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LIQUISOLID TECHNIQUE: A NOVEL TECHNIQUE FOR ENHANCING DISSOLUTION RATE OF POORLY SOLUBLE DRUG.

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Abstract: The novel feature of this technique is to improve the dissolution rate of poorly soluble drug by delivering the drug as a liquisolid compacts. According to the concept of liquisolid systems, liquid lipophilic drugs, or water-insoluble solid drugs dissolved in suitable non-volatile solvents, may be converted into free-flowing and readily compressible powders by a simple admixture with selected powder excipients referred to as the carrier and coating materials. Due to their significantly improved wetting properties a greater drug surface area is exposed to the dissolution media, resulting in an increased dissolution rate and bioavailability.

Keywords: Liquisolid compacts, Dissolution rate, non-volatile solvents

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INTRODUCTION

About 40% of drug candidates identified via combinatorial screening programmes are poorly water soluble. The aqueous solubility of poorly water-soluble drug is usually less than 100µg/ml. the dissolution rate is rate limiting factor in drug absorption for class II (low solubility and high permeability) and class IV (low solubility and low permeability) drug as defined in the Biopharmaceutics Classification System, BCS. Release enhancement of poorly soluble drug may be achieved by an increase of the drug surface area, the drug solubility, or by formulating in its dissolve state. Various technique have been employed to formulate oral drug delivery system that would enhance the dissolution profile and in turn, the absorption efficiency of water insoluble drug such as drug micronization, solid dispersions, coprecipitation, lyophilization, micro– encapsulation, use of pro-drug and drug derivatization processes, and inclusion of drug solutions into soft gelatine capsules (Kapsi, 2001). Micronization is the most common method used to increase the surface area of the drug, but this becomes less effective when they are formulated as tablets or encapsulations (Aguiar *et al.,* 1979; Finholt, 1968; Lin *et al.,* 1968).

The most promising and new technique for promoting dissolution is the formulation of liquisolid tablets among the various novel technique. Liquisolid technique basically originate form Powder solution technolgy has been implemented to prepare water-insoluble drugs into prompt release solid dosage forms. The Liquisolid techniques are considered as pleasantly flowing and compressible powdered forms of liquid medications. These liquid medications may be regenerated into dry looking or moistureless, nonadherent free-flowing and readily compressible powders by a simple admixture with selected carriers and coating materials. In this technique, the drug might be in solid dosage form and dissolved in solution or a solvent. Drug is solubilized in a maximum molecularly dispersed state. Therefore, this is due to their significantly increased wetting properties and increased surface area of drug available for dissolution. Water– insoluble or poorly water soluble drugs may be expected to have increased dissolution rate properties as well as improved bioavailability.

DEFINITIONS

Liquid medication: liquid lipophilic drugs and drug suspensions or solutions of solid water – insoluble drugs in suitable non volatile solvent systems are called Liquid medication.

Solubility: water insoluble drugs include those drugs that are “sparingly water soluble” (one part solute into 30-100 parts of water), slightly water- insoluble (one part solute into 1000 - 10,000 parts of water) and practically “water-insoluble” or insoluble (one part solute into 10,000 or more parts of water).

The liquisolid technique systems refers to powdered forms of liquid medications formulated by changing to liquid lipophilic drugs or drug suspensions or solutions of water insoluble solid drugs in suitable non-volatile solvent systems into dry-looking, non-adherent, free moderately flowing.

Liquisolid systems based on the type of liquid medication can be classified into three sub groups:

(i)"Powdered drug solutions"

(ii)"Powdered drug suspensions"

(iii)"Powdered liquid drug "

The first two groups may exist or be produced by changing drug solutions and drug suspensions while the third is produced from the formulation of liquid drugs into liquisolid systems.

"Liquisolid compacts": refers to immediate sustained-release tablets or capsules that are described under "liquisolid systems".

"Liquisolid Microsystems": refers to capsules prepared by "liquisolid systems" plus the inclusion of an additive resulting in a unit size that may be as much as five times less than that of a liquisolid compact.

Flowable liquid-retential potential" (ϕ-value): its ability to retain a specific amount of liquid While maintaining good How 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/powder admixture.

compressible liquid-retential potential or ('Ψ-number): its ability to retain a specific amount of liquid While maintaining good compression properties.The Ψ-number is defined as the maximum weight of liquid that can be retained per unit Weight of the poWder material in order to produce an acceptably compressible liquid/powder admixture, i.e., being able to yield tablets of satisfactory mechanical crushing strength (hardness) Without presenting any liquid squeezing out of the liquisolid mass during compaction.

Liquid load factor (Lf): defined as the ratio of the amount of liquid medication (W) over the quantity of carrier material (Q) in the system.

L f = weight of non-volatile solvent(W) / weight of carrier or coating material (Q or q)

Carrier: Coating Material Ratio (R): Ratio between the quantities of carrier (Q) and coating materials (q) present in the formulation.

R = Weight of carrier (Q) / weight of coating material (q)

"Carrier material": refers to a preferably porous material possessing sufficient absorption properties.

"Coating Material": refers to a material possessing fine and highly adsorptive particles.

Calculation of Loading Factor

Loading Factor was calculated by equation:

Loading factor Lf = ΦCa + ΦCo x 1/R

Lf = W/Q

R = Q/q

Where,

ΦCa = liquid retention potential for carrier material

ΦCo = liquid retention potential for carrier material

R = ratio of carrier to coating material; Carrier:Coating

W = weight of liquid medication

Q = amount of carrier material

q = amount of coating material

For R = 5

Lf = 0.132 + 0.5 x 1/5 = 0.232

Q = 100/0.232 = 431

q = 86.2

For R = 10

Lf = 0.132 + 0.5 x 1/10 = 0.182

Q = 100/0.182 = 549.4

q = 54.9

Table no 1: list of some Φ values

Nonvolatile solvents with Φ values				
Carriers	Propylene glycol	PEG 400	Tween 80	PEG 200
Neusilin	0.39	0.33	0.435	0.410
Fugicalin	0.188	0.122	0.270	0.268
Avicel PH 102	0.16	0.005	0.227	0.156
Avicel PH 202	0.26	0.02	0.241	0.09

ADVANTAGE

1) Large number of Bio – Pharmaceutical classification class 2 drugs with high permeability, slightly or very slightly water soluble and practically insoluble liquids and solid drugs can be formulated into Liquisolid systems.

2) Improvement of Bio-availability of an orally administered water insoluble drugs is achieved

3) This principle governs or administers the mechanism of drug delivery from liquisolid systems of powdered drug solutions and it is mainly responsible for the improved dissolution profiles exhibited by this preparations.

4) Drug is formulated in a tablet form or encapsulated dosage form and is held in solubilized liquid state, which confers developed or improved drug wetting properties thereby improving drug dissolution profiles.

5) In this technique, production cost is low compared to soft gelatin capsules.

6) This liquisolid system is specifically for powdered liquid medications.

7) Greater drug surface area is exposed to the dissolution medium.

8) These Liquisolid systems formulate into immediate release or sustained release dosage forms.

9) Optimized sustained release Liquisolid tablets or capsules of water insoluble drugs demonstrate constant dissolution rates (Zero Order Release).

DISADVANTAGES

1) This technique is only for water insoluble drugs.

2) However, for formulation of high dose insoluble drugs the liquisolid tablet is one of the limitations of this technique.

3) In order to achieve acceptable flow ability and compactability for liquisolid powder formulation, high levels of carrier material and coating materials should be added. This will increase the weight of tablets to above one gram which makes them difficult to swallow. Therefore, it is impossible with conventional tablet methods to convert high dose to liquisolid tablets with a tablet weight of less than50 mg. Dissolution profile enhancement occurs in the presence of low levels of hydrophilic carrier, where coating material is not significant.

FORMULATION DESIGN

Non-Volatile solvents: Poly Ethylene Glycol (PEG)-400. PEG- 200, PEG- 4000, PEG- 6000, Polysorbate80, Tween–80, Propylene Glycol (PG), Acrysol EL 135, Transceutol, Labrafill, etc.

Carriers: Avicel® RTM 105, Avicel® PH 102 granular Microcrystalline cellulose (MCC) grade, Avicel ® PH 200 coarse granular MCC grade, experimental grade of granular amorphous cellulose (E.G.C) starch, lactose used as carrier materials. Some novel and easily available carrier like Neusilin and Fugicalin also be used. Neusilin having large surface area 300 m2/gm possessing large amount of liquid adsorbtion and reduce unnecessary weight of Tablet as compare to Avicel (MCC).

Super Disintegrates: Sodium starch glycolate (SSG), Crospovidone, Sodium croscarmellose

Coating Materials: Aerosil® PH 200, Colloidal silica, Cab-O-sil RTM M5 used as coating material. By adding PVP to liquid medication, it would be possible to produce dry powder formulations containing liquid with a high concentration of drug.

General Procedure For Liquisolid Preparation.

The drug was initially dispersed in nonvolatile systems (PEG 200 OR Tween 80) termed as liquid vehicles at different concentration.To this liquid medication, the calculated amount of the carrier was added by continuous mixing in the mortar. Then, coating material was carefully added and mixed until mortar contents start to look like dry powder.To the above binary mixture crosscarmellose as disintegrant and lubricant are added and mixed in mortar.All

liquisolid preparations were compacted into tablets using a rotary press tablet machine having flat-faced punch of 12mm diameter with a compression force that provide acceptable tablet hardness.

Evaluation parameters

Solubility Studies:

Solubility studies were conducted for the selection of high solubility of the pure drug form in the non volatile solvents, This involves pure drug dissolved in different non-volatile solvents. Excess amounts of pure drug were added to the non-volatile solvents, followed by saturation solution transfer to a rotatory shaker for 48 hours at 25 0c under constant vibration. After a 48-hour period the saturated solution was filtered through a 0.45 µm Millipore filter and analyzed.

Bulk properties

Rania et al. (2008) suggested pre compression studies of the Liquisolid powder systems. In the study, he suggested flowability of a powder is of major importance in the production of pharmaceutical dosage forms in order to attain a uniform feed and reproducible filling of tablet dies. The following parameters describe a measure of the flow properties of liquisolid systems that will be selected and compressed into tablets.

Angle of Repose Method:

In this method, a fixed height cone method procedure was performed in triplicate and average angle of repose calculated (Rania *et al.*,2008).

Angle of repose $\text{Tan } \theta = h / r$

Bulk Density:

This procedure involves the fixed height of each liquisolid powder substrate with prepared and fixed weight. This powder was placed in a graduated cylinder and the powder occupation volume measured and initial bulk density D B min calculated. The graduated cylinder was then allow to tap at constant velocity until a constant volume is obtained, when the powder was considered to have reached the most stable arrangement, the final bulk volume was recorded. Final bulk density D B max was then calculated. (Rania *et al.*,2008).

$$\text{Carr's index \%} = \frac{DB\ max - DB\ min}{D^{B\ max}} \times 100$$

"Hausner" s ratio was calculated from the equation

$$\text{“Hausner’s” ratio} = \frac{DB_{max}}{D^{B\,min}}$$

Angle of Slide:

For the determination of angle of slide, an approximately weighed amount of coating material was placed at one end of a metal plate with a polished surface. This end was raised gradually until the plate formed an angle with the horizontal at which the powder was about to slide. This angle θ represents the angle of slide. It was taken as a measure for the flow characteristics of powders. An angle of slide of 330 corresponds to optimal flow properties (Spireas *et al.*, 1999).

Contact Angle:

For assessment of wettability, contact angle of Liquisolid tablets was measured according to the imaging method. To measure the contact angle, a drop of liquid is directly placed on a flat surface of the solid in the–so-called imaging method. The liquid drop is prepared using a saturation solution of the drug in Simulated Gastric Fluid, Simulated Intestinal Fluid media and an excessively large amount of pure drug was added to this media, shaken for 24 hours at a constant rate then the upper solution was centrifuged. A drop of this solution was placed on the surface of the tablet, and pictures were taken using a digital camera. By measuring the height and diameter of the sphere drop on the (Spireas *et al.*, 1999) liquisolid tablets and direct compressed tablets, contact angle was measured. Liquisolid tablet contact angle is less than that of direct compressed tablets. Polysorbate 80 showed the lowest contact angle in the liquisolid tablets.

Dissolution studies on Liquisolid tablets

This entails the optimization of the hardness of the Liquisolid tablet, without applying excessive compression force yet assuring rapid disintegration and dissolution. In other words, tablets should be sufficiently hard to resist breaking during normal handling and yet quickly disintegrate properly after swallowing.

Dissolution rate (DR) is explained according to the “Noyes – Whitney” equation and “diffusion layer model” dissolution theories.

$$DR = (D/h)\, S\, (Cs - C)$$

According to this equation, stagnant diffusion layer thickness is h, and formed by the dissolving liquid around the drug particles. D is the diffusion coefficient of the drug molecules transported through it, S is the surface area of the drug available for dissolution, C is the drug concentration in the bulk of the dissolving medium, Cs is the saturation solution of the drug in the dissolution

medium. Dissolution tests for liquisolid tablets were done at constant rotational speed and in identical dissolution media, thus allowing estimation of the thickness of the stagnant diffusion layer (h). From this equation, dissolution rate is directly proportional not only to the concentration gradient of the drug in the stagnant diffusion layer (Cs- C), but also to its surface area (S) available for dissolution. For estimation and comparison, drug dissolution rates (DR) of drug were used, with amount of drug dissolved per min presented by each tablet formulation during the first 10 minutes.

$$DR = \frac{(M \times D)}{1000}$$

Where, M is the total amount of pure drug in each tablet and D is the percentage of drug dissolved in the first 10 minutes (Spireas *et al.,* 1998)

Importance Of Carrier And Coating Material Ratio(R):

Liquisolid systems pre compression and drug release properties increase with powder excipient ratios (R) from 5:1 to 50:1. A linear relationship exists between the liquid load factors Lf and the reciprocal powder excipient ratios (1/R) required to produce acceptable flowing and readily compressible liquid / powder admixtures. The linear relationship between Lf and the 1/ R plot of liquisolid systems possesses Y intercept and slope equal to the Φ values of the cellulose carrier powder and silica coating material (Javadzadeh *et al.,* 2007)

Liquisolid system dissolution rate profiles are affected by powder excipients ratio R in which results exhibited within the 5 minutes of the dissolution process against the r values 5 to 20 range R values. The dissolution rates increased almost proportionally to R until reaching an apparent maximum plateau at powder excipient ratios greater than 20.

Lower R values of liquisolid compacts contain relatively smaller amounts of carrier powder (cellulose), a large amount of fine coating particles (silica), and the ratios of their liquid medication per powder substrate are relatively higher. From the low liquid / powder ratios, a high presence of cellulose and low presence of silica may be directly associated with enhanced wicking, disintegration, and degradation properties. Low R values should justifiably display relatively poor dissolution profiles. After disintegration, low R values of liquisolid tablets are overloaded with liquid medication producing the primary particles.

On other hand, in some cases, the drug diffusion through the primary particles may be rapid and might lead to overwhelming (solubility- wise) of the stagnant dissolution layers with drug. After maximum levels of dissolution are reached at 35 to 45 R values, a slight gradual decrease of dissolution rate occurs with increasing powder excipient ratios. For R values higher than 50, they may be attributed to the slower diffusion of the liquid medication through the numerous

porous carrier powder particles into which the drug solution has been embedded during the formulation process. To determine the effect of different type of carriers such as Avicel, lactose, starch or sorbitol, dissolve in solution containing 10% w/w of drug in liquid medication. Carriers show the potential to absorb the liquid medication. Large amounts of these carriers are necessary for regenerating liquid medication to dry looking and non adherent powder. Avicel ® PH 102 showed better results, due to its large specific area in comparison with other carriers such as lactose and starch (Javadzadeh *et al.,* 2007).

Type of carrier might affect the unit size of liquisolid tablets. Higher Avicel® PH 102 concentrations show uniform distribution of the drug by either adsorption onto or absorption into the carrier. Between the hydrogen groups, hydrogen bonds on adjacent cellulose molecules in Avicel® PH 102 may account exclusively for the strength and cohesiveness of compacts. Avicel® PH 102 compressibility and compactness characteristics can be explained by the nature if crystalline cellulosic particles themselves which are held together by hydrogen bonds which when compressed, are deformed plastically and a strong compact is formed due to the extremely excessive number of surfaces brought into contact during the plastic deformation, and the strength of the hydrogen bonds are formed (Fahmy *et al.,*2008).

Surface active agent Polysorbate 80 was shown to facilitate wetting of drug particles by decreasing interfacial tension between dissolution medium and the tablet surface. Increase in the wetting properties of liquisolid tablets by the dissolution media is one of the main reasons for the dissolution rate enhancement. High R values 30 to 60 evidence better uniform distribution of the drug in the carrier material (Tayel *et al.,* 2007).

Table no.2 Formulations of liquisolid systems with enhanced drug release

Drug	Nonvolatile solvent	Carrier : coating
Aceclofenac	PEG 400	MCC & HPMC
Bromhexine HCl	PG	MCC & Colloidal Silica
Carbamazepine	PEG 200	MCC & Colloidal Silica
Clofibrate (liquid)	Tween 80	Neusilin & Colloidal Silica
Famotidine	PG	MCC & Colloidal Silica
Glibenclamide	PEG 400	MCC & Colloidal Silica

Ibuprofen	PEG 300	MCC & Colloidal Silica
Indomethacin	PG	MCC & Colloidal Silica
Naproxen	Cremophor® EL	MCC & Colloidal Silica
Piroxicam	Polysorbate 80	MCC & Colloidal Silica
Paliperidone	Tween 80	Neusilin & Aerosile 200

CONCLUSION

In conclusion, Liquisolid technology was effective for improving dissolution rate as well as 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 ratio.

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