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ENHANCEMENT OF SOLUBILITY OF POORLY SOLUBLE DRUGS BY LIQUISOLID COMPACT TECHNIQUE

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ABSTRACT

Most of newly developed drugs of about 40-50% are lipophilic and poorly water soluble. Enhancement of dissolution and bioavailability of the drugs is a major challenge for the pharmaceutical industry. Liquisolid compacts were used to formulate water insoluble drugs in non volatile solvents and convert to acceptable flowing compressible powders by blending with selected powder excipients. By using this method dissolution rate and bioavailability of Biopharmaceutics Classification System (BCS) class-2 drugs can be increased. It is a novel and advanced approach to tackle the issue. The objective of this article is to present over view of liquisolid technique and its applications in pharmaceutical industry and also study the methods of pre compression parameters like Angle of repose, Bulk density, Tapped density, Carr's index and Hausner's ratio and post compression parameters such as Weight variation, Thickness, Hardness, Friability, Disintegration tests, *In vitro* drug release test, Differential Scanning Calorimetry (DSC), X-Ray diffraction, Scanning Electron Microscopy (SEM). Overall, liquisolid technique is newly developed and promising tool for enhancing drug dissolution and sustaining drug release.

KEYWORDS: Liquid medication, Liquisolid compacts, Liquid Load Factor (L*f*), Coating material ratio (R), Carrier material, Coating material.

INTRODUCTION

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 water 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 drygs are solid dispersions, inclusion complexes with β-cyclo dextrins, micronization, an eutectic mixtures and spray drying technique.[1]

Many suitable formulation approaches have been developed to increase the solubility of poorly water soluble drugs. Micronization technique is the most commonly used approach to improve drug solubility due to an increase in surface area, but the agglomeration tendency of micronized hydrophobic drugs makes it less effective to circumvent the solubility problem, especially when the drug is formulated into tablets or encapsulations. Solid dispersion has gained an active research interest for improving drug dissolution in the past few decades, however its commercial application is very limited and only a few products, such as Kaletra and Gris-PEG have become commercially available. The reason mainly lies on its poor stability during storage and lack of understanding of its solid state structure.[2]

The new developed technique by spire as liquisolid system improves the dissolution properties of water insoluble or poorly soluble drugs. The term liquisolid system (LS) is a powdered form of liquid drug formularted 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.[3]

Various grades of cellulose, starch, lactose, etc. are used as the carriers, where as very fine silica powder is used as the coating material. The good flow and compressible properties of liquisolid may be attributed due to large surface area of silics and fine particle size of Avicel. Hence, liquisolid compacts containing water insoluble drugs expected to display enhanced dissolution characteristics and consequently improved oral bioavailability.[3]

SOLUBILITY

Solubility is the ability for a given substance (solute) to dissolve in a solvent. It is measured in terms of the maximum amount of solute dissolved in a solvent at equilibrium. The resulting solution is called saturated solution.

POORLY SOLUBLE DRUGS

Poorly soluble drugs are which dissolves slowly in the Gastro Intestinal tract. These drugs comes under class 2 and class 4 drugs. These classes are according to Biopharmaceutics Classification System (BCS).

LIQUISOLID COMPACT TECHNIQUE

Water insoluble and poorly soluble drugs which are converted to rapid release solid dosage forms. The term Liquisolid compact technique refers to process of immediate (or) sustained release tablets (or) capsules using the Liquisolid system combined with inclusion of appropriate excipients required for Tabletting (or) Encapsulating. Nearly 1/3rd of the drugs are water insoluble drugs. The dissolution rate is the rate limiting factor in drug absorption for class 2 and class 4 drugs according to Biopharmaceutics Classification System (BCS).[4]

More effective than various techniques which have been employed to enhance the dissolution profile and, in turn, the absorption efficiency and bioavailability of water insoluble drugs. Micronization, adsorption on the high surface area carriers, lyophilization, co-precipitation, micro-encapsulation, solubilization by surfactants, solid dispersions, solid solutions. Micronization is the most common method to increase the drug surface area. But this becomes less effective when they are formulated as tablets or encapsulations. The most promising method for promoting dissolution is the formation of liquisolid tablets. A liqusolid systems refers to formulations formed by conversion of liquid drugs, drug suspensions or drug solutions in non-volatile solvents, into dry, non-adherent, free flowing and compressible powder mixtures by blending the suspensions or solution with selected carriers and coating materials. These techniques are carefully selected on the bases of properties of drug, excipients and dosage forms.[5]

ADVANTAGES OF LIQUISOLID SYSTEM

- Capability of industrial production is also possible.
- Drug release can be enhanced by using suitable formulation Ingredients.
- Exhibits enhanced *in-vitro* and *in-vivo* drug release as compared to commercial counter falls, including soft gelatin capsule preparations.
- Production of liquisolid system is similar to that of conventional tablets.
- Better availability of an orally administered water insoluble drug.
- Number of water-insoluble solid drugs can be formulated into liquisolid systems.

- Can be used in controlled drug delivery.
- Can be used for formulation of liquid oily drugs.
- Lower production cost than that of soft gelatin capsules.
- Drug can be molecularly dispersed in the formulation.

DIS-ADVANTAGES

- 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.
- Not applicable for the formulation of high dose insoluble Drugs.
- If more amount of carrier is added to produce free flowing powder, the tablet weight increases to more than one gram which is difficult to swallow.
- Introduction of this method on industrial scale and to overcome the problems of mixing small quantities of viscous liquid solutions on to large amount of carrier material may not be feasible.

APPLICATIONS OF LIQUISOLID TECHNIQUE

- Solubility and dissolution enhancement.
- These can be efficiently used for water insoluble solid drugs Or liquid lipophilic drugs .
- Rapid release rates.
- Designed for controlled release tablet.
- Designed for sustained release of water soluble drugs such as propronolol hydrochloride.
- Application in probiotics.

MECHANISMS OF ENHANCED DRUG RELEASE FORM LIQUISOLID SYSTEM

Several mechanisms of enhanced drug release have been postulated for liquisolid 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 wet ability of the drug particles.

The three mechanisms are:

a) Increased drug surface area
b) Increased aqueous solubility of the drug
c) Improved wetting properties.[6]

a) Increased drug surface area

If the drug within the liquisolid 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 the drug available for release is much greater than that of drug particles within directly compressed.[6]

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 liquisolid systems. Infact, the relatively small amount of liquid vehicle in a liquisolid compact is not sufficient to increase the overall solubility of the drug in 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 micro environment 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 act as a co-solvent.[7]

c) Improved wetting properties

Due to the fact that the liquid vehicle can either act as surface active agent or as a low surface tension, wetting of the liquisolid primary particles is improved. Wet ability 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.[7]

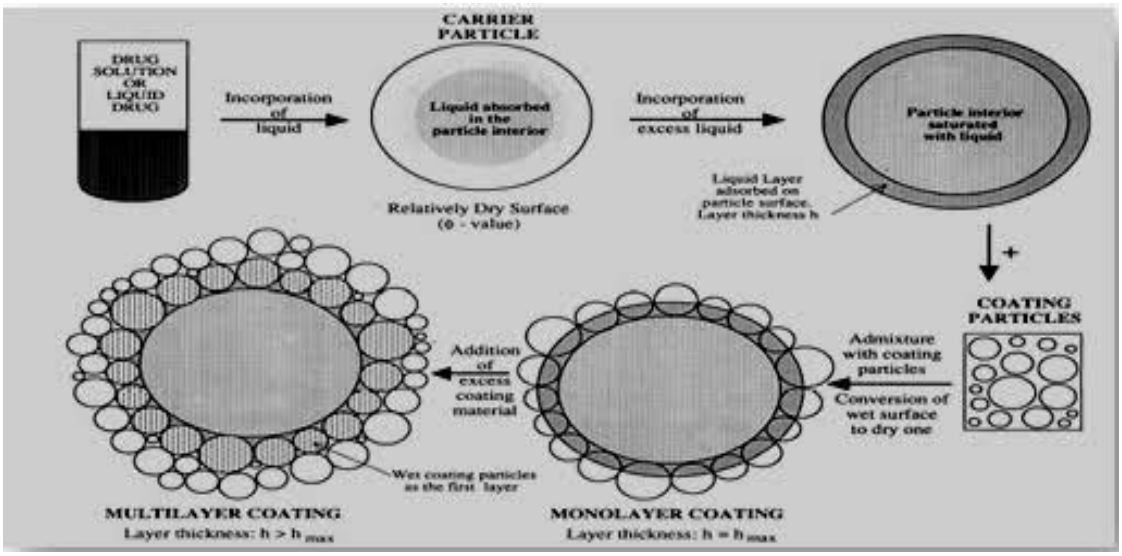

Figure No 1: Mechanism of formation of Liqui-solid system.

THEORY OF LIQUISOLID SYSTEM

A powder can only retain limited amount of liquid medication while maintaining acceptlable flowability and compressability. Therefore, in order to attain a liquisolid system with acceptable flowable and compressable properties, mathematical model induced and validated by spireas is recommended to calculate the appropriate quantities of carrier and coating material. The model is based on two fundamental properties of a powder, i.e., flowable liquid retention potential (Φ) and compressible liquid retention potential (Ψ). The Φ and Ψ values of a powder excipient represent the maximum quantity of liquid vehicle that can be retained in the powder bulk without compromising flowability and compressability. The Φ value is preferably determined by measuring the angle of slide of the prepared liquid powder admixture. And the Ψ value can be measured by an experiment called plasticity, which is defined as maximum crushing strength of a tablet with a tablet weight of 1gm when compressed at sufficient compression force.[8,9]

Depending on the excipient ratio (R) of the powder substrate an acceptably flowing and compressable liquisolid system can be obtained only if a maximum liquid load on the carrier material is not exceeded. The 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 flow ability.

(L*f*) can be determined by:

L*f* = Φ+φ(1/R)------- (3)

Where Φ and φ are the Φ-values of the carrier and coating material, respectively. Similarly, the liquid load factor for preparation of liquisolid systems with acceptable compact ability.

(ΨL*f*) can be determined by:

ΨL*f* = Ψ +$_{\psi}$. (1/R) -------(4)

Where Ψ and $_{\psi}$ are the Ψ numbers of the carriers and coating material, respectively.

Therefore, the optimum liquid load factor (Lo) 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 quantity of carrier (Qo) and coating (qo) material required to convert a given amount of liquid formulation (W) into an acceptably flowing and compressible liquisolid system may be calculated as follows:

Q0 = W/Lo------- (5) And q0 = Q0/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.[10]

MATERIALS

Materials are used for formulation design of liquisolid system. They are mainly four types. They are:

A) Liquid vehicle (Non volatile liquids)

B) Carriers

C) Coating materials

D) Additives

A) Liquid vehicle

Liquid vehicles used in liquisolid systems should be orally safe, inert, not highly viscous, and preferably water miscible non volatile organic solvents. The solubility of drug in non volatile solvent has an important effect on tablet weight and dissolution profile. Higher drug solubility in the solvent leads to lower quantities of carrier and coating material, and thus lower tablet weight can be achieved. On the other hand, the higher the drug solubility in the solvent, the greater Fm value (the fraction of molecularly dispersed drug) will be, which confers an enhancement of the dissolution rate. The selection of liquid vehicle mainly depends on the aim of study. Namely, a liquid vehicle with high ability to solubilize drug will be selected in case of dissolution enhancement. While if the aim is to prolong drug release, liquid vehicle with the lowest capacity for solubilizing drug may be choosen. In addition to the drug solubility in liquid vehicle, several other physical chemical parameters such as the polarity, lipophilicity, viscocity, and chemical structure also have significant effects on drug release profile.[11]

eg: propylene glycol 200, 400, Glycerine, Poly sorbate 80, Tween 80.

B) Carriers

Carriers should possess porous surface and high liquid absorption capacity. As carriers allow an incorporation of large amount of liquid medication into the liquisolid structure, the properties of carriers, such as (SSA) and liquid absorption capacity, are of great importance in designing the formulation of liquisolid system. The liquid adsorption capacity mainly depends on the SSA value. Additionally, it is also influenced by the type of coating material and the physicochemical properties of the liquid vehicle, such as polarity, viscosity, and chemical structur.[12]

eg : Grades of micro crystalline cellulose such as PH 102 and avicel PH 200 and 20, Starch, Lactose, Granular amorphous Cellulose.

C) Coating materials

Coating materials refers to very fine and highly adsorptive materials in a powder form. These materials play a contributory role in covering the wet carrier particles to form a apparently dry, non adherent, and free flowing powder by adsorbing any excess liquid. It was proved that the replacement of aerosol 200 by neusiln US2 as a coating material in liquisolid system considerably increased the liquid adsorption capacity and reduced tablet weight.[13]

eg: Aerosil 200, Neusilin and Calcium silicate (or) Magnesium aluminometasilicates.

D) Additives

The disintegration of solid dosage forms obviously influences drug release. Therefore, disintegrants of usually included in liquisolid tablets to allow a fast disintegration. The materials which has the potential the to incorporate high amount of drug into liquisolid systems, and thus reduce the tablet weight.[14]

eg: Starch Glycolate, Croscarmellose sodium, and low substituted hydroxyl propyl cellulose, Poly vinyl pyrrolidine (PVP).

Table 1: Details of studies carried out on liquisolid compacts.

S.NO	DRUG	CO-SOLVENT	CARRIER MATERIAL	COATING MATERIAL	USES	AUTHORS
1	Aceclofenac	PEG 400	MCC	HPMC	NSAID	Abimanya Saha et al 2013.[15]
2	Methyclothiazide	PEG 400	MCC	SILICA	Diuretic	Spiro Spireas et al 1999.[16]
3	Carbamazapine	PEG 200, Propylene glycol	MCC, Avicel PH 102	Cab-o-sil, Aerosil 300	Anti-epileptic	Yousef Javadzadeh et al 2007.[17]
4	Piroxicam	Tween 80, Propylene glycol	MCC, MCC	Silica, Silica	NSAID	Yousef Javadzadeh et al 2005.[18]
5	Indomethacin	2-Pyrrolidone,	CollodionCL-M,	Aerosil 300,	NSAID	Majid Saeed et al

		Propylene glycol, PEG 400	MCC, MCC	Silica, HPMC		2011.[19]
6	Hydrochlorthiazide	PEG 200, PEG 200	Avicel PH 101/102, MCC, Magnesium Carbonate	Aerosil, Colloidal silica	Diuretic	Amjad Khan et al 2015.[20]
7	Griseofulvin	PEG 400	MCC	Colloidal silica	Anti-Fungal	CM Hentzschel et al 2012.[21]
8	Famotidine	Propylene glycol	MCC	Colloidal silica	Anti-Ulcer	Rania H Fahmy et al 2008.[22]
9	Furosemide	Synperonic PE/L 81	MCC	Colloidal silica	Diuretic	EZ Jassim et al 2017.[23]
10	Ibuprofen	PEG 300	MCC	Colloidal silica	NSAID	Ajit Kulkarni et al 2010.[24]
11	Repaglinide	Tween 80	MCC	Colloidal silica	Anti-Diabetic	Mohammed A Osman et al 2014.[25]
12	Brom hexine HCl	PG	MCC	Colloidal silica	Expectorant	Sanjeev Gubbi et al 2009.[26]
13	Genfibrosil	Tween 80	AvicelPH200	Cab-o-sil M-5	Lipid lowering agent	Spiro Spireas et al 1998.[27]
14	Nifedipine	PEG 400	AvicelPH200	Cab-o-sil M-5	Anti-Hypertensive	P Vinod Kumar et al 2018.[28]
15	Lamotrigine	PEG 400	MCC	Colloidal silica	Anti-Epileptic	Rania H Fahmy et al 2008.[29]
16	Naproxen	CremothorEL	MCC	Colloidal silica	NSAID	Ramarao Tadikonda et al 2011.[30]
17	Polythiazide	PEG 400	MCC	Colloidal silica	Diuretic	Vijay Kumar Nagabandi et al 2011.[31]
18	Prednisolone	Propylene glycol	Avicel PH 101, Lactose, MCC	Cab-o-sil, Colloidal silica	Rheumatoid arthritis, Anti Asthma	Srinivas Sadu et al 1998.[32]
19	Hydro cortisone	Propylene glycol	AvicelPH 200, MCC	Cab-o-sil, Colloidal silica	NSAID	Spiro Spireas et al 1998.[33]
20	Glibenclamide	PEG 400	AvicelPH102	Aerosil	Anti-Diabetic	H Javaheri et al 2014.[34]

MCC= Microcrystalline Cellulose PEG= Poly Ethylene Glycol HPMC= Hydroxy Propyl Metyl Cellulose.

GENERAL PROCEDURE FOR PRREPARATION OF LIQUISOLID SYSTEM

Calculated amount of drug and liquid vehicle are mixed, and then heated or completely solubilising or evenly blending. The following mixing process of the resulted liquid medication with other excipients used in the liquisolid formulation is carried out in three steps as described by spireas and Bolton. During the first stage, the resulted liquid medication poured one to calculated quantity of carrier material blended at an approximate mixing rate of one rotation per second one minute to facilitate a homogeneous distribution of liquid medication throughout the carrier powder. Then coating material in calculated amount is added and mixed homogenously. In the second stage, the prepared powder mixture is spread as a uniform layer on the surface of mortar and left standing for five minutes to facilitate a complete absorption of a drug medication into the interior frame work of carrier and coating materials. In the third stage, disintegrant is added and mixed thoroughly with the above

powder mixture, and a final liquisolid system is abtained. The prepared liquisolid system can be further compressed or encapsulate.[35]

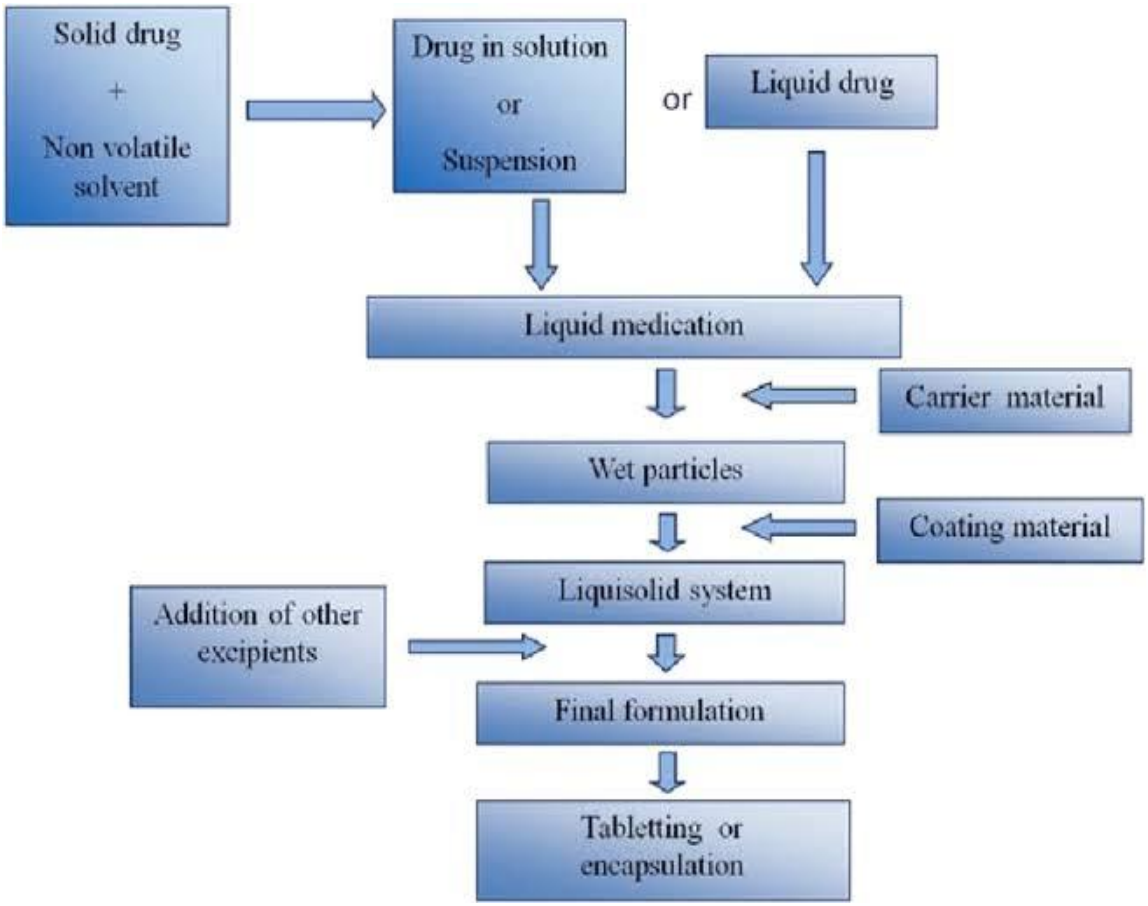

Figure No 2: General procedure for liquisolid compact preparation.

METHODOLOGY

1) Pre compression parameters:evaluation[36]

A) Angle of repose

The angle of repose for the powder blend was determined by fixed funnel method. Angle of repose was calculated using equation:

$\tan \theta = h/r$

Where, h= height of powder heap in cm

r= radius of powder heap in cm

B) Tapped bulk density (TBD)

About 5gm of powder sample was poured gently through a glass funnel into a 10ml graduated cylinder. The cylinder was tapped from height of two inches until a constant

volume was obtained. Volume occupied by the sample after 100 tapping were recorded and tapped density was calculated as follows:

Tapped density = Mass/ Tapped volume.

C) Bulk density (BD)

Bulk density of the powder was determined by pouring gently 5gms of sample through a glass funnel into a 10ml graduated cylinder. The volume occupied by sample was recorded. The bulk density was calculated as follows:

Bulk density = Mass / Bulk volume

D) Carr's compressibility index (CI)

The compressibility index of the powder blend was determined by using carr's compressibility index.

CI = tapped bulk density –bulk density/tapped bulk density* 100

E) Hausner's ratio

It was determined for characterization of powder blend. The Hausner's ratio greater than 1.25 is considered to be an indication of poor flowability. Formula used was as follows:

Hausner's ratio = Tapped bulk density / Bulk density.

2) Post compression evaluations[37]

A) Hardness and Thickness

The resistance of tablets to shipping or breakage under conditions of storage, transportation and handling before usage depends on its hardness. The hardness of tablet of each formulation was measured by Monsento hardness tester (Nevtex). The hardness was measured in terms of kg/cm2. Thickness and diameter of tablets were important for uniformity of tablet size. Thickness and diameter were measured using digital vernier caliper.

B) Friability

Friability is the measure of tablet strength. Roche friabilator was used for testing the friability using the following procedure. Ten tablets were weighed accurately and placed in the tumbling apparatus that revolves at 25rpm dropping the tablets through a distance of 6 inches with each revolution. After 4 min, the tablets were weighed and the percentage loss in tablet was determined.

C) Uniformity of Weight

20 tablets were weighed randomly and average weight was calculated. Not more than two of the individual weights deviated from the average weight by more than the percentage shown in the table and none deviates by more than twice that percentage.

D) Weight variation

20 tablets were weighed individually and then all together. Average weight was calculated from the total weight of all tablets. The individual weights were compared with the average weight. The percentage difference in the weight variation should be with in the permissible limits as specified in USP, not more than two tablets should differ in their average weight by more than percentages stated in USP. No tablet must differ by more than double the relevant percentage.

E) Disintegration test

The disintegration time was determined in water maintained at 37 ± 2^0C. the disintegration apparatus with a basket rack assembly containing 6 open- ended tubes and 10-mesh screen on the bottom was used. A tablet was placed in each tube of the basket and the time for complete disintegration of the 6 tablets was recorded.

F) *In vitro* dissolution test

The dissolution rates of all formulations were measured by using tablet dissolution apparatus USP type-2. Dissolution studies were carried out using 900ml of phosphate buffer pH 5.8 at 50 rpm and at temperature of 37 ± 0.5^0C. 10ml of the medium was withdrawn at a suitable time interval, filtered and diluted with phosphate buffer pH 5.8. sink conditions were maintained throughout the study. The samples were than analysed at 277nm by U.V/VISIBLE spectrophotometer. The study was carried out in triplicate.

G) Differential scanning calorimetry (DSC)

Samples (3-5mg) were placed in an aluminum pan and heated in the DSC 60-plus at a constant rate of 10^0C/min in an atmosphere of nitrogen over a temperature range of 25-300^0C. the DSC studies were performed on the pure drug, a physical mixture of the optimized liquisolid system, and on the liquisolid tablet.

H) Fourier- Transformed infrared spectroscopy (FTIR)

It was performed using the infrared spectrophotometer. Samples of 2-3 mg were mixed with about 100 mg of dry potassium bromide powder and compressed into transparent discs then scanned over a wave range of 400cm^{-1} in FTIR instrument. FTIR spectra were performed on the pure drug, sodium starch glycolate, crospovidone, co-processed super disintegrant at a ratio (1:1), a physical mixture of optimized liquisolid system and on the liquisolid tablet.

I) X-ray powder diffraction (XRPD)

X-ray diffractograms of pure furosemide, physical mixture of liquisolid and liquisolid tablet were obtained using analytical XRD instrument. The scanning range was from 30-60^{0}C at 2 theta scale and 5$_o$/min. the voltage and strength of the electric current were 40KV and 30mA, respectively.

CONCLUSION

The liquisolid technique is a promising alternative to enhance the absorption as well as the dissolution rate thereby it may enhance the bioavailability of a poorly soluble, liquid drugs, insoluble or lipophilic drugs. Liquisolid tablets were prepared found in terms of fast disintegration time, dissolution profile, acceptable tablet properties and stability. This technique is used to design immediate release or sustained release systems. Therefore, this technique has the potential as safer and efficacious method. Hence, should considered to be manufactured on large scale. Moreover, the technique has exhibited great potential in reducing the effect of PH variation on drug release and improve the drug photo stability in solid dosage forms. Currently, much research work still focuses on the formulation on the development of liquisolid systems and the investigation of *In-vitro* drug release profiles. Future works on the measurement of loading high dose water in soluble drugs, and *In-vivo* evaluation of liquisolid systems need to be explored and strengthened.

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