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LIQUISOLID COMPACTS: A REVIEW

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ABSTRACT

At present 40% of the drugs in the development pipelines, and approximately 60 % of the drugs coming directly from synthesis are poorly soluble. The limited solubility of drugs is a challenging issue for industry, during the development of the ideal solid dosage form unit. Liquisolid technique is a novel and promising approach to overcome this consequence. The technique is based upon the dissolving the insoluble drug in the nonvolatile solvent and admixture of drug loaded solutions with appropriate carrier and coating materials to convert into acceptably flowing and compressible powders. The selection of non toxic hydrophilic solvent, carrier, coating materials and its ratios are independent of the individual chemical moieties. The increased bioavailability is due to either increased surface area of drug available for release, an increased aqueous solubility of the drug, or improved wettability of the drug particles.

INTRODUCTION[6-15]

Solubility of drugs is a major factor in the design of pharmaceutical formulations lead to variable oral bioavailability. Dissolution is an important factor for absorption of drugs especially in case of water insoluble or poorly soluble drugs.The rate limiting step for most of the pharmaceutical formulations is dissolution. Various methods used to increase the solubility of poorly water soluble drugs are solid dispersions, inclusioncomplexes with β- cyclodextrins, micronization, eutectic mixtures and spraydrying technique. The new developed technique by Spireas liqui-solid system improves the dissolution properties of water insoluble or poorly soluble drugs. The term 'liqui-solid systems' (LS) is a powdered form of liquid drug formulated by converting liquid lipophilic drug or drug suspension or solution of water-insoluble solid drug in suitable non-volatile solvent systems, into dry looking, non-adherent, free-flowing and readily compressible powdered mixtures by blending with selected carrier and coating materials.Various grades of cellulose, starch, lactose, etc. are used as the carriers, whereas very fine silica powder is used as the coating (or covering) material. The good flow and compression properties of Liqui-solid may be attributed due to large surface area of silica and fine particle size of avicel. Hence, Liqui-solid compacts water-insoluble drugs expected to display enhanced dissolution characteristics and consequently improved oral bioavailability. The in vitro drug dissolution rates of such preparations were compared to those ofconventionally prepared directly compressed tablets using a USP-II apparatus9. Liquid lipophilic drugs (e.g. Chlorpheniramine and Clofibrate) or solid drugs (e.g., prednisone, prednisolone, hydrocortisone, theophylline, Polythiazide and Spiranolactone) dissolved in non volatile, high-boiling point solvent systems (e.g., polyethylene and polypropylene glycols ,glycerin, N,N-dimethylacetamide, various oils) have been formulated in powdered solutions by admixture with various carriers (e.g., cellulose) and coating materials (e.g., silica). This technique has been reported to produce improved dissolution profiles as compared to the commercially available products. Liao11 proposed mathematical expressions for the calculation of the amount of excipients needed for powdered solution formulations. The major drawback of this approach was that the final product exhibited poor and erratic flow ability due to the inadequacy of the proposed model to calculate the appropriate amount of excipients required to produce powder admixtures of acceptable and consistent flow properties. Mathematical model expressions based on powder properties and the fundamentals principles and mechanisms of powdered solutions are derived.

ADVANTAGES OF LIQUISOLID SYSTEMS[1-5]:

• Number of water-insoluble solid drugs can be formulated into liquisolid systems.

• Can be applied to formulate liquid medications such as oily liquid drugs.

• Better availability of an orally administered water insoluble drug.

• Lower production cost than that of soft gelatin capsules

• Production of liquisolid systems is similar to that of conventional tablets.

• Can be used for formulation of liquid oily drugs

• Exhibits enhanced in-vitro and in-vivo drug release as compared to commercial counterparts, including soft gelatin capsule preparations.

• Can be used in controlled drug delivery.

• Drug release can be modified using suitable formulation ingredients

• Drug can be molecularly dispersed in the formulation.

• Capability of industrial production is also possible.

• Enhanced bioavailability can be obtained as compared to conventional tablets.

CLASSIFICATION OF LIQUISOLID SYSTEMS.[13]

Based on the type of liquid medication contained therein, liquisolid systems may be classified into three sub-groups.

- Powdered drug solutions
- Powdered drug suspensions
- Powdered liquid drugs

Powdered drug solutions and suspensions may be produced from the conversion of drug solutions or drug suspensions into liquisolid systems and powdered liquid drugs are produced from the formulation of liquid drugs into liquisolid systems. Simultaneously, based on the formulation technique used, liquisolid systems may be classified into two categories namely,

- Liquisolid compacts
- Liquisolid Microsystems

The term “liquisolid compacts” refers to immediate or sustained release tablets or capsules prepared, combined with the inclusion of appropriate adjuvants required for tabletting or encapsulation, such as lubricants, and for rapid or sustained release action, such as disintegrants or binders, respectively. The term “liquisolid Microsystems” refers to capsules prepared by combining the drug with carrier and coating materials, combined with inclusion of an additive e.g., PVP in the liquid medication wherein the resulting unit size may be as much as five times that of liquisolid Compacts.

THEORY OF LIQUISOLID SYSTEMS[12, 16, 17]:

A powder can retain only limited amounts of liquid while maintaining acceptable flow and compression properties. To calculate the required amounts of powder excipients (carrier and coating materials) a mathematical approach for the formulation of liquisolid systems has been developed by Spireas. This approach is based on the flowable (Φ-value) and compressible (Ψ-number) liquid retention potential introducing constants for each powder/liquid combination. The Φ-value of a powder represents the maximum amount of a given non-volatile liquid that can be retained inside its bulk [w/w] while maintaining an acceptable flowability. The flowability may be determined from the powder flow or by measurement of the angle of repose. The Ψ-number of a powder is defined as the maximum amount of liquid the powder can retain inside its bulk [w/w] while maintaining acceptable compactability resulting in compacts of sufficient hardness with no liquid leaking out during compression. The compactability may be determined by the so-called "pactisity" which describes the maximum (plateau) crushing strength of a one-gram tablet compacted at sufficiently high compression forces. The terms "acceptable flow and compression properties" imply the desired and thus preselected flow and compaction properties which must be met by the final liquisolid formulation.

Depending on the excipient ratio (R) of the powder substrate an acceptably flowing and compressible liquisolid system can be obtained only if a maximum liquid load on the carrier material is not exceeded. This liquid/carrier ratio is termed "liquid load factor Lf [w/w] andis defined as the weight ratio of the liquid formulation (W) and the carrier material (Q) in the system:

$$Lf = W/Q \text{------} (1)$$

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

$$R = Q/q \text{------} (2)$$

The liquid load factor that ensures acceptable flowability (Lf) can be determined by:

$$Lf = \Phi + \varphi . (1/R) \text{ ----- } (3)$$

Where Φ and φ are the Φ-values of the carrier and coating material, respectively. Similarly, the liquid load factor for production of liquisolid systems with acceptable compactability (ΨLf) can be determined by:

$$^{\Psi}L_f = \Psi + \psi \cdot (1/R) \text{ ------- } (4)$$

Where Ψ and ψ are the Ψ-numbers of the carrier and coating material, respectively. Therefore, the optimum liquid load factor (Lo) required to obtain acceptably flowing and compressible liquisolid systems are equal to either ΦLf or ΨLf, whichever represents the lower value.

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

Q0 = W/Lo ----- (5) and q0 = Q0/R ------- (6)

validity and applicability of the above mentioned principles have been tested and verified by producing liquisolid compacts possessing acceptable flow and compaction properties.

MECHANISM OF ENHANCED DRUG RELEASE FROM LIQUID-SOLID SYSTEMS[15-17]:

Several mechanisms of enhanced drug release have been postulated for liqui-solid systems. The three main suggested mechanisms include an increased surface area of drug available for release, an increased aqueous solubility of the drug, and an improved wettability of the drug particles. Formation of a complex between the drug and excipients or any changes in crystallinity of the drug could be ruled out using DSC and XRPD measurements.

a. Increased Drug Surface Area

If the drug within the liqui-solid 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.

b. Increased Aqueous Solubility of the Drug

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

c. 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 liqui-solid primary particles is improved (Fig-3). Wettability of these systems has been demonstrated by measurement of contact angles and water rising times. Many

poorly soluble drugs have been formulated as liquisolid systems showing enhanced drug release. Different liquid vehicles, carrier and coating materials were used to formulate these drug delivery systems.

PREPARATION OF LIQUID SOLID COMPACTS[12, 18, 19]:

As shown in figure, a liquid lipophilic drug (e.g.Chlorpheniramine, Clofibrate, etc.) can be converted into a liqui-solid system without being further modified. On the other hand, if a solid water-insoluble drug (e.g. Hydrochlorothiazide, 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.

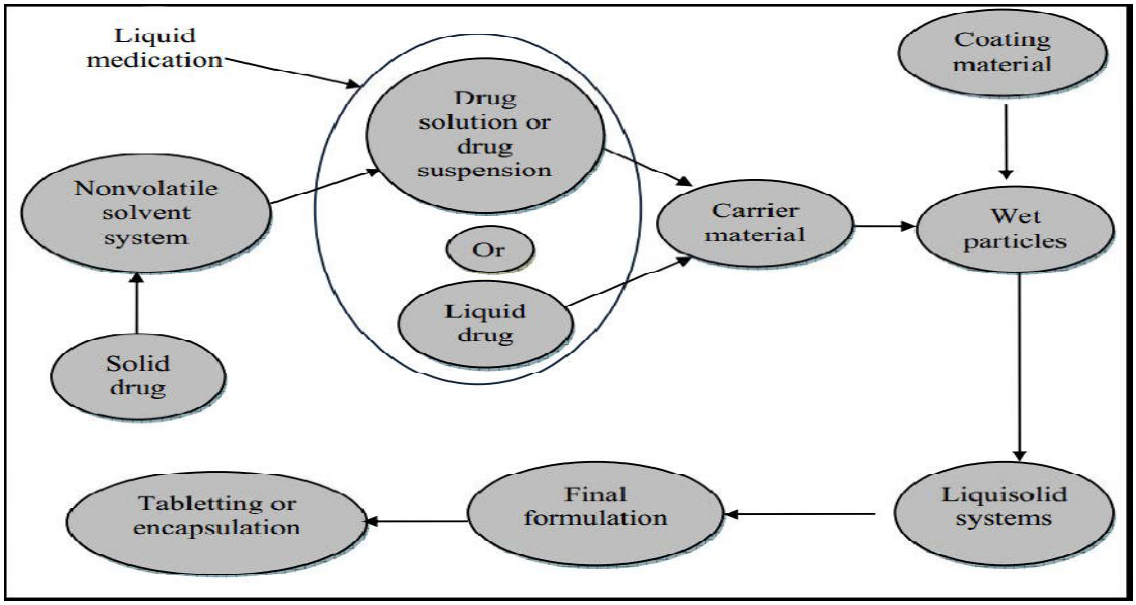

Fig.1: Steps involved in the preparation of liquid solid Systems

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 (silica), are most suitable for this step. Before compression or encapsulation, various adjuvants such as lubricants and disintegrates (immediate) or binders (sustained-release) may be mixed with the finished liqui-solid systems to produce liqui-solid compacts i.e. tablets or capsules.

FORMULATION COMPONENTS:

The major formulation components of liqui-solid compacts are:

Carrier Material[12, 20, 21]:

These are compression-enhancing, relatively large, preferably porous particles possessing a sufficient absorption property which contributes in liquid absorption.

e.g. various grades of cellulose, starch, lactose, sorbitol etc.

Coating Material[12, 18, 19]:

These are flow-enhancing, very fine (10 nm to 5,000 nm in diameter), highly adsorptive coating particles (e.g., 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.

Non-volatile Solvents:

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

Disintegrants:

Most commonly used disintegrant is sodium starch glycolate (Explotab13, Pumogel, etc.)

PRE-COMPRESSION STUDIES:

Flow property[22].

Flow property is important in formulation and industrial production of tablet dosage form. Angle of repose, Carr'sindex, compressibility index, tapped density etc., have to be performed.

Differential scanning calorimetry (DSC) [24, 25].

It is used to determine the interactions between drug and excipients, which indicates 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.

Fourier Transform Infrared spectroscopy (FTIR) [23].

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

X-ray diffraction (XRD) [15]. XRD studies are used to determine the whether the drug is solubilised or in amorphous form. The disappearance of characteristic peaks of drug and their by appearance of peaks which belongs to carrier is observed.

***In vitro* release studies (USP 2005)**

The *in vitro* release studies were performed by using the dissolution apparatus and compared the liquisolid tablets with direct compression tablets. The percentage drug release was estimated.

Scanning electron microscopy (SEM)[24].

SEM analysis was performed to determine the crystallinity of drug in liquisolid system. The Disappearance of crystalline nature of drug indicate that the drug is solubilised in the system.

APPLICATION OF LIQUISOLID TECHNIQUE:

1. Enhanced solubility and dissolution rate

Famotidine[24]

Famotidine is a histamine H2-receptor antagonist that inhibits stomach acid production, and it is commonly used in the treatment of peptic ulcer disease. The liquisolid tablet formulations Famotidine showed higher drug dissolution rates than the conventional directly compressed tablets. The drug release was 78.36% during the first 10 min which is 39% higher than that of the directly compressed tablets

Naproxen[26].

Naproxen is a non-steroidal anti-inflammatory drug (NSAID) commonly used for the reduction of pain, fever, and inflammation. Liquisolid technique changes the properties of naproxen particles by simply dispersing the drug particles in a non-volatile hydrophilic liquid vehicle, which increase the wetting properties of drug particles, and hence improve the dissolution profiles and might improve bioavailability of the drug. At present, naproxen is available commercially in high dose tablets between 250 and 500 mg; the liquisolid formulations may help in reduction of dose.

Bromhexine hydrochloride (BXH) [27].

Bromhexine hydrochloride is a mucolytic agent used in the treatment of respiratory disorders associated with viscid or excessive mucus. BXH has a poor solubility which is a major factor in the design of pharmaceutical formulations. Liquisolid compacts of BXH were distinctly higher as compared to directly compressed tablets, which show significant benefit of liquisolid in increasing wetting properties and surface area of drug available for dissolution.

Carbamazepine[21].

Carbamazepine (CBZ), 5H-dibenzazepine-5- carboxamide, is a sodium channel blocker belongs to BCS class II drug and its bioavailability is limited by its poor dissolution rate in GI. It is used in the treatment of epilepsy and trigeminal neuralgia for over 40 years. Different liquisolid formulations of carbamazepine were prepared by dissolving the drug in the non volatile solvents and adsorbing the liquid medication onto the surface of carrier coating material. In order to reduce

the amounts of carrier and aerosol in liquisolid formulations, some additives polyvinylpyrrolidone (PVP), hydroxypropyle methylcellulose (HPMC) and polyethylene glycol (PEG 35000) were added. The increase in PVP concentration in liquid medication caused a dramatic increase in dissolution rate.

Rofecoxib[29].

Rofecoxib is a practically insoluble nonsteroidal anti-inflammatory drug. The liquisolid tablets of Rofecoxib showed significant increased in dissolution profiles compared to commercial tablets.

Piroxicam[30].

Piroxicam belongs to BCS class II, the rate of its oral absorption is often controlled by the dissolution rate in the gastrointestinal. The dissolution behaviour of piroxicam liquisolid compacts was investigated in simulated gastric fluid (SGF, pH 1.2) and simulated intestinal fluid (SIF, pH 7.2) showed markedly increase in dissolution rate compared to commercial formulations.

2. Enhancement of bioavailability

Atorvastatin calcium[32].

Atorvastatin calcium (ATR) is a BCS class II drug used as a lipid lowering agent by acting as HMG CoA reductase inhibitor. The prepared liquisolid compacts of ATR showed higher release rates compared to the directly compressed tablets. The pharmacokinetic parameters of liquisolid compacts of ATR, such as the AUC, tmax and Cmax, showed the better bioavailability compared with the conventional formulation

Hydrochlorothiazide[33].

Hydrochlorothiazide is often used in the treatment of hypertension and diuretic. The prepared liquisolid formulations of hydrochlorothiazide tablets showed significantly greater extent of absorption and bioavailability than the commercial tablets which was evaluated in beagle dogs.

3. Formulation of Sustained release tablets[34,35].

Sustained release dosage forms are designed to release the drug at a predetermined rate by maintaining a constant drug release for specific period of time with minimum side effects in terms of efficacy, safety and patient compliance. Ideally, controlled release formulations will provide therapeutic concentration of the drug in blood which is maintained throughout Dosing interval.

Propranolol hydrochloride[31].

Propranolol hydrochloride is a β- adrenergic blocking agent having short elimination half-life of 3 hr. Propranolol hydrochloride liquisolid compacts were prepared by dispersing the drug in polysorbate 80 and used hydrophobic carrier, Eudragit RL. This investigation showed that the

release of drug from the formulations followed zero-order release kinetics and Tween 80 has important role in sustaining the release of drug from liquisolid compacts.

Tramadol hydrochloride[36].

Tramadol hydrochloride is a centrally acting opioid analgesic, used in treatment of moderate to severe pain with half life of 5.5hr. Liquisolid sustained release formulations were prepared by using HPMC K4M as a sustained release agent and compared with the marketed preparations. The release profiles of drug followed the Peppas model which is the best-fit model for sustained release dosage forms.

Theophylline[37].

Theophylline is a methylxanthine drug used in therapy for respiratory diseases such as chronic obstructive pulmonary disease (COPD) and asthma. Liquisolid tablets were prepared by mixing liquid medication with silica–Eudragit RL or RS followed by the compaction. The effect of co-solvent and HPMC on theophylline release was determined. The sustained release was enhanced in liquisolid compacts by HPMC.

CONCLUSION

Liquisolid system contains liquid medications in powdered form and this novel technique is an efficient method for formulating water insoluble drugs. Rapid disintegration rates are observed compared to conventional tablets showed improved release rates and greater bioavailability. The use of non-volatile solvent causes increased wettability and ensures molecular dispersion of drug in the formulation. By using hydrophobic carriers can modify release (sustained release) of drugs from the liquisolid tablets.

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