IJPSR (2014), Vol. 5, Issue 12 **(Review Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 28 April, 2014; received in revised form, 26 June, 2014; accepted, 08 August, 2014; published 01 December, 2014

LIQUISOLID TECHNIQUE: A NOVEL APPROACH FOR SOLUBILITY ENHANCEMENT

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Keywords:

Liquisolid technique, bioavailability, poorly soluble drugs, non volatile solvent.

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ABSTRACT: Liquisolid Technique is one of the novel approach for drug delivery system for oral route. Bioavailability of any drug is mainly dependent upon its dissolution rate and dissolution rate is dependent upon solubility of that drug. So, if any drug has less solubility then of course its bioavailability will be less. Hence there is need of enhancement of solubility of poorly soluble drugs for enhancing their bioavailability. There are various methods which are used for enhancing bioavailability of poorly soluble drugs like micronization, nanonisation, supercritical fluid recrystallisation, spray freezing in to liquid, use of surfactants, use of salt forms, pH adjustment, solid dispersion, chemical modification, micellar solubilization.etc. Nowdays liquisolid technique is used as one of the method for enhancing solubility of poorly soluble drugs. Liquisolid technique is also called as "Powdered Solution Technology" In this technique liquid drugs or drug suspensions or solutions of water insoluble solid drugs in suitable nonvolatile solvent system into non adherent, freely flowing, readily compressible powder by blending it using suitable carrier material and coating material. It is also used as a best alternative for soft gelatin capsules.

INTRODUCTION: Solubility of any drug is one of the important factor for bioavailability of that drug. Nowadays there are number of poorly soluble drugs available and hence their formulation is very critical task. Mainly oral route is preferred for administration of the drugs because of patient compliance, convenience and low cost factor. When oral route for administration of the drug is choosen then that drug should be sufficiently dissolved in gastric fluids for its proper absorption. If the drugs have less solubility in the gastric fluids then it will be less available for its absorption and due to this its bioavailability will be less.

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.5(12).5119-26

Article can be accessed online on: www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.5(12).5119-26

Specially class II drugs having less water solubility as well as less permeability. There are various methods for enhancing solubility of drugs like size reduction which includes two methods like micronization, nanonisation, spray freezing in to liquid, supercritical fluid recrystallization, use of cosolvents, use of salt forms, adjustment of pH, solid dispersions, molecular inclusions using cyclodextrin, use of surfectants etc.[1]

Various methods used for enhancing solubiliy and hence bioavailability of the poorly soluble drugs:[2, 3]

Micronization:

This process involves reducing the size of the drug particles to 1 to 10 microns commonly by spray drying or by use of air attrition methods (fluid energy or jet mill).The process is also called as micro milling. e.g. micronization of griseofulvin and several steroidal sulpha drugs.

Nanonisation:
It is the process in which drug powder is converted in to nanocrystals of sizes 200-600nm. e.g. amphotericin B. There are three basic technologies currently in use to prepare nanoparticles.

- Pearl milling
- Homogenisation in water (wet milling as in a colloid mill)
- Homogenisation in non aqueous media.

Use of surfactants:
Surfactants are very useful as absorption enhancers and enhances both dissolution rate as well as permeability of drug. They enhance dissolution rate primarily by promoting wetting and penetration of dissolution fluid into the solid drug particles.

Use of salt forms:
Salts have improved solubility and dissolution as compared to the orignal drug. Alkali metal salts of acidic drugs like penicillins and strong acid salts of basic drugs like atropine are more water soluble than parent drug.

Salt formation has some limitations as follows:

- It is not feasible to form salts of neutral compounds.
- It may be very difficult to form salts of very weak bases or acids.
- The salt may be hygroscopic, exhibit polymorphism or has poor processing characteristics.

Alteration of pH of the drug microenvironment:
This can be achieved in two ways –in situ salt formation and addition of buffers to the formulation. e.g. buffered aspirin tablets.

Supercritical fluid recrystallization:
Supercritical fluids (e.g. carbon dioxide) are the fluids whose temperature and pressure are greater than their critical temperature (Tc) and critical pressure (Tp), allowing it to assume properties of both liqid and gas. At near critical temperature, SCFs are highly compressible allowing moderate changes in pressure to greatly alter the density and mass transport characteristics of a fluid that determines it's solvent power. Once drug particles solubilised in SCFs, they may be greatly recrystallised at greatly reduced particle sizes.

Solid dispersions:
These are generally prepared by solvent or co precipitation method whereby both the guest solute and carrier solvent are dissolved in common volatile solvent system such as alcohol. The liquid solvent is removed by evaporation under reduced pressure or by freeze drying which result in amorphous precipitation of guest in a crystalline carrier.

Molecular encapsulation with cyclodextrin:
The beta and gamma cyclodextrins and their several derivatives are unique in having the ability to form molecular inclusion complexes with hydrophobic drugs having poor aqueous solubility. e.g. thiazide diuretics, barbiturates, benzodiazepines and number of NSAIDs.

Use of Amorphs, Anhydrates, Solvates and Metastable Polymorphs:
Depending upon internal structure of solid drugs, selection of proper form of drug is with greater solubility is important. In general amorphs are more soluble than metastable polymorphs, anhydrates are more soluble than hydrates and solvates are more soluble than non-solvates.

NEED OF LIQUISOLID TECHNOLOGY:
Oral route is mainly preferred for administration of the drugs due to its patient compliance, convenience and low cost. Hence the drug should be sufficiently dissolved in gastric fluid for its maximum absorption. So improvement of solubility of poorly soluble drugs is the key factor for enhancing bioavailability of the drugs. In market there are about 40% of the drugs having poor water solubility and about 55% drugs undergoing problems during formulation. (Specially class II drugs)

Liquisolid technique is also one of the methods of solubility enhancement in which liquid drug or drug suspensions or drug solutions having poorly soluble drugs get converted in to freely flowing, dry, non adherent, readily compressible powder having less particle size.

LIQUISOLID TECHNIQUE:

It is one of the novel techniques which increases solubility and hence increases dissolution rate and hence increases bioavailability of poorly soluble drugs. It is first described by Spires. It is also called as "Powdered Solution Technology". The schematic presentation for the liquisolid system is also shown in **Fig.1**.

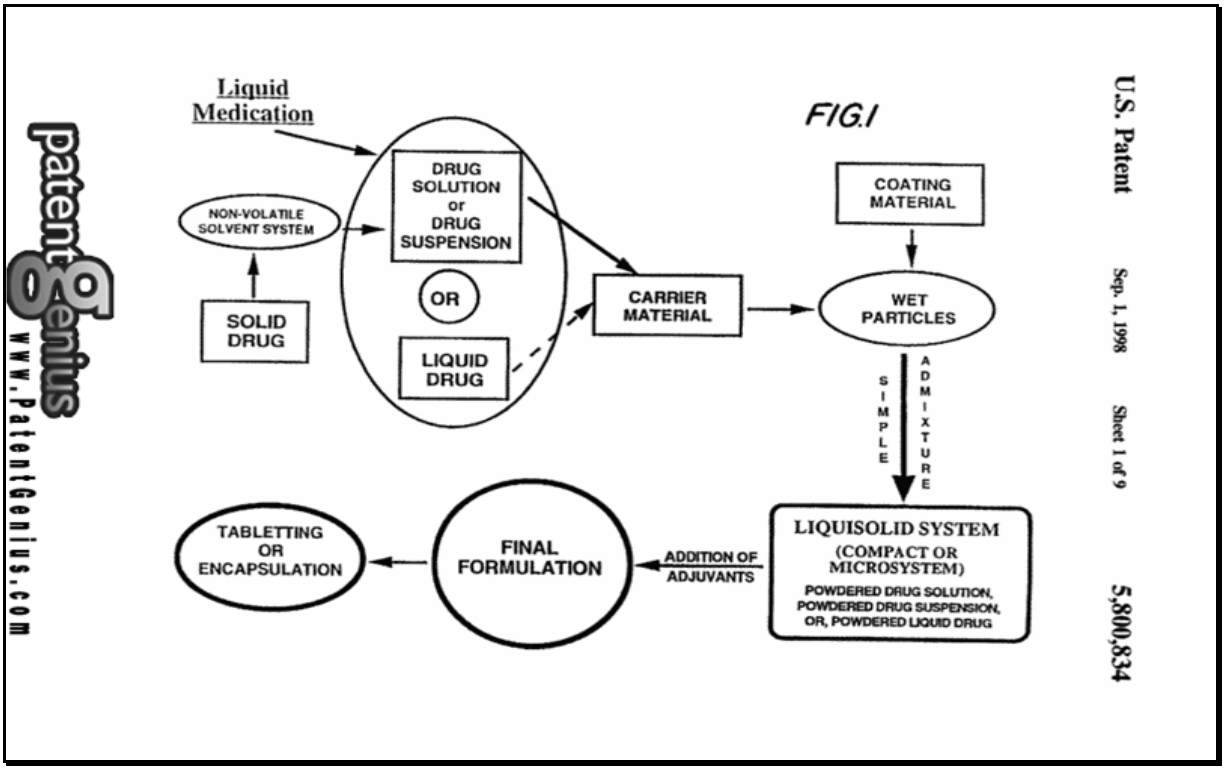

FIG 1: SCHEMATIC PRESENTATION FOR THE FORMULATION OF LIQUISOLID SYSTEM.(SPIREAS S.UNITED STATES PATENT,2002).

During this process poorly soluble drug is mixed with non volatile solvent. This mixture is then incorporated in the suitable carrier material. Then this carrier particle having mixture of drug and solvent is saturated with former non-volatile solvent. After this saturation now the external layer is liquid. This is then coated with suitable coating material. Due to this now the external layer on particle is solid layer which gives dry, free flowing, non adherent, readily compressible powder. Such away liquid drug or drug suspension or solutions of poorly soluble drugs get transformed in to dry, non adherent, freely flowing, readily compresible powdered form.[4, 5]

TYPES OF LIQUISOLID TECHNIQUE:

Based upon liquid medication used:

- Powdered drug suspension.
- Powdered liquid drug
- Powdered drug solutions.

Based upon technique of formulation:

- Liquisolid microsystems.
- Liquisolid compacts.[6]

VARIOUS COMPONENTS USED FOR THE FORMULATION OF LIQUISOLID COMPACTS:

- Non volatile solvent.
- Drug candidate.
- Disintegrant.
- Carrier material.
- Coating material.

Non volatile solvent:
Ideal characteristics:

- It should be inert.
- It should have high boiling point.
- It should be preferably water misscible.
- It should not be highly viscous organic solvent system.

- It should be compatible with having ability to solubilise the drug.
- The non volatile solvents used in the liquisolid system mainly acts as binding agent.
- E.g. PEG 200, PEG 400, Polysorbate 80, Propylene glycol, Glycerine etc.[7]

Drug candidate:
Mainly liquisolid technique is used for drug candidates comes under class II and class IV drugs. Because these drugs are having low solubility and hence having low dissolution rate. By using liquisolid technology dissolution rate of such poorly soluble drugs get improved by improving their solubility.

E.g. Digitoxin, Digoxin, Prednisolone, Hydrocortisone, Famotidine, Spironolactone, Indomethacin, Carbamazepine, Piroxicam, Naproxen, Polythiazides, Chlorpheniramine.etc.

Carrier materials:
Carrier materials should be sufficiently porous so that can enhance absorption properties and hence can absorb liquid sufficiently to enhance the solubility.
E.g. Avicel PH 102 and 200, Eudragit RL and RS, starch, cellulose, lactose, sorbitol.etc.[7]

Disintegrant:
Mainly superdisintegrants increases rate of drug release, its wettability and increases solubility of drug particles within short period of time.
E.g. Sodium Starch Glycolate (SSG), Crosspovidone etc.

Coating material:
Coating material should be such away that having high adsorptive property so that when used for coating the carrier particles can adsorb the excessive non volatile solvent layer over the carrier particles and can give dry solid appearance to the saturated carrier particles having liquid external layer of non volatile solvent. Hence can give dry, non adherent, free flowing powder particles.

E.g. Silica of various grades like Cab-o-Sil M5, Aerosil 200, Syloid 244 FP etc.[4, 8]

PREFORMULATION STUDIES:

- Determination of solubility of the drug in different non volatile solvents.
- Determination of angle of slide.
- Determination of flowable liquid retention potential.
- Calculation of liquid load factor(LF)
- Liquisolid compressibility test.

Study of solubility of drug:
This study is carried out by praparing saturated solution of drugs in different nonvolatile solvents. These saturated solutions are prepared by adding excess amount of drug in to non volatile solvent. This solution is then shaked by using shakers for a specific period of time. After shaking this solution is then filtered and is analyzed by using spectrophotometer.

Determination of angle of slide:
This test is performed for testing flow behaviour of the powders. In this flow properties are measured using a well polished metal slide. A required amount of powder is weighed and is taken on the metal slide. This metal slide is raised by its one end till powder particles on the slide starts to flow. Then the angle between the horizontal surface and the slide is measured which is nothing but the angle of slide. Angle of 33^{o} is considered as optimum angle of slide.[9]

Determination of flowable liquid retention potential: (Φ value)

The term liquid retention potential is nothing but it is the ability of the powder to retain specific amount of liquid in to it and also maintain good flow behaviour.

The Φ value is defined as maximum amount of liquid retained per unit weight of the powder material in order to show flow ability in an acceptable range.
Φ value can be calculated by using following formula.
Φ value =weight of liquid /weight of solid.

Calculation of liquid load factor:
For this various concentrations of non volatile solvent are taken and specific amount of drug is dispersed in it. This mixture is added in to the

coating material-carrier material admixture and it is blended. After this drug loading factors are calculated for determining amount of each carrier and coating material in each of the formulation.
Formula: Loading factor=Wt. of liquid medication/wt. of carrier material.[5]

Compressibility for liquisolid tablets:
This test is used to determine Φ value and involves similar steps as preparing drug-non volatile solvent mixture. Addition of admixture of carrier and coating materials into it. After that compression of it into liquisolid tablets is take place. Then determination of avg. hardness, avg. liquid content of tablets as well as determination of spunge index, Φ value, loading factor and plasticity of the liquisolid tablets.

FORMULATION OF LIQUISOLID TABLETS:
Various steps for preparation of liqusolid tablets are as follows:

- Suitable drug candidate is dispersed in suitable non volatile solvent like Polysorbate 80, PEG 200 etc. having different Drug: Solvent ratios.
- In this step suitable carrier material with other excipients are added into initial mixture of drug and non volatile solvent. During this continuous mixing in the mortar should be going on.
- In the third step suitable superdisintegrants like sodium starch glycolate or crosspovidone is added in the prepared mixture with continuous shaking in a mortar.
- In this step suitable coating material is added which adsorbs the layer of excess non volatile solvent over the carrier material. Due to this the liquid layer gets converted in the solid layer and this gives the dry, non adherent, free flowing powder particles.
- These formulation steps are also shown in **Fig.2.**
- The final mixture is then allowed to compress by using tablet compression machine.
- The prepared liquisolid tablet is then evaluated for its solubility, dissolution, compressibility, flow ability and also for the physical as well as chemical properties.

ADVANTAGES:

- Liquisolid technique is used mainly for converting liquid drugs or drug suspensions or solutions of poorly soluble drugs in to solid dosage form.
- It is also used to formulate sustained release dosage forms.
- It is also used to formulate controlled drug delivery system.
- Production cost of liquisolid system is also less as compared to soft gelatin capsules.
- It enhances dissolution rate of poorly water soluble drugs by increasing their solubility.
- It is mainly used for class II and class IV drugs for enhancing their bioavailability.
- Its production is also simple as that of tablet formulation.
- It is also used for the formulation of liquid oily drugs.

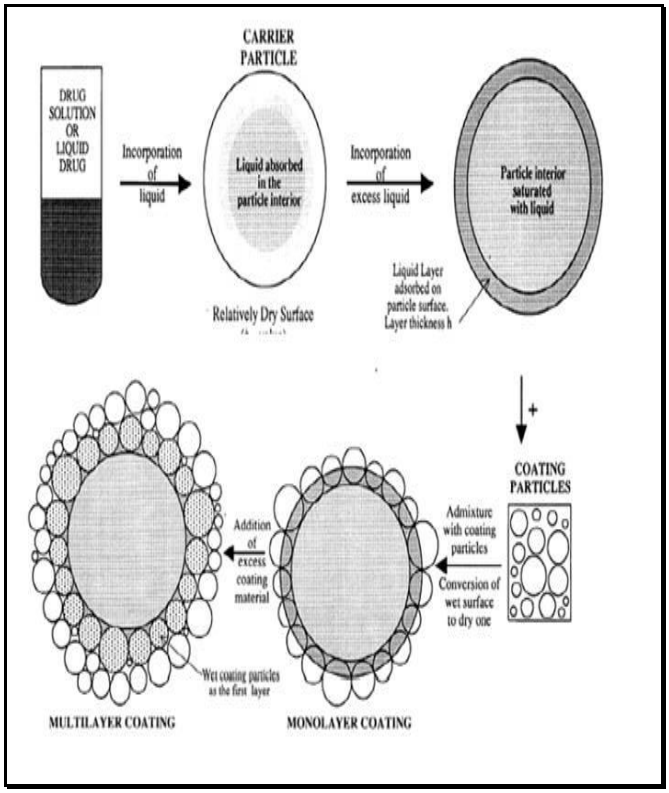

FIG 2: METHOD OF PREPARATION OF LIQUISOLID TABLETS

DISADVANTAGES:

- For maintaining flow ability and compressibility of liquisolid powder in an acceptable range high quantity of carrier and coating materials can be required which can result in increase in weight of the tablet more than 1 gm which is difficult to swallow.
- More efficient excipients are required which have high adsorptive properties which can enhance release rates of the drug from the dosage form.
- The liquisolid systems have less drug loading capacity and it also require high solubility of the drug in a non-volatile solvent.

APPLICATIONS:

- It is used for enhancing rate of dissolution of the many poorly soluble drugs by enhancing their solubiliy.
- Bioavailability of many class II and class IV drugs get enhanced by using liquisolid technique.
- Release rates of many poorly water soluble drugs get increased by using liquisolid system.
- It is also used for designing controlled drug delivery system.
- Liquisolid technique is also successfully used for the formulation of many water insoluble or liquid lipophillic drugs.
- It is also used to formulate sustained release dosage forms.

EVALUATION OF LIQUISOLID TABLETS:

Flow properties:

Checking flow properties of granules is very important factor in the formulation of tablets. Flow behaviour of granules is checked by measuring angle of repose. It is nothing but the angle between the pile of the powder and the horizontal surface on which granules fall through the funnel.

Formula for angle of repose:

$\theta = \tan^{-1} h/r$

where,

θ = angle of repose.

h = distance between the tip of the funnel and horizontal surface.

r = radius of the conical pile.

If the value for angle of repose is $\leq 30^o$ then it shows that powder is free flowing and if it is $\geq 40^o$ then it shows that powder flow is poor.

Flow properties of powder are also determined by calculating Hausner's ratio and Carr's index.

Precompression studies for prepared liquisolid powder system:

For checking suitability of the excipients used Fourier Transform Infrared Spectroscopy, X Ray Diffraction, Differential Scanning Calorimetry, Scanning Electron Microscopy are performed.

X Ray diffraction (XRD):

XRD pattern is checked generally for the drugs, excipients or for physical mixture of drugs and excipients. It is used mainly for determining that drug or excipient in the formulation is in crystalline form or in a solubilized form in a solvent. Appearance of specific constructive peak in the diffractogram shows that drug is in the crystalline form. If that peak is get dissapeared in the diffractogram then it shows that drug is get converted in to amorphous form or in to its solubilized form. This solubilized form of the drug should be there for the liquisolid system which shows that drug is completely solubilized in to the carrier system which helps to improve its solubility and hence enhances its dissolution rate.[5]

Differential Scanning Calorimetry (DSC):

DSC is specifically used for determining whether there are some interactions between drug and excipients or not. If there is absence of any specific characeristic peak of that specific drug in DSC thermogram then it shows that now the drug is molecularly dispersed in the carrier system which is required for liquisolid system.[10]

Scanning Electron Microscopy (SEM):

Scanning electron microscopy shows that there is presence or absence of crystal form of the drug or excipients in the formulation. If SEM shows that there is absence of crystal form of the drug then it shows that now the drug is completely solubilized in to carrier system. After complete formulation liquisolid tablets also get evaluated for wt. variation, thickness, friability, moisture content (by

using Karl Fischer's method),disintegration test, dissolution test and content uniformity.[10]

Stability studies:
In stability studies drug content is determined by charging up the crystals of the drug to accelerated stability conditions according to ICH guidelines. In this study samples are taken after each specific interval of the time. These samples are then analyzed by using spectrophotometer.

Wettability:
For wettability of the liquisolid tablets imaging method is used. In this imaging method contact angle for the liquisolid tablet is measured. The contact angle is measured directly for a drop of liquid rest on the plane surface of the liquisolid tablet. It is measured by measuring the height and radius of the sphere drop on the tablet surface.

Dissolution study:
Dissolution study of liquisolid tablets is carried out using USP II apparatus at $37^{o}C \pm 2^{o}C$. During dissolution study many researchers observed that if there is low drug concentration in liquid formulation then there is rapid drug release from the formulation. If dissolution rates for liquisolid tablets are higher then the absorption rate will also be higher which enhances drug bioavailability.

***In -vivo* bioavailability:**
The bioavailability of any drug from liquisolid system is checked by estimating various pharmacokinetic parameters in the animals like rabbits, beagle dogs etc.

CONCLUSION: Liquisolid technology is one of the efficient method for enhancement of solubility of poorly soluble drugs as well as liquid lipophillic drugs like the drugs come under class II and class IV. Due to enhancement of solubility the dissolution rate of such drugs get increases. This results in increase in the release rate of drug from the formulation which enhances bioavailability of such drugs by increasing their absorption rates. This happens because in liquisolid technique wetting properties of the poorly soluble drugs and their surface area get increases which result in increase in dissolution rate. Mainly non volatile solvents are used for liquisolid technique for enhancing wettability of water insoluble drugs so that can give molecular dispersion in the formulation. The liquisolid technique is also used to design sustained release formulation in which the drug release is sustained by using specific biodegradable polymers. It is also used to formulate controlled drug delivery system.

ACKNOWLEDGEMENT: We would like to express heart full thanks to our beloved parents for their support and blessings, our respected teachers for their valuable guidance and friends/classmates for their support and good wishes for the completion of this review article.

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How to cite this article:
Kapadnis DG and Savakare AD: Liquisolid Technique: A Novel Approach for Solubility Enhancement. Int J Pharm Sci Res 2014; 5(12): 5119-26.doi: 10.13040/IJPSR.0975-8232.5 (12).5119-26.