probiotics.

CONCLUSION

Liquisolid compact refers to formulations formed by conversion of solid state to liquid state, drug suspensions or drug solution in non-volatile solvents into dry, nonadherent, free-flowing and compressible powder mixtures by blending the suspension or solution with selected carriers and coating agents. The formed liquisolid tablets dosage form showed significantly greater extent of absorption due to their solubility and dissolution improvement. The technique is also used to design sustained release systems by using hydrophobic carriers instead of hydrophilic carries in liquisolid systems. Therefore, this formulation of the drug has the potential to be considered for human study in order to be manufactured on large scale.

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