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LATEST REVIEW ON LIQUISOLID TECHNIQUE

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Abstract: The liquisolid technique is a new and promising approach towards dissolution enhancement. Liquisolid compacts possess acceptable flowability and compressibility properties. They are prepared by simple blending with selected powder excipients referred to as the carriers and the coating materials. Many grades of cellulose, starch, lactose etc. can be used as carriers, whereas silica's of very fine particle size can be used as coating materials. In such systems, the drug existed in a molecular state of subdivision and systems were free flowing, non-adherent, dry looking powders. This technique was successfully applied for low dose water-insoluble drugs. Due to significantly increased wetting properties and surface area of drug available for dissolution, liquisolid compacts of water insoluble substances may be expected to display enhanced drug release characteristics and consequently, improved oral bioavailability. Since dissolution of a non polar drug is often the rate limiting step in gastrointestinal absorption, better bioavailability of an orally administered water-insoluble drug is achieved when the drug is already in solution, thereby displaying enhanced dissolution rates. The technique of liquisolid compacts has been successfully employed to improve the in vitro release of poorly water soluble drugs such as Carbamazepine, Famotidine, Piroxicam, Indomethacin, Hydrocortisone, Naproxen and Prednisolone etc.

Keywords: Water insoluble drugs, Dissolution, Bioavailability, Liquisolid compacts

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INTRODUCTION

It is well established that the active ingredient in a solid dosage form must undergo dissolution before it is available for absorption from the G.I.T. The poor dissolution of water insoluble drugs is a substantial problem confronting the pharmaceutical industry. The absorption rate of a poorly water-soluble drug, formulated as an orally administered solid dosage form, is controlled by its dissolution rate in the fluid at the absorption site. The dissolution rate is often the rate-determining step in drug absorption. Therefore, the solubility and dissolution behavior of a drug are the key determinants of the oral bioavailability.

The oral route remains the preferred route of drug administration due to its convenience, good patient compliance and low medicine production costs. In order for a drug to be absorbed into the systemic circulation following oral administration, the drug must be dissolved in the gastric fluids. Thus, one of the major challenges to drug development today is poor solubility, as an estimated 40% of all newly developed drugs are poorly soluble or insoluble in water. In addition, up to 50% of orally administered drug compounds suffer from formulation problems related to their low solubility and high lipophilicity. Bioavailability of poorly water soluble hydrophobic drugs is limited by their solubility and dissolution rate. Several studies have been carried out to increase the dissolution rate of drugs by decreasing the particle size, by creating nanoparticles and microparticles. However, the fine drug particles have high tendency to agglomerate due to van der Waals attraction or hydrophobicity, which both result in a decrease in surface area over time. To overcome the problem, the technique of liquisolid compacts is a new and promising approach towards dissolution enhancement of poorly soluble drugs.

Strategies to increase the amount of dissolved drug at the absorption site:

Together with the permeability, the solubility behavior of a drug is a key determinant of its oral bioavailability. There have always been certain drugs for which solubility has presented a challenge to the development of a suitable formulation for oral administration. Consideration of the modified Noyes-Whitney equation[5] provides some hints as to how the dissolution rate of even very poorly soluble compounds might be improved to minimize the limitations to oral availability.

$$dC/dt = AD(Cs-C)/h$$

Where dC/dt is the rate of dissolution, A is the surface area available for dissolution, D is the diffusion coefficient of the compound, Cs is the concentration of drug at stagnant layer at time t and h is the thickness of the diffusion boundary layer adjacent to the surface of the dissolving compound, C is the concentration of drug at the bulk of the solution.

The main possibilities for improving dissolution according to this analysis are to increase the surface area available for dissolution by decreasing the particle size of the solid and/or by optimizing the wetting characteristics of the compound surface, to ensure sink conditions for dissolution and last but definitely not least, to improve the apparent solubility of the drug under physiologically relevant conditions of these possibilities, changes in the hydrodynamics are difficult to invoke in vivo and the maintenance of sink conditions will depend on how permeable the gastrointestinal mucosa is to the compound as well as on the composition and volume of the luminal fluids. Although some research effort has been directed towards permeability enhancement using appropriate excipients, results to date have not been particularly encouraging. Administration of the drug in the fed state may be an option to improve the dissolution rate and also to increase the time available for dissolution; the likely magnitude of the food effect can be forecasted dissolution tests in bio relevant media.

Over the years, various techniques have been employed to formulate drug delivery systems which would enhance the dissolution profile and, in turn, the absorption efficiency of water-insoluble solid drugs such as digoxin, digitoxin, prednisolone, hydrocortisone, prednisone, spironolactone, hydrochlorothiazide, polythiazide, and/or liquid lipophilic medications such as clofibrate, chlorpheniramine, water-insoluble vitamins, fish oil, etc[3] .

Different approaches have been attempted to increase aqueous solubility of poorly soluble drugs, such as conversion of crystalline molecule to its amorphous state, a particle size reduction via micronization, solubilization in surfactant systems, co-solvency, hydrotropic solubilization, cyclodextrin complexation. However, there are some practical limitations of the above-mentioned techniques[8].

Salt formation may increase hygroscopicity leading to stability problems. Solubilization technique lead to liquid formulations that are usually undesirable from patient acceptability and commercialization. The most common method to increase the surface area of the drug is micronization. But, in practice the effect of micronization is often disappointing, especially when the drugs are encapsulated or tableted. Micronized drugs also have the tendency to agglomerate as a result of their hydrophobicity, thus reducing their available surface area.

Presenting the compound as a molecular dispersion combines the benefits of local increases in the solubility and maximizing the surface area of the compound that comes in contact with the dissolution medium as the carrier dissolves.

Solid dispersions improve solubility, wettability, dissolution rate of the drug. However, only few solid dispersion products are commercially available. This is due to poor physical characteristics for dosage form formulation. Similarly use of large quantity of organic solvent in preparation of solid dispersions may pose environmental and safety concerns. The surface solid dispersions

were introduced to overcome these shortcomings. But still there are limitations of this technique which lie with the use of solvents for preparation of surface solid dispersions. Finding a suitable solvent to dissolve the drug and carrier is difficult. Complete removal of solvent is difficult and residual solvent toxicity should be considered.

Solubilization using surfactants usually defined as the process of incorporation of an insoluble substance into surfactant micelles. Alkhamis et al studied the solubilization of gliclazide by surfactants. They found that anionic and cationic surfactants exhibited good solubilizing ability.

The solubility enhancement by the strategy of co-solvent solubilization can often be accomplished by a combination of water and co-solvent (reduced polarity). The normally used co solvents include propylene glycol, ethanol, glycerol, poly ethylene glycol 400 and dimethyl acetamide. The solubilization of drugs inorganic solvents or in aqueous media by the use of surfactants and co solvents leads to liquid formulations that are usually less desirable from the viewpoints of patient acceptability and commercialization.

The use of aqueous soluble derivatives or salts can improve solubility and dissolution properties and may also enhance the oral absorption. Salt formation is not feasible for neutral compounds and the synthesis of appropriate salt forms of drugs that are weakly acidic or weakly basic may not be achieved in many cases because of the reconversion of salts into aggregates of their respective acid or base forms. The term hydrotropy has been used to designate in solubility of various substances in water, due to the presence of large amount of additives.

Despite their high production cost and technologically demanding, patented and advanced preparations, soft gelatin capsules represent a unique approach for the formulation of liquid oily medications and/or drug solutions of water-insoluble solid drugs. Comparing various digoxin oral solid dosage forms Nelson, in his review, points out that the availability of drug for absorption from various types of oral formulations, usually decreases in the following order: solution, suspension, powdered-filled capsule, compressed tablet, coated tablet.

LIQUISOLID COMPACTS:

The liquisolid technique as described by Spireas a novel concept where 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. Inert, preferably water-miscible organic solvent systems with high boiling point such as propylene glycol, liquid polyethylene glycols, or glycerine are best suitable as liquid vehicles. Once the carrier is saturated with liquid, 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. Microcrystalline cellulose is used as carrier material and amorphous silicon dioxide (colloidal silica) as coating material usually. Various excipients such as lubricants and disintegrants (immediate release) or matrix forming materials (sustained release) may be added to the liquisolid system to produce liquisolid compacts. Liquisolid compacts of poorly water soluble drugs containing a drug solution or drug suspension in a solubilising vehicle illustrate enhanced drug release due to an increased surface area of drug available for release, an improved wettability of the drug particles and an increased aqueous solubility of the drug. Therefore, this enhanced drug release may result in a higher drug absorption in the gastrointestinal tract and thus, an improved oral bioavailability.

The Liquisolid Technique is also used in retarding the drug release. Sustained release oral dosage forms are advantageous with regard to patient compliance because of the reduced dosing frequency. Superlatively, a sustained release dosage form leads to therapeutic plasma levels, which are maintained throughout the dosing interval. It has been pragmatic that by using the hydrophobic carriers such as Eudragit RL and RS in place of hydrophilic carriers, sustained release systems may be obtained. Sustained release from liquisolid compacts with the conventional carrier and coating materials may also be obtained after addition of a matrix forming material such as hydroxyl propyl methylcellulose[12].

Principle of liquisolid compact[11]

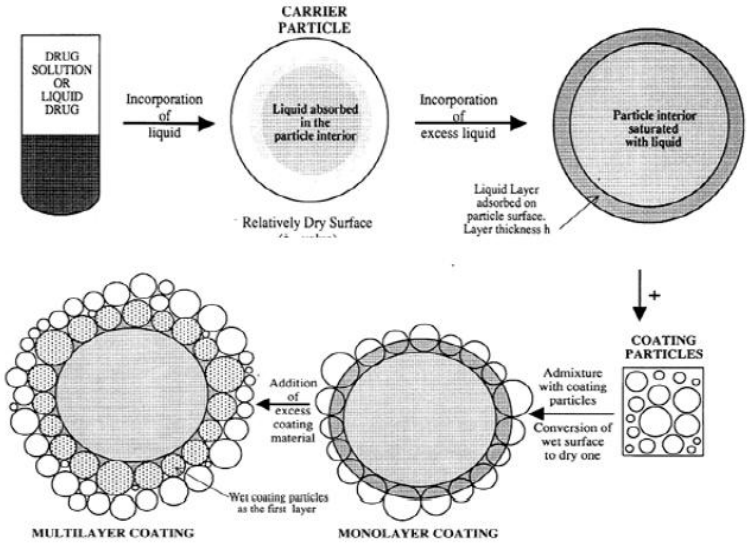

Figure1. Schematic representation of liquisolid systems

With the liquisolid technology, a liquid may be transformed into a free flowing, readily compressible and apparently dry powder by simple physical blending with selected excipients named the 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.

DEFINITIONS[19]

The term "liquid medication" includes liquid lipophilic drugs and drug suspensions or solutions of solid water insoluble drugs in

The term "liquisolid systems" refers to of water insoluble solid drugs in suitable non-volatile solvent systems, into dry, non-adherent, free-flowing and readily compressible powder admixtures by blending with selected carrier and coating materials.

The term "liquisolid compacts" refers to immediate or sustained release suitable powdered forms of liquid medications formulated by converting liquid lipophilic drugs, or drug suspensions or solutions non-volatile solvent systems.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.

The term "flowable liquid-retention potential (Φ-value)" of a powder material describes its ability to retain a specific amount of liquid while maintaining good flow properties. The Φ-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 flowing liquid or powder admixture.

The term "carrier material" refers to a preferably porous material possessing sufficient absorption properties, such as microcrystalline and amorphous cellulose, which contributes in liquid absorption.

The term "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.

The developed mathematical expressions were shown to successfully allow for calculation of the optimum amounts of ingredients required to produce liquid/powder admixtures possessing, to a pre-specified desirable degree, acceptable flow characteristics.

ADVANTAGES [11]

1) A Large number of liquid and solid drugs which are slightly soluble or practically insoluble in water can be converted in to Liquisolid systems.

2) Bio- availability of an orally administered water insoluble drugs can be improved to a significant extent as a result of the increased wettability and improved dissolution profiles of these systems.

3) Cost of production of liquid solid systems is less compared to that of soft gelatin capsules.

4) Liquisolid systems can be used to fomulate particularly the powdered liquid drugs.

5) Increased drug release is achieved as a result of greater drug surface area exposed to the dissolution medium.

6) These can be conveniently formulated into both immediate release and sustained release forms.

7) Optimized sustained release Liquisolid systems demonstrate a consistent dissolution rate (Zero Order Release).

DISADVANTAGES [19]

1) Acceptable flow property and compactabilty for Liquisolid powder formulation is achieved by incorporating high levels of carrier material and coating materials resulting in increased weight of the tablet to above one gram thus leading to difficulty in swallowing the medication.

2) Not applicable for formulation of high dose insoluble drugs.

3) Acceptable compression properties may not be achieved since during compression liquid drug may be squeezed out of the liquisolid tablet resulting in tablets of unsatisfactory hardness. Introduction of this method on industrial scale and to overcome the problems of mixing small quantities of viscous liquid solutions onto large amounts of carrier material may not be feasible

4) Low drug loading capacities.

APPLICATIONS[2]

1. Solubility and dissolution improvement:

In order to overcome the limited solubility of the pharmaceutical, pharmaceuticals were formulated as liquisolid tablets. The method of preparation of liquisolid tablets as well as the effect of various formulation and processing variables on the preparation and the release properties of the tablets were studied y number of scientists. This technique was successfully applied for low dose water insoluble drugs. However, formulation of the high dose insoluble drugs as liquisolid tablets is one of the limitations of the liquisolid technique.

In fact, when the therapeutic dose of drug is more than 50mg, dissolution enhancement in the presence of low levels of hydrophilic carrier and coating material is not significant. But by adding some materials such as polyvinyl pyrrolidone (PVP) to liquid medication (microsystems), it would be possible to produce dry powder formulations containing liquid with high concentration of drug. By adding such materials to the liquid medication, low a mount of carrier is required to obtain dry powder with free flowability and good compatibility.

2. Flowability and compressibility:

Liquisolid compacts possess acceptable flowability and compressibility properties. They are prepared by simple blending with selected powder excipients referred to as the carriers and the coating materials. Many grades of cellulose, starch, lactose, etc. can be used as carriers, whereas silicas of very fine particle size can be used as coating materials.

In order to have acceptable flowability and compactability for liquisolid powder formulation, high levels of carrier and coating materials should be added and that in turn will increase the weight of each tablet above 1 gm which is very difficult to swallow. Therefore, in practice it is impossible with conventional method to convert high dose drugs to liquisolid tablet with the tablet weight of less than 1gm.

In such systems, the drug existed in a molecular state of subdivision and systems were free flowing, on-adherent, dry looking powders. In further studies, compression enhancers were added to these powdered solutions like microcrystalline cellulose. However, the compression of these latter systems resulted in a significant 'Liquid Squeezing Out' phenomenon.

In this system liquid medication is to be mixed with the excipients and then compressed to tablets. It was proved that the smaller the drug concentration in the liquid medication, the more rapid the release rates, since drugs in a high concentration tend to precipitate within the

polymers pores. Polymers possessing large surface areas, and diluents like microcrystalline cellulose of fine particle size and granular grades produced good flow and compression properties, resulting in Acceptable tablets.

3. For designing of sustain release tablet:

Development of sustained release oral dosage forms is beneficial for optimal therapy in terms of efficacy, safety and patient compliance. Ideally, a controlled release dosage form will provide therapeutic concentration of the drug in the blood that is maintained throughout the dosing interval. There are several techniques for preparation of sustained release formulations, among which control of drug dissolution is one of the best and most successful methods due to its simplicity and lowcost. To achieve this aim, several methods have been developed such as preparation of salt form of drug, coating with special materials and incorporation of drugs into hydrophobic carriers. Liquisolid technique is a new and promising method that can change the dissolution rate of drugs. It is claimed that if hydrophobic carriers such as Eudragit RL and RS are used instead of hydrophilic carries in liquisolid systems, sustained release systems can be obtained. Therefore, it is suggested that the method have the potential to be optimized for the reduction of drug dissolution rate and thereby production of sustained release systems.

4. Bioavailability improvement:

In the liquisolid and powdered solution systems the drug might be in a solid dosage form, it is held within the powder substrate in solution, or in a solubilized, almost molecularly dispersed state. Therefore, due to their significantly increased wetting properties and surface of drug available for dissolution, liquisolid compacts of water-insoluble substances may be expected to display enhanced drug release properties, and consequently, improved bioavailability.

CLASSIFICATION OF LIQUISOLID SYSTEMS[17]

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

1. Powdered drug solutions
2. Powdered drug suspensions
3. 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.

Based on the formulation technique used, liquisolid systems may be classified into two categories namely,

1. Liquisolid compacts
2. 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.

THEORY OF LIQUISOLID SYSTEMS:

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[10]. This approach is based on the flowable (Φ-value) and compressible (Ψ-number) liquid retention potential introducing constants for each powder/liquid combinatio (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 L_f [w/w] and is defined as the weight ratio of the liquid formulation (W) and the carrier material (Q) in the system:

$L_f = W/Q$------ (1)

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

R =Q/q------ (2)

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

$L_f = \Phi_{carrier} + \phi_{coating}. (1/R)$ ----- (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 (ΨL_f) can be determined by:

$\Psi L_f = \Psi_{carrier} + \psi_{coating} .(1/R)$------- (4)

Where Ψ and ψ are the Ψ-numbers of the carrier and coating material, respectively.

Therefore, the optimum liquid load factor (L_o) required to obtain acceptably flowing and compressible liquisolid systems are equal to either ΦL_f or ΨL_f, whichever represents the lower value.

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

$Q_o = W/L_o$-----(5) and

$Q_o = Q_o/R$-------(6)

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

Mechanisms of enhanced drug release from liquisolid systems [11]

The three recommended 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.

1. Increased drug surface area

When the drug within the liquisolid system is absolutely dissolved in the liquid vehicle it is positioned in the powder substrate 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.

Consequently, with increasing drug content beyond the solubility limit and thus, increasing fraction of undissolved drug in the liquid vehicle the release rate decreases. It has been pragmatic with various drugs that the release rates are directly proportional to the fraction of the molecularly dispersed drug (F_M) in the liquid formulation. F_M is defined by Spireas as the ratio between the drug's solubility (S_d) in the liquid vehicle and the actual drug concentration (C_d) in this vehicle carried by each system. Therefore,

$$F_M = S_d/C_d$$

Where $F_M = 1$ if $S_d \geq C_d$

2. 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 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. However, at the solid/liquid interface between an individual liquisolid primary particle and the release medium it is possible that in this microenvironment the amount of liquid vehicle diffusing out of a single liquisolid particle together with the drug molecules might be sufficient to increase the aqueous solubility of the drug if the liquid vehicle acts as a co solvent.

3. **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 confirmed by measurement of contact angle and water rising times.

COMPONENTS OF LIQUISOLID SYSTEMS[19]

1. Selection of Solvent

To select the best non-volatile solvent for dissolving or suspending the drug in liquid medication, solubility studies of drug were carried out in different non-volatile solvents. Saturated solutions were prepared by adding excess drug to the vehicles and it was shaked on the shaker for 48hrs at 25°C under constant vibration. After this period the solutions were filtered through a 0.45 µm Millipore filter, and analysed by UV-spectrophotometer at λmax of the drug against blank sample (blank sample containing the same concentration of the specific solvent used without drug). Some of the solvents mentioned can be incorporated to formulate Liquisolid compact viz. Poly ethylene glycol (PEG 200, 400, 600), Propylene Glycol, Polysorbate 80, Glycerol, Tweens, Spans,castor oil and poloxamer 181. The solvent should have the characteristic of a non-toxic and non-volatile solvent.

2. Selection of Carriers and Coating Agents

In this approach the carrier play as a major role in obtaining the dry form of powder from the liquid medication. Each carrier has its unique property; selection of carrier will depend upon liquid holding capacity, flow ability of powder and which, requires less compression force. Some

example of carriers are like microcrystalline cellulose, lactose, di calcium phosphate etc. Amorphous silica (200 nm) was ideal for coating of the formulation.

3. Role of Additive in Liquisolid Compact

Additive mixing was a major advantage in liquisolid compact; it can increase the loading factor. Additives with low viscosity grade polymers such as Hydroxyl propyl methyl cellulose (HMPC E3 LV), Polyvinyl Pyrrolidine (PVP K 25), Poly Ethylene Glycol (PEG 6000) etc., were suitable for enhancement of dissolution rate of drug. For extended release formulation, various grades of polymers can be used viz. Eudragit RS and RL, Guar gum, Xanthan gum Hydroxy Propyl Methyl Cellulose (HPMC K4M) etc.

4. Role of Disintegrants in Liquisolid Compact

Disintegrants are indirectly effect the dissolution parameter since the immediate next step is dissolution. For fast disintegration super disintegrants can be chosen like Sodium starch glycolate, Crospovidone, Croscaramellose etc.

Optimization of Liquisolid Formulations[12]

Optimization of liquisolid compacts with enhanced drug release

The Liquisolid Technique has been successfully useful to low dose, poorly water soluble drugs. The formulation of a high dose, poorly soluble drug is one of the limitations of the Liquisolid Technique. As the release rates are directly proportional to the fraction of molecularly dispersed drug (F_M) in the liquid formulation a higher drug dose requires higher liquid amounts for a desired release profile. Therefore, to obtain liquisolid systems with acceptable flowability and compactability high levels of carrier and coating materials are required. However, this results in an increase in tablet weight ultimately leading to tablet sizes which are difficult to swallow. Therefore, to overcome this and various other problems of the Liquisolid Technique several formulation parameters may be optimized.

Table:1 Optimization of formulation parameters for liquisolid systems with immediate drug release

S.no	Formulation parameters	Optimization	Effect
1.	Liquid vehicle	High drug solubility in vehicle	Increased fraction of the molecularly dispersed drug (F_M)
2.	Carrier and coating material	High specific surface area	Increased liquid load factor(L_f)
3.	Addition of excipient	Polyvinyl pyrollidone (PVP) Superdisintegrant	Increased L_f Increased viscosity of liquid vehicle Inhibition of precipitaion
4.	Excipient ratio(R)	High-R value	Fast disintegration Inhibition of precipitation

In various studies the effect of different types of non-volatile liquid vehicles has been investigated. The results reveals that the selection of a liquid vehicle with a high solubilizing capacity for the drug and thus, an increased F_M, leads to enhanced release profiles. It means that by selection of a liquid vehicle with optimum solubilizing properties the amount of liquid and thus, the weight and size of the liquisolid compacts can be reduced. However, in addition to the drug solubility in the liquid vehicle other physicochemical characteristics of the liquid vehicles such as polarity, viscosity, molecular weight, chemical structure, and lipophilicity may also have an effect on drug release.

A further approach to minimize tablet weight is to increase the liquid load factor by addition of carrier and coating materials with a high specific surface area or by adding PVP to the liquid formulation. It was found that the higher the specific surface area of an excipient the higher the liquid load factor. For instance, the liquid adsorption capacity of microcrystalline cellulose (1.18 m^2/g) is higher than that of lactose (0.35 m^2/g), starch (0.6 m^2/g), and sorbitol (0.37 m^2/g). Fujicalin® (30 m^2/g), a spherically granulated dicalcium phosphate anhydrous, and Neusilin® US2 (300 m^2/g), a magnesium aluminometasilicate, turned out to be very effective excipients for liquid adsorption while maintaining acceptable flow and compaction properties[12]. Khaled[16] observed precipitation and consequently retention of the drug in the cavities of porous excipients upon contact of the liquid formulation with the release medium. This retention could be minimized by using either a diluted drug solution or PVP as crystallization inhibitor. However, PVP may also act as binder during compaction leading to an increase of the liquid load factor.

The release rate of a drug from a dosage form is dependent on its disintegration and the dissolution rate of the drug. Therefore, it is very important for liquisolid systems with enhanced drug release to ensure that disintegration is not the rate-limiting step and drug dissolution is not hindered by a slow disintegration of the dosage form. It was found that the release rate increases by addition of superdisintegrants such as sodium starch glycolate or crosscarmellose sodium to the liquisolid formulation[2].

Another formulation parameter that may be optimized is the ratio of carrier to coating material (R). An increase in the R-value results in an enhanced release rate if microcrystalline cellulose and colloidal silica are used as carrier and coating materials, respectively. Liquisolid compacts with high R-values contain high amounts of microcrystalline cellulose, low quantities of colloidal silica, and low liquid/powder ratios. This is associated with enhanced wicking, disintegration and thus, enhanced drug release. In contrast, if high amounts of colloidal silica are used, which means that the R-value is low, the liquisolid compact is overloaded with liquid formulation due to a high liquid load factor. In such cases, even though drug diffusion out of the primary particles may be rapid, oversaturation might occur resulting in local precipitation/ recrystallization of the drug and thus decreased release rates. Moreover, as colloidal silica is a hydrophobic material high amounts of it can cause retardation of drug release. Therefore, Spireas et al. recommend 20 as a minimum R-value. In the case of liquisolid sustained release compacts lower R-values may be used.

Optimization of Liquisolid formulations with sustained drug release

Sustained drug release liquisolid formulations may be optimized by selection of low R-values, suspensions with a high percentage of undissolved drug and by avoidance of disintegrants. If the R-value is low, which means that the applied amount of silica is high, the liquisolid compacts are overloaded with liquid formulation due to a high liquid load factor. In such cases oversaturation might occur resulting in local precipitation of the drug and thus, decreased release rates[3].Furthermore, the higher the percentages of undissolved drug in the liquid formulation the slower the release rate. This is principally important for poorly soluble drugs, as the dissolution rate of these drugs is low. In addition, as drug release from a tablet is dependent on the disintegration of the tablet and the subsequent dissolution of the drug, the absence of disintegrants, which prevents disintegration, will slow down drug release.

Drugs that can be incorporated into liquisolid systems

Antihistaminic: chlorpheniramine

Antiarrthymic: digoxin, digitoxin

Antihypertensive: nifedipine

Antilipidemics: clofibrate, gemfibrozil

Antiepileptic: Carbamazepine, valproic acid.

Chemotherapeutic agent: etoposide.

Diuretics: Hydrochlorothiazide, methylchlorthiazide, polythiazide, spironolactone.

Glucocorticoids: prednisolone, hydrocortisone, prednisone.

NSAIDS: piroxicam, indomethacin, ibuprofen.

Water-insoluble vitamins: vitamins A, D, E, &K.

PREFORMULATION STUDIES

Solubility studies[4]

For the selection of suitable non volatile solvents solubility studies are used, in this procedure, pure drug was dissolved in different non volatile solvents. Pure drug was added to the above solvents. The saturated solutions were shaken on the rotary shaker for 72 hours at 25 ^{0}C. After 72 hours period the saturated solution were centrifuged for 2 hrs and supernated liquid was analyzed by UV spectrophotometer.

Calculation of loading factor (L_f)

Loading factors were calculated for different carriers, using various solvents. By using L_f = W/Q formula (W: Amount of liquid medication and Q: Amount of carrier material), the drug loading factors were obtained and used for calculating the amount of carrier and coating materials in each formulation. The results showed that if the viscosity of the solvent is higher, lower amounts of carrier and coating materials are needed to produce flowable powder.

Drug- excipient compatibility studies

1. FT-IR

The FT-IR spectra for the samples were obtained using KBr disk method using an FT-IR spectrophotometer (Bruker, Alpha). Samples were mixed with crystalline KBr dried at 60°C for 2 hours in a 1:10 (sample: KBr) ratio and pellets were prepared using hydraulic press. A spectrum was collected for each sample within the wave number region 4,000-400 cm^{-1}. A base-line correction was made using dried potassium bromide and then the spectrum of the pure drug, excipients was obtained.

2. DSC

This was also carried out to find out possible interaction between the drug and polymer. This was performed for pure drug, liquisolid system physical mixture using a thermal analyzer. The sample was sealed in a flat bottomed aluminum pan and the pan was placed in the DSC instrument and The scanning rate was 10°C/min, and the scanning temperature range was between 30°C and 300°C.

3. X-ray diffraction studies

These studies are performed to estimate crystalline properties .For the characterization of crystalline state.

Precompression evaluation of liquisolid systems[2]

1. Angle of repose

The angle of repose physical mixtures of liquisolid compacts were determined by fixed funnel method. The accurately weighed physical mixtures of liquisolid compacts were taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touches the apex of the heap of the powder. The powder was allowed to flow through the funnel freely into the surface. The height and diameter of the powder cone was measured and angle of repose was calculated.

$$\text{Tan } \theta = h/r$$

2. Bulk Density: The loose bulk density and tapped density were determined by using bulk density apparatus. Apparent bulk density was determined by pouring the blend into a graduated cylinder. The bulk volume (V_b) and weight of the powder (M) was determined. The bulk density was calculated using the formula

$$D_b = M/V_b$$

Where, M is the mass of powder, V_b is bulk volume of powder

3. Tapped Density: The measuring cylinder containing a known mass of blend was tapped for a fixed time. The minimum volume (V_t) occupied in the cylinder and the weight (M) of the blend was measured. The tapped density was calculated using the formula

$$D_t = M/V_t$$

Where, M is the mass of powder, V_t is tapped volume of powder.

4.Carr's Index (%) : The compressibility index has been proposed as an indirect measure of bulk density, size and shape, surface area, moisture content and cohesiveness of material because

all of these ca influence the observed compressibility index. The simplest way for measurement of free flow of powder is Carr's Index, a indication of the ease with which a material can be induced to flow is given by Carr's index (CI) which is calculated as follows

CI (%) = [(Tapped density (ρt) – Bulk density (ρb)/ Tapped density(ρt)] x 100

5. Hausner's Ratio: Hausner's ratio is an indirect index of ease of powder flow. It is calculated by the following formula.

Hausner's Ratio=Tapped density (ρ_t) / Bulk density (ρ_b)

Preparation of liquisolid tablets[20]

Preparation of drug solution: For the preparation of liquisolid compacts a non-volatile solvent is chosen for dissolving the drug. Various ratios of carrier to coating materials and ratios of drug to solvents are selected. Desired quantities of drug and solvent were accurately weighed in a beaker and then heated Resulting hot medication was incorporated into calculated quantities of carrier contained in a mortar.

Mixing: The mixing procedure was conducted in three stages. During the first stage, the system was blended at an approximate mixing rate of one rotation/sec for approximately one minute in order to evenly distribute the liquid medication into the powder. In the second mixing stage, calculated quantities of coating material was added to the system and blended for 2 min. the liquid/powder admixture was evenly spread as a uniform layer on the surfaces of the mortar and left standing for approximately 5 min to allow the drug solution to be absorbed in interior of the powder particles. In the third stage, the powder was scraped off the mortar surfaces by means of aluminium spatula , then producing the final liquisolid formulation to be compressed.

Post compression evaluation of liquisolid tablets[17]

1. Weight variation: Twenty (20) tablets from each batch were individually weighed and the average weight and standard deviation were calculated, individual weight of each tablet was also calculated using the same and compared with average weight. Not more than two of the individual weight deviates from the average weight by 10 % and none should deviate by more than twice that percentage. The percent deviation was calculated using the following formula:

% Deviation = (Individual weight – Average weight / Average weight) X 100

2. Thickness: The thickness of liquisolid tablets was determined by using screw guage. Ten individual tablets from each batch were used and the results averaged.

3. Hardness: Hardness (diametric crushing strength) is a force required to break a tablet across the diameter. The hardness of a tablet is an indication of its strength. The tablet should be stable to mechanical stress during handling and transportation.The hardness was tested using Monsanto tester. "Hardness factor", the average of the three determinations, was determined and reported. The force was measured in kilograms per centimeter square.

4. Friability: Permitted friability limit is 1.0 %. Roche's friabilator was used to measure the friability of the tablets. Ten tablets were weighed collectively and placed in the chamber of the friabilator. In the friabilator, the tablets were exposed to rolling, resulting free fall of tablets (6 inches within the chamber of the friabilator). It was rotated at a rate of 25 rpm. After 100 rotations (4 minutes), the tablets were taken out from the friabilator and intact tablets were again weighed collectively.

Percentage friability was calculated using the following equation.

$$\text{Friability} = ([W_O - W] / W_O) \times 100$$

Where,

W_O = weight of the tablet at time zero before revolution.

W = weight of the tablet after 100 revolutions.

5. Disintegration test: Tablets were taken randomly from each batch and placed in each of the six tubes of the USP disintegration apparatus. The time in seconds taken for complete disintegration of the tablet with no palatable mass remaining in the apparatus was measured in seconds

6. Content of uniformity: The content of drug in five randomly selected liquisolid tablets of each formulation was calculated. The five tablets were powdered, from which powder equivalent to 10 mg was dissolved in 100 ml of Solvent by sonication for 30 min and filtered through filter paper. The drug content was analyzed spectrophotometrically by using UV spectrophotometer.

7. Dissolution: Drug release from liquisolid tablets was determined by using dissolution test Apparatus type II (paddle Type).

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 there by increasing the bioavailability.

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