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LIQUISOLID TECHNOLOGY: A NOVEL APPROACH FOR ENHANCEMENT OF SOLUBILITY AND BIOAVAILABILITY

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ABSTRACT

Liquisolid technique is a new approach for enhancement of solubility and bioavailability of poorly or water insoluble drugs and also for immediate or sustained release formulation through oral route. The liquisolid technique as described by Spires. It is a novel concept of drug delivery that can change the dissolution rate of water insoluble drugs. It is also called as "powdered solution technology"**,** applied to prepare water-insoluble drugs into rapid-release solid dosage forms. It can also useful to formulate liquid medications. Designing of this technique proposed by Spireas & new mathematical model was approached for formulations. The drug is dissolved or dispersed in suitable non-volatile solvent and this liquid medication is converted to free flow powder by using carrier and coating material. By addition of suitable excipients into the powder tablets were formulated by direct compression.

INTRODUCTION

The oral route is the preferred route for drug administration because of high patient compliance and drug development. Because of some problems occurs in this oral route the plasma drug concentration may not be reached. The solubility of the drug is major concern. Solubility is the phenomenon of dissolution of solid in liquid phase. Solubility is one of the major factors to achieve desired concentration of drug in systemic circulation. The poorly water soluble drugs may have poor dissolution rate and incomplete bioavailability. The most of the hydrophobic drugs are sparingly soluble, slightly soluble and very slightly soluble drugs, for such drug substances dissolution is the rate limiting step. The challenge for poorly water soluble drugs is to enhance the dissolution. Therapeutic response of a drug depends upon the bioavailability which is dependent on the solubility and dissolution rate of drug molecules. Solubility is one of the important parameter to achieve desired concentration of drug in systemic circulation for pharmacological response to be shown. The drugs which are poorly water soluble will be inherently released at a slow rate owing to their limited solubility within the GI contents. The dissolution rate is often the rate determining step in the drug absorption. The challenge for these drugs is to enhance the rate of dissolution or solubility. This in turn subsequently improves absorption and bioavailability. Formulation methods targeted at dissolution enhancement of poorly soluble substances are continuously introduced. There are different types of techniques are available to increase the solubility of poorly water soluble drugs there are as,

1. Micronization
2. Lyophilisation
3. Solid dispersions
4. Complexation
5. Co solvency
6. Chemical modification
7. pH adjustment
8. Solubilisation by surfactants
9. Solid solutions
10. Inclusion complex
11. Salt formation.
12. Nanosuspension
13. High Pressure Homogenization.

These above mentioned techniques have been introduced to increase the dissolution rate, absorption and bioavailability. But some limitations found in these types of techniques. Micronization is the process of size reduction, due to the reduction in particle size the expected dissolution & absorption rates may not be achieved because of fine particles form aggregates/ agglomerates due to increase in surface energy & Vander Waals force of attraction. Solid dispersions are important for improving solubility, wettability, dissolution rate and bioavailability of drugs. However, only few products are available commercially, because of their poor physical characteristics for dosage form formulation. Solid dispersions prepared by melting technique may leads to stability problems. Salt formation leads to hygroscopicity and may be caused by stability problems. By the use of co solvents precipitation may occurs upon dilution. To overcome all these types of problems the "Liquisolid Technique" is introduce and liquisolid technology also called as "Powder Solution Technology". It is the most promising & novel techniques to improve the dissolution rates of the poorly water soluble drugs. The concept of powder solution technology is to convert the liquid drug into free flowing readily compressible powder. Here the liquid drug/ liquid medication is the water insoluble drug and dissolved in a non-volatile solvent. These liquid drugs are converted to free flowing & compressible powder by the addition of suitable excipients like carriers, coating materials, lubricants, disintegrants & glidants etc. The compression can be carried out by direct compression and slugging method.

Liquid medication includes liquid lipophilic drugs and drug suspensions or solutions of solid water insoluble drugs in suitable non-volatile solvent systems. Liquisolid systems refers to powdered forms of liquid medications formulated by converting liquid lipophilic drugs, or drug suspensions or solutions of water insoluble solid drugs in suitable nonvolatile solvent systems, into dry, non-adherent, free-flowing and readily compressible powder admixtures by blending with selected carrier and coating materials. Carrier material refers to a preferably porous material possessing sufficient absorption properties, such as microcrystalline and amorphous cellulose, which contributes in liquid absorption. Coating material refers to a material possessing fine and highly adsorptive particles, such as various types of silica, which contributes in covering the wet carrier particles and displaying a dry looking powder by adsorbing any excess liquid.[1-35]

LIQUISOLID TECHNOLOGY

Liquisolid technique is a new and promising method for change in the dissolution rate of water insoluble drugs. The liquisolid technique as described by Spires. It is a novel concept

of drug delivery that can change the dissolution rate of water insoluble drugs. It is also called as "powdered solution technology", applied to prepare water-insoluble drugs into rapid-release solid dosage forms. In this, a liquid may be transformed into a free flowing, readily compressible and apparently dry powder by simple physical blending with selected 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. 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 by this technique.[12, 15]

CLASSIFICATION OF LIQUISOLID SYSTEMS

The liquisolid systems are classified into two types are as,

1) Based on the formulation technique used, there are two types

a) Liquisolid compacts

b) Liquisolid Microsystems

2) Based on type of liquid medication contained therein, there are 3 different formulation systems are as,

a) Powdered drug solutions

e. g. Prednisolone solution in propylene glycol.

b) Powdered drug suspensions

e. g. Gemfibrozil suspension in Polysorbate 80

c) Powdered liquid drugs

e. g. Clofibrate, vitamins etc.

Non-volatile solvents are used to dissolve the drug, the liquid vehicle does not evaporate so the drug carried as it is throughout the product.[1-22, 25]

COMPONENTS

There are various components used in the liquisolid compact formulations involved in it, they are as, 1) Drug: The drug used in liquisolid systems must be water insoluble, low dose drugs. It must be in BCS class I and IV. e.g: Digoxin, Digitoxin, Prednisolone, Hydrocortisone, Water insoluble vitamins, Fish oil etc.

2) Non-volatile solvent: It must be inert water miscible, not highly viscous and should have high boiling point. e.g: PEG 200 and 400, Glycerin, Span 80 & 90 , Tween 80 & 90, Propylene glycol and Fixed oils etc.

3) Carrier materials: These are highly porous materials & have a wide surface area and the recommended to absorb the drugs on to them. e.g: Cellulose (microcrystalline & amorphous), starch, sorbitol, Lactose, Avicel (pH102), Eudragit RS & RL etc.

4) Coating materials: There are fine materials having a particle size range from 10 nm to 4560 mm in diameter. These must be highly adsorptive to cover the carrier particles and show dry form, e.g: Silica of various grades like cab-o-sil M5, Aerosil 200 and Syloid 244 etc.

5) Disintegrants These are used to break the compacts to smaller particles. e.g: Crosscarmellose sodium, Crosspovidone, Explotab and Pre-gelatinized starch etc.

6) Lubricants: These are intended to reduce the friction. e.g: Stearic acid, Stearic acid salts and Talc etc.

7) Glidants: Intended to promote the flow between particles by reducing the friction. e.g: Silica derivatives, Talc and Corn starch etc.[1-12]

THEORY OF LIQUISOLID SYSTEMS

The powder can retain only certain limited amount of liquid while maintaining the flowability & compressibility. To calculate the quantities of powder excipients required for the formulation of liquisolid system, a mathematical approach is required and it has been developed by Spireas et. al. This approach is based on flowable (Ø-value) and compressible (Ψ-number) liquid retention potential. The flowable liquid retention potential of a powder defined as the maximum amount of a given non-volatile liquid that can be retained inside the bulk (w/w) while maintaining acceptability.

The compressible liquid retention potential of a powder defined as the maximum amount of liquid that can be retained inside its bulk (w/w) while maintaining acceptable compatability to produce suitable hardness & friability.

The Ψ number of powders may be determined using new method called ‘pactisity theories’ to evaluate compaction properties of powders.

Depending on the excipients ratio (R) or carrier : coating ratio.

$$R= Q/q$$

Where,

R= ratio between carrier & coating materials

Q=weight of carrier

q= weight of coating material

The free flowing and compressible liquisolid systems can be prepared if the liquid on the carrier should not exceed the maximum amount and is termed as liquid load factor. Liquid load factor (f) defined as the ratio of liquid medication and weight of carrier powder.

$$Lf = W/Q.$$

Where,

W = weight of liquid medication

Q = weight of carrier.[12-41]

MECHANISMS INVOLVED IN LIQUISOLID SYSTEMS

Several mechanisms are developed to enhance the drug release. Three important mechanisms include an increase in drug surface area, an increase in aqueous solubility and an improved wettability of drugs.

A) Increased surface area: By increasing the surface area of drug the dissolution of drug with the liquid vehicle is increased. Accordingly with increasing the limit of solubility the undissolved amount is also increases. Hence the drug release rate decreases.

B) Increased aqueous solubility: A relatively small amount of liquid vehicle is not sufficient to solubilize the total amount of drug. But at the solid liquid interface between the particles and dissolution medium, it is possible that a small amount of liquid vehicle diffuses from the total amount along with drug and this less amount of liquid is sufficient to increase the aqueous solubility of drug if it acts as a co solvent.

C) Improved wetting properties: The liquid vehicle can improve the wettability of liquisolid primary particle by acting as a surface active agent or by reducing the surface tension. Wettability of liquisolid systems has been demonstrated by measurement of contact angles and water rising times.[7-22]

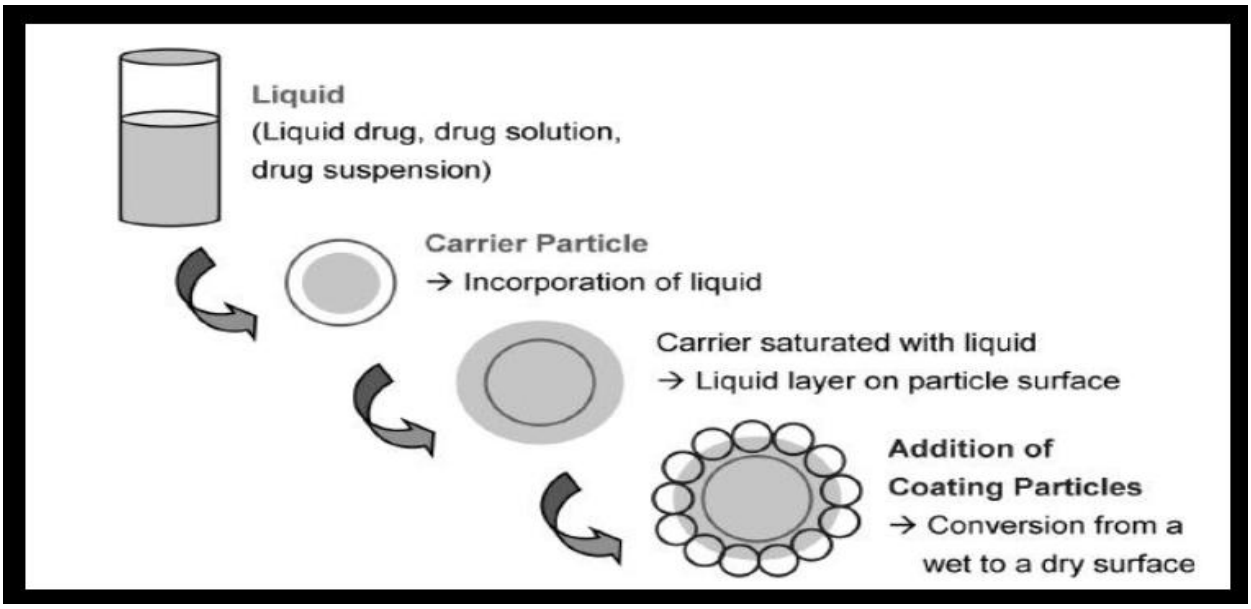

Fig 1: Schematic representation of Liquisolid Systems

ADVANTAGES

1. Formulate slightly and very slightly water-soluble and practically water-insoluble liquid and solid drugs.
2. Increases bioavailability of poorly water soluble drugs.
3. Less production cost compared to soft gelatin capsules.
4. Suitable for industrial production.
5. Suitable for controlled drug delivery
6. Production cost is lower than soft gelatin capsules.
7. useful for formulation of liquid medications
8. Drug release can be modified by changing suitable ingredients
9. Improvement in drug wetting properties and also improving the drug dissolution profiles.
10. Sustained release formulations having water insoluble drugs exhibit zero order release.
11. Exhibits enhanced in-vitro and in-vivo drug release as compared to commercial products, including soft gelatin capsule preparations.
12. Used for formulation of liquid oily drugs.[1-8, 10, 11]

DISADVANTAGES

1. Liquisolid system requires low drug loading capacities.
2. Requires more efficient excipients and it should provide faster drug release with smaller tablet size.
3. Higher amounts of carrier and coating materials are required.[1-6]

LIMITATIONS

1. Not suitable for formulation of high dose water insoluble drugs.
2. If more amounts of carrier is added it increase the flow properties of powder, it may increases the tablet weight too, hence it is difficult to swallow.
3. It does not require chemical modification of drugs.
4. Acceptable compression may not be achieved because the liquid drug may be squeezed out during compression resulting in unsatisfactory tablet weight.[1-10]

PREPARATION OF LIQUISOLID TABLETS

The required quantities of drugs are weighed and then added to the non-volatile solvent. After that it is heated to dissolve the drug. This liquid drug solution is added to the carrier and

coating materials and then it is mixed properly. The mixing process is carried out in three steps as described by Spireas et al. These steps are as,

1. The system is blended at a rate of one rotation per second for approximately one minute in order to distribute the drug evenly in liquid.
2. This admixture is evenly spread over the motor surface and left standing for 5min.to absorbs the drug into the powder particle.
3. Then powder is scraped off and then blended with other excipients for another 30sec. similar to first step. This gives the final formulation of liquisolid tablets.

The liquisolid systems made into compacts by the addition of excipients, lubricants and disintegrants were used for sustained release liquisolid systems.[6-27]

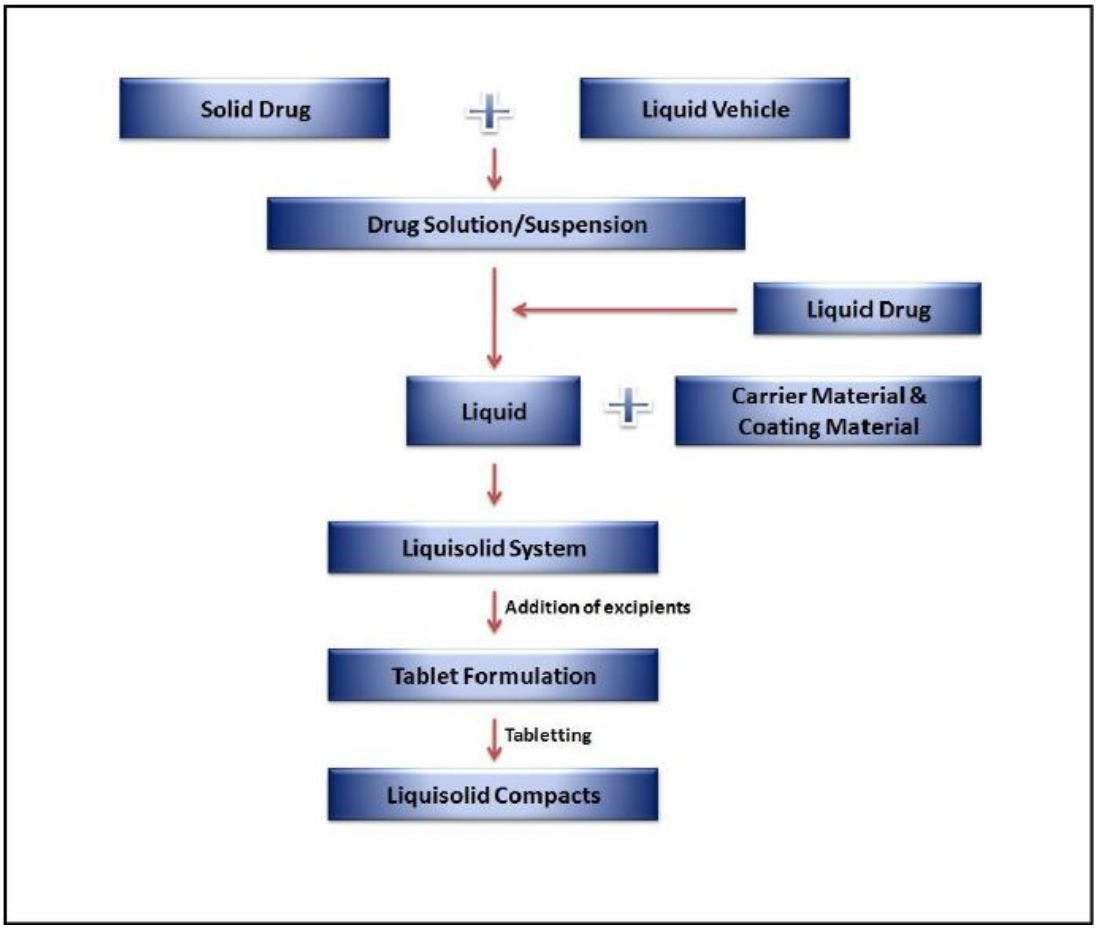

Fig 2: Flow chart of the steps involved in the preparation of liquisolid compacts

EVALUATION OF LIQUISOLID COMPACTS

1. Pre-compression Parameters

Flow Property

Flow property is the important parameter in formulation and industrial production of tablet dosage forms. It includes Angle of repose, Carr's index, bulk density, tapped density, Hausner's ratio etc have been performed.

Fourier Transform Infrared Spectroscopy (FTIR)

FTIR studies are performed to determine the chemical interaction between the drug and excipients used in the formulation. The presence of drug peaks in the formulation and absence of extra peaks indicates that there is no chemical interaction between drug & excipients.

Differential Scanning Calorimetry (DSC)

It is used to determine the interactions between drug and excipients, which shows the success of stability studies. The drug has a characteristic peak, absence of this peak in DSC thermogram indicates that the drug is in the form of solution in liquid formulation and it is molecularly dispersed within the system.

Powder X-ray Diffraction (XRD)

XRD studies are used to determine the crystalline property of liquisolid compact mixture. The disappearance of characteristic peaks and retaining of extra peaks of carriers in the liquisolid formulation is observed. It indicates the drug converted to amorphous form or to stabilized form.

Scanning Electron Microscopy (SEM)

SEM analysis was performed to determine the crystallinity of drug in liquisolid system. The disappearance of crystalline nature shows confirmation about drug is totally solubilized in liquisolid system.

By using the above parameters the liquisolid compacts were evaluate these pre-compression characteristics of the powdered mixture and shows their behavior.[6-8, 12, 15, 17-27]

2. Post Compression Parameters

Hardness

The hardness of tablet is an indication of its strength. Measure the force required to break the tablet. The force is measured in kg and the hardness of about 3-5 kg/cm^2 is considered to be satisfactory for uncoated tablets. Hardness of 10 tablets from each formulation is determined by Monsanto hardness tester, Pfizer hardness tester etc.

Weight variation

The weight variation test is carried out in order to ensure uniformity in the weight of tablets in a batch. First the total weight of 20 tablets from each formulation is determined and the average is calculated. The individual weight of the each tablet is also determined to find out the weight variation.

Friability

Friability is the loss of weight of tablet in the container due to removal of fine particles from the surface. Friability test is carried out to access the ability of the tablet to withstand abrasion in packaging, handling and transport. Roche friabilator is employed for finding the friability of the tablets. Weigh the tablets which have average weight more than 6.5gm from each batch and place in Roche friabilator that will rotate at 25 rpm for 4 minutes. Dedust the all tablets and weigh again. The percentage of friability can be calculated and the limit not exceeds above 1%.

Drug Content

Drug content uniformity test was evaluated for determination of actual weight/content of drug in the liquisolid compact formulations. This consists of comparison of average content of drug found in that formulation.

Disintegration Time

Disintegration test was performed in simulated gastric fluid at 37±0.5°C using Electrolab Disintegration tester by USP. This test consists of six tablets were selected randomly from each batch for their evaluation. It states the time required to break the tablet in the gastric contents & varying temperature conditions.

Dissolution Study

Dissolution study of liquisolid compact formulations were studied by USP type II paddle type apparatus at 37°C±0.2°C temperature. From this study, it shows the amount of drug release from the formulation in percent and their pattern of release kinetics following the mathematical model for dissolution kinetics study.

Stability Study

The stability studies are conducted to know the shelf life of the products. Shelf life is defined as the time requires reducing the concentration of reactant upto 90 percent of its initial concentration. To know the information on the stability of liquisolid systems, the effect of storage on drug release profile and the crushing strength of liquisolid compacts were investigated. Stability studies of liquisolid systems containing hydrocortisone (ambient conditions, 10 months), Piroxicam (24^{o}C/76% R.H., 4 weeks), carbamazepine (24^{o}C/76% R.H., 6 months), Indomethacin (24^{o}C/76% R.H.,12 months) shows the storage at different conditions may not affect the hardness and drug release profile of liquisolid compacts. This indicates that the technology is a promising technique to enhance the release rate without any physical stability problems.

From the above parameters, the formulation shows their nature after the compression also shows the post-compression characteristics behavior of the tablet formulation of compact mixtures.[7-20]

APPLICATIONS OF LIQUISOLID TABLETS

- This technology is powerful tool to improve the solubility & bioavailability of poorly water soluble drugs.
- Rapid release rates are obtained in liquisolid formulations.
- These can be efficiently used for water insoluble solid drugs or liquid lipophilic drugs.
- Sustained release of drugs which are water soluble drugs such as propranolol hydrochloride has been obtained by the use of this technique.
- Solubility and dissolution enhancement.
- Designing of controlled release tablets.
- Application in probiotics.
- Flowability and compressibility.[10, 12, 15]

CONCLUSION

Nowadays there are so many methods are described to improve the bioavailability of drug. Among those the liquisolid technology is the most promising approach for improvement in solubility. Also effective for improving bio-availability in practically water insoluble drugs with non-volatile solvents. The technique also sustained the drug release properties of the water soluble drugs by using suitable biodegradable polymers with appropriate excipient ratios. The liquisolid approach is a promising technology because of the simple manufacturing process, low production costs and the possibility of industrial manufacture due to the good flow and compaction properties of liquisolid formulations.

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