Review Article ***Current Pharma Research***
ISSN: 2230-7842
CPR 3(1), 2012, 735-749.

Liquisolid: A Novel Technique for Dissolution Enhancement of Poorly Soluble Drugs

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Abstract
The poor dissolution characteristic of water insoluble drugs is a major challenge for formulation scientists. About 50% of orally administered drugs suffer from formulation difficulties related to their water insolubility. Thus it is rate limiting step for achieving optimum bioavailability of such drugs by pharmaceutical industry with developments of new pharmaceutical products.There are various methods but liquisolid technique is a new and promising method that can change the dissolution rate of water insoluble drugs. According to the new formulation method of liquisolid compacts, liquid medications such as solutions or suspensions of water insoluble drugs in suitable nonvolatile liquid vehicles can be converted into acceptably flowing and compressible powders by blending with selected powder excipients. In this case, even though the drug is in a solid dosage form, it is held within the powder substrate in solution or, in a solubilized, almost molecularly dispersed state, which contributes to the enhanced drug dissolution and release properties. Liquisolid system is characterized by flow behavior, wettability, powder bed hydrophilicity, saturation solubility, drug content, differential scanning calorimetry, Fourier transform infra red spectroscopy, powder X-ray diffraction, scanning electron microscopy, *in-vitro* release and *in-vivo* evaluation.

Key Words
Bioavailability, Insoluble drugs, Non-volatile liquid, liquisolid compacts.

Introduction

Oral route is the most desirable and preferred method of administering therapeutic agents for their systemic effects. In addition the oral route medication is generally considered as the first avenue investigated in the discovery and development of new chemical entities and pharmaceutical formulations mainly because of patient acceptance, convenience in administration and cost effective manufacturing process. For many drug substances, conventional immediate release formulation provide clinically effective therapy while maintaining the required balance of pharmacokinetic and pharmacodynamic profile with an acceptable level of safety to the patient. Thus one of the major challenges to drug development today is poor solubility, as an estimated 40%

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of all newly developed drugs are poorly soluble or insoluble in water[1]. About 50% of orally administered drugs suffer from formulation difficulties related to their water insolubility. As a result, much research has been conducted into methods of improving drug solubility and dissolution rates to increase the oral absorption of hydrophobic drugs. One way of improving dissolution involves the reduction of particle size and/or increasing saturation solubility [2]. One of the most common approaches used to reduce particle size is milling, a mechanical micronization process. Milling is a well established technique which is relatively cheap, fast and easy to scale-up. However, milling has several disadvantages, the main one being the limited opportunity to control important characteristics of the final particle such as size, shape, morphology, surface properties and electrostatic charge. In addition, milling is a high energy process which causes disruptions in the drug's crystal lattice, resulting in the formulation of disordered or amorphous regions in the final product[3]. An alternative to milling involves the size enlargement of drug particle with different polymers and excipients, for example compaction, melt granulation and liquisolid technique. The compaction of drug with hydroxypropyl methylcellulose (HPMC) and other hydrophilic polymers shows change in crystal form and habit may change the solubility, dissolution rate and other physicochemical properties. These are the easily scalable methods to combine poorly water-soluble drugs and dissolution rate enhancing polymers without the use of solvent or heat addition[4,5].

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: vitamin A, D, E, and K

Development of Dosage Forms with Poorly Water Soluble Drugs

The increased emergence of poorly water soluble active compounds presents specific obstacles for the development of both immediate release and modified release dosage forms. Poorly water soluble drugs will be inherently released at a slow rate owing to their limited solubility within the GI contents. The challenge for poorly water soluble drugs is to enhance the rate of dissolution. This in turn subsequently improves absorption and bioavailability[6].

Formulation methods targeted at dissolution enhancement of poorly soluble substances are continuously introduced[7,8].

Various methods used to increase the solubility of poorly water soluble drugs which are given below.

Micronization

The particle size reduction technique enhance the solubility and dissolution rate of poorly water soluble drugs due to the enormous surface that is generated.

Solvent Deposition

In this method, the poorly aqueous soluble drug such as nifedipine is dissolved in an organic solvent like alcohol and deposited on a inert, hydrophilic, solid matrix such as starch or microcrystalline cellulose evaporation of solvent.

Use of soluble Prodrug

Here the physico-chemical properties of the drug are improved by bio-reversible chemical alteration. The most common prodrug strategy involves the incorporation of polar or ionizable moiety into the parent compound to improve aqueous solubility[9].

Solid dispersion

It involves dispersion of one or more active ingredients in an inert carrier or matrix at solid state. Melting (fusion) method, solvent evaporation method or melting evaporation methods can be employed for the preparation of the solid dispersions. The dissolution rate of the solid dispersion depends on the type of carriers used or the type of the matrix forming polymers used[10].

Liquisolid technique

The new developed technique by Spireas liquisolid system improves the dissolution properties of water insoluble or poorly soluble drugs[11]. The liquisolid technique is 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. 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[12]. Among them, liquisolid compacts is one of the most promising and new techniques which promotes dissolution rate of water insoluble drugs.

The term liquisolid compact refers to immediate release or sustained release tablets or capsules, combined with the inclusion of appropriate adjuvant required for tabletting or encapsulating.

Need of Liquisolid System

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[13]. In addition, up to 50% of orally administered drug compounds suffer from formulation problems related to their low solubility and high lipophilicity[14,15,16]. Bioavailability of poorly water soluble hydrophobic drugs (class II in biopharmaceutics classification system) is limited by their solubility and dissolution rate. The dissolution rate of these drugs can be improved by decreasing particle size, decreasing crystallinity, and/or increasing the surface area. 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. Another way of increasing the dissolution rate is adsorption of the drug onto a high-surface area carrier. In this technique, the drug is dissolved in an organic solvent followed by soaking of the solution by a high-surface-area carrier such as silica. Here, agglomeration of the drug particles is prevented due to the binding of drug to the carrier. However, due to the presence of the residual solvent in the drug formulation, it is disadvantageous to use toxic solvents[17,18,19]. To overcome the problem, the technique of 'liquisolid compacts' 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 silicas 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, on-adherent, dry looking powders[20,21]. 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 nonpolar 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.

Advantages of Liquisolid Systems

A great number of slightly and very slightly water-soluble and practically water-insoluble liquid and solid drugs,

such as those previously mentioned, can be formulated into liquisolid systems using the new formulation-mathematical model. It is well established that better availability of an orally administered water-insoluble drug is achieved when the drug is in solution form. In liquisolid compacts, even though the drug is in a tabletted or encapsulated dosage form, it is held in a solubilized liquid state, which consequently contributes to increased drug wetting properties, thereby enhancing drug dissolution. Another advantage of liquisolid systems is that their production cost is lower than that of soft gelatin capsules because the production of liquisolid systems is similar to that of conventional tablets. Still another possible advantage of liquisolid systems, particularly for powdered liquid drugs, should be mentioned. During dissolution of a liquisolid tablet, after the disintegration process is completed, the drug solution or liquid drug, carried on the suspended and thoroughly agitated primary particles, is dispersed throughout the volume of the dissolution medium; such a phenomenon does not extensively occur during the dissolution process of soft gelatin capsule preparations. Therefore, since more drug surface is exposed to the dissolving medium, liquisolid systems exhibit enhanced drug release. Most liquid or solid water-insoluble drugs may be formulated into immediate-release or sustained-release'liquisolid compacts' or 'liquisolid microsystems [22, 23, 24, 25, 26]. Optimized rapid-release liquisolid tablets or capsules of water-insoluble drugs exhibit enhanced in-vitro and in-vivo drug release as compared to their commercial counterparts, including soft gelatin capsule preparations. Optimized sustained-release liquisolid tablets or capsules of water-insoluble drugs exhibit surprisingly constant dissolution rates (zero-order release) comparable only to expensive commercial preparations that combine osmotic pump technology and laser-drilled tablets.

Disadvantages

Formulation of high dose lipophilic drugs the liquisolid tablet is one of the limitations of this technique. In order to achieve acceptable flowability 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. Consequently, it is impossible with conventional tablet methods to convert high dose to liquisolid tablets with a tablet weight of less than 50mg. Dissolution profile enhancement occurs in the presence of low levels of hydrophilic carrier, where coating material is not significant.

Principle of Liquisolid Compacts

Important terminologies in Principle

Liquid medication includes liquid lipophilic drugs and drug suspensions or solutions of solid water insoluble drugs in suitable non-volatile solvent systems.

Liquisolid system refers to powdered forms of liquid medications formulated by converting liquid lipophilic drugs, or drug suspensions

or solutions of water insoluble solid drugs in suitable non-volatile solvent systems, into dry, nonadherent, free-flowing and readily compressible powder admixtures by blending with selected carrier and coating materials.

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

Coating material refers to a material possessing fine and highly adsorptive particles, such as various types of silica, which contributes in covering the wet carrier particles and displaying a dry looking powder by adsorbing any excess liquid.[27]

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 (Fig. 1).

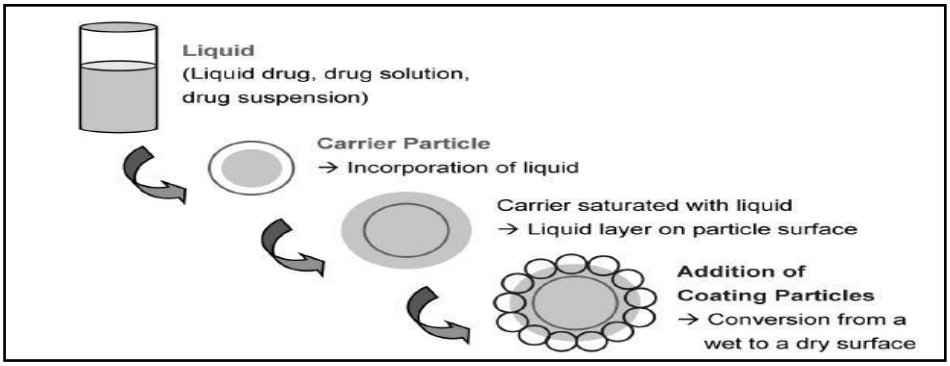

Fig 1: Schematic representation of liquisolid systems.

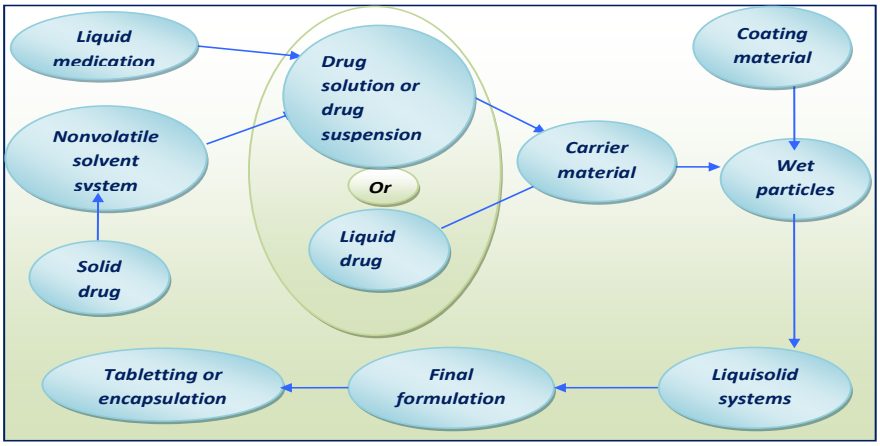

Fig. 2: Schematic outline of the steps involved in the preparation of liquisolid compacts.

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. Usually, microcrystalline cellulose is used as carrier material and amorphous silicon dioxide (colloidal silica) as coating material. Various excipients such as lubricants and disintegrants may be added to the liquisolid system to produce liquisolid compacts (Fig. 2).

Methodology

Spireas et al proposed the new mathematical model in accordance to retain good flow behaviour and compressibility to design the formulation for Liquisolid technique [28,29]. Mandatory requirements for this technique are suitable drug candidate, suitable non-volatile solvent, carrier and coating materials. According to Spireas et al the basic properties of Liquisolid powder for good flow behaviour and compressibility proposed are "Flowable liquid retention potential" (value) and compressible liquid retention potential" (ψ value), respectively.

Flowable liquid retentional potential defined as maximum weight of liquid (solvent) that can be retained per unit weight of powder (excipient) material to produce good flow. *Compressible liquid retention potential* defined as the compression force applied to produce tablets with acceptable strength without squeezing out any liquid during compression.

Excipient ratio (R) defined as Carrier to coating ratio as,

$$R = Q/q$$

Q= Carrier material, q= Coating material.

Liquid load factor (Lf) defined as weight of liquid medicament (W) to weight of carrier (w).

$$Lf = W/Q$$

The Ø value is for calculating excipients quantities.

Equation is,

$$Lf = Ø + Ø\ (1/R)$$

Where, Ø and Ø are values of carrier and coating material.

Materials Required For Formulation

Drug candidate: These are poorly soluble or else insoluble drugs in water.

Non volatile solvent: preferably water-miscible, inert high boiling point and not highly viscous organic solvent systems. E.g. propylene glycol, liquid polyethylene glycols, N, N dimethylacetamide, polysorbates, glycerin, fixed oils etc., are most suitable as vehicles [30].

Disintegrant: Sodium starch glycolate[31], Explotab, Pumogel, Crosspovidone[32], Sodium croscarmellose [33,34], Pre gelatinized starch [35].

Carrier material: These are as porous substance possessing adequate absorption properties. Various grades of microcrystalline cellulose (MCC) such as pH101, and 200 Avicel® RTM 105, Avicel® pH 102 granular Microcrystalline cellulose (MCC)

grade, Avicel ® pH 200 coarse granular MCC grade, experimental grade of granular amorphous cellulose, starch, lactose used as carrier materials. Starch 1500, Silica possessing large surface areas and MCC of fine particle size granular grades produced good flow properties and compression properties resulting in good tablets.

Coating material: It is a substance possessing fine and highly adsorptive particles. 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, Syloid244FP etc., contributes in covering the wet carrier particles and displaying a dry-looking powder by adsorbing any excess liquid [36,37,38,39].

Formulation of Liquisolid Compact

The formulation part of liquisolid compact mainly includes Pre-formulation studies and Formulation of liquisolid compact system.

Pre-formulation Studies

Pre-formulation Studies includes:

1. Determination solubility of drug in different non-volatile solvents
2. Determination of angle of slide
3. Determination of flowable liquid retention potential (Φ value)
4. Calculation of liquid load factor (Lf)
5. Liquisolid compressibility test (LSC)

Solubility studies

Solubility studies are carried out by preparing saturated solutions of drug in non-volatile solvent and analyzing them spectrophotometrically[40]. Saturated solutions are prepared by adding excess of drug to non volatile solvent and shaking them on shaker for specific time period under constant vibration. After this, the solutions are filtered and analyzed spectrophotometrically[41].

Determination of angle of slide

Angle of slide is used as a measure of the flow properties of powders. Determination of angle of slide is done by weighing the required amount of carrier material and placed at one end of a metal plate with a polished surface. The end is gradually raised till the plate becomes angular to the horizontal at which powder is about to slide. This angle is known as angle of slide. Angle of 33º is regarded as optimum[42].

Determination of flowable liquid retention potential (Φ value)

The term "flowable liquid-retential 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/powder admixture. The Φ values are calculated according to equation

Φ value = weight of liquid / weight of solid … (1)

Calculation of liquid load factor (Lf)

Different concentrations of non-volatile solvents are taken and the drug is dissolved. Such liquid medication is added to the carriercoating material admixture and blended. Using equation (2) drug loading factors are determined and used for calculating the amounts of

carrier and coating materials in each formulation.

Lf = weight of liquid medication / weight of carrier material… (2)

Liquisolid compressibility test (LSC)

Liquisolid compressibility test is used to determine Φ values and involves steps such as preparing carrier coating material admixture systems, preparing several uniform liquid or powder admixtures, compressing each liquid or powder admixtures to tablets, assessing average hardness, determination of average liquid content of crushed tablets, as well as determining plasticity, sponge index and Φ value and Lf .

Evaluation of Liquisolid Systems

Flow behaviour

The flowability of a powder is of critical importance in the production of pharmaceutical dosage forms in order to reduce high dose variations. Angle of repose, Carr's index and Hausner's ratio were used in order to ensure the flow properties of the liquisolid systems.

Pre compression studies of the prepared liquisolid Powder systems

In order to ensure the suitability of the selected excipients, Fourier Transform Infra Red Spectroscopy, Differential scanning Calorimetry, X-ray Diffraction and Scanning Electron Microscope studies are to be performed. In addition, flowability studies are also to be carried out to select the optimal formulae for compression, prior to the compression of the powders the dosage forms such as into tablets and capsules.

Dissolution studies

In-Vitro release profiles of drug from the preferred tablets were studied using dissolution apparatus and compared with the formulated Liquisolid tablet. Drug release, % drug dissolved can be calculated of both the formulation results are estimated.

Differential scanning calorimetry (DSC)

This is prerequisite to know if any possible interaction present between the excipients and the drug used in the formulation. The characteristic peak in the DSC thermogram belongs to drug is absent that indicates that the drug is present in moleculary dispersed in this system[43].

X- ray diffraction (XRD)

To get justification that the drug is in the solubilised state or converted into amorphous form because of disappearance of characteristic peaks belongs to drug and their by appearance of peaks which belongs to carrier is absorbed[44].

Scanning electron microscopy (SEM)

This study confirms that there are any crystals present, or else drug is present in the solubilised form by absence of crystals of drug[45].

Stability studies

Drug content was determined after the crystals were charged for accelerated stability studies according to ICH guidelines. Samples were taken and analysed for specified intervals.

Liquisolid Tablets

The liquisolid tablet preparation method involves, first a mathematically calculated amount of

pure drug weighed and dissolved in the suitable amount of solvent in a molecularly dispersed state. For attaining good flow properties trial and error methods were used i.e. changing the carrier: coating material ratio from 50:1 to 5:1 ratios according to new mathematical model expressions proposed by Liao[46]. This liquid medication is poured on the suitable amount of carrier material. The liquid medication is absorbed into the carrier material internally and externally and then a suitable disintegrant was added to this material. Finally, coating material was added for dry looking, adherent to the carrier material for achieving good compression properties. Liquid medication is incorporated into carrier material which has a porous surface and closely matted fibers in its interior as cellulose[47]. Both absorption and adsorption take place, i.e. the liquid absorbed into the interior of the particles is captured by its internal structure and after saturation of this process, adsorption of the liquid onto the internal and external surface of the porous carrier particles occurs[45]. 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 ingredients such as lubricants, disintegrates or Polymers, and binders may be mixed with the finished liquisolid systems to produce liquisolid compacts in the dosage form of tablets or capsules[48,49,50].

Liquisolid tablets advantages over the conventional tablets

1. Liquisolid systems are low cost formulations than soft gelatin capsules.
2. Production of them is similar to that of conventional tablets.
3. Drug release can be modified using suitable formulation ingredients.
4. Drug can be molecularly dispersed in the formulation.
5. Capability of industrial production is also possible.
6. Enhanced bioavailability can be obtained as compared to conventional tablets.
7. Omit the process approaches like nanonisation, micronization techniques.
8. Differentiate the dosage form by admixture of colour into liquid vehicle.
9. To minimize excipients in formulation compare with other formulations like solid dispersions.

Applications [51, 52,53,54,55]

1. Rapid release rates are obtained in liquisolid formulations
2. These can be efficiently used for water insoluble solid drugs or liquid lipophilic drugs.
3. Sustained release of drugs which are water soluble drugs such as propranolol hydrochloride has been obtained by the use of this technique.
4. Solubility and dissolution enhancement.

5. Designing of controlled release tablets.
6. Application in probiotics.

References

1. Naseem A, Olliff C J, Martini LG, Lloyd AW, Effects of plasma irradiation on the wettability and dissolution of compacts of griseofulvin Int. J. Pharm. 2004, 269, 443-450.
2. Wong SM, Kellaway IW, Murdan S, Enhancement of the dissolution rate and oral absorption of a poorly water soluble drug by formation of surfactant-containing microparticles Int. J. Pharm. 2006, 317, 61–68.
3. Saleki-Gerhardt A, Ahlneck C, Zografi G, Assessment of disorder in crystalline solids, Int. J. Pharm. 1994, 101, 144.
4. Iskandarsyah, Fudholi A, Riswaka, S, The effect of two cellulose derivatives as solid dispersion carriers on physical properties and dissolution rate of dexamethasone tablets. Maj Farm Indones. 1999, 10, 1-8.
5. Sugimoto M, Okagaki T, Narisawa S, Koida Y, Nakajima K, Improvement of dissolution characteristics and bioavailability of poorly water-soluble drugs by novel co- grinding method using water-soluble polymer. Int J Pharm. 1998, 160, 11–19.
6. Charman S A, Charman, WN, Oral modified release delivery systems, In: Rathbone MJ, Hadgraftb J, Roberts MS. Modified release drug delivery technology, New York, Marcel Dekker Inc. 2003, P.
7. Darwish AM., Dissolution enhancement of glibenclamide using liquisolid tablet technology, Acta Pharm. 2001, 51, 173-181
8. Patel VP, Patel NM, Dissolution enhancement of glipizide using liquisolid tablet technology, Ind Drugs, 2008, 45, 318-323.
9. Rajesh V, Areefulla S, Mallikarjun V, Solubility and Dissolution Enhancement: An overview. Journal of Pharmacy Research.2010, 3, 141- 145.
10. Saindane D.S, Kulkarni A. S, Khade T.S, Patil .M.D, Enhancing Drug Solubility And Oral Bioavailability Using Solid Dispersions: A Review. International Journal of Biopharmaceutics. 2011,2, 22-30.
11. Spireas S, Liquisolid System An Method Of Preparing Same. U.S Patent 5800834. 1998.
12. Narender T, Sukhbirlal K, Dharmesh S, NaseebSingh T, Rahul P, Vikrant A. A Review on Pharmaceutical Applications of Liquisolid Technique. American Journal of Pharmtech Research. 2011,1,1-18.
13. Naseem A, Olliff C J, Martini LG and Lloyd AW, Effects of Plasma Irradiation on the Wettability and Dissolution of Compacts of Griseofulvin. Int J Pharm. 2004, 269,443–450.

14. Gursoy RN and Benita S, Self-Emulsifying Drug Delivery Systems (SEDDS) for Improved Oral Delivery of Lipophilic Drug Biomed. Pharmacother. 2004, 58,173–182.
15. Kapsi S G and Ayres J W, Processing Factors in Development of Solid Solution Formulation of Itraconazole for Enhancement of Drug Dissolution and Bioavailability. Int J Pharm. 2001, 229,193–203.
16. Finholt P and Solvang S, Dissolution Kinetics of Drugs in Human Gastric Juice the Role of Surface Tension. J Pharm Sci. 1968, 57, 1322–1326.
17. Gladys E, Granero C and Gordon L, Dissolution and Solubility Behavior of Fenofibrate in Sodium Lauryl Sulfate Solutions. Drug Development and Industrial Pharmacy. 2005, 31,917–922.
18. Rasenack N, Hartenhauer H and Muller B,. Microcrystals for Dissolution Rate Enhancement of Poorly Water-Soluble Drugs. Int J Pharm. 2003, 254,137–145.
19. Javadzadeh Y, Siahi MR, Barzegar Jalali M and Nokhodchi A, Enhancement of Dissolution Rate of Piroxicam Using Liquisolid Compacts IL Farmaco. 2005, 60,361–365.
20. Nokhodchi A, Javadzadeh Y, Siahi MR and Barzegar-Jalali M, The effect of Type and Concentration of Vehicles on the Dissolution Rate of a Poorly Soluble Drug (indomethacin) from Liquisolid Compacts. J Pharm Pharmaceutics Sci. 2005, 8, 18–25.
21. Fahmy RH and Kassem MA, Enhancement of Famotidine Dissolution Rate Through Liquisolid Tablets Formulation: In Vitro and in Vivo Evaluation. Eur J Pharm Biopharm. 2008, 69,993–1003.
22. Spiras S, Liquisolid systems and methods for preparing same, United States patent. 2002, 6, 339B1, 423.
23. Spiras S, Bolton SM, Liquisolid systems and methods for preparing same, United States patent. 2000, 6, 096, 337.
24. Spiras S, Bolton SM, Liquisolid systems and methods for preparing same, United States patent. 2000, 5, 968, 550.
25. Spiras S, Bolton SM, Liquisolid systems and methods for preparing same, United States patent. 1998, 800,834.
26. Spireas S, Sadu S, Grover R. In vitro release evaluation of hydrocortisone liquisolid tablets, J Pharm Sci. 1998, 87, 867-872.
27. Rajesh V, Areefulla S, Mallikarjun V, Solubility and Dissolution Enhancement: An overview. Journal of Pharmacy Research.2010,3,141- 145.
28. Smirnova I, Suttiruengwong S, Seiler M, Arlt M, Dissolution

rate enhancement by adsorption ofpoorly soluble drugs on hydrophilic silica aerogels. Pharm Dev Tech. 2004, 9,443-452.
29. Spireas S, Bolton M. Liquisolid Systems and Methods of Preparing Same. U.S. Patent. 1999,968,550.
30. Ajit SK, Nagesh H, Aloorkar, Madhav S, Mane, Gaja JB, Liquisolid systems: a review: Int J of Pharm Sciences and Nanotech. 2010,1,795-802.
31. Ferrari F, Investigation on Bonding and Disintegration Properties of Pharmaceutical Materials. Int J Pharm.1996, 136, 71-79.
32. Sanjeev RG, Jarag R. Formulation and characterization of atorvastatin calcium liquisolid compacts, Asian J Pharm Science. 2010, 5, 50-60.
33. Bhise SB, Nighute AB, Yadav AV, Yadav VB, Aceclofenac size enlargement by non aqueous granulation with improved solubility and dissolution, Arch Pharm Sci & Res. 2009, 1,115-122.
34. Yadav VB, Yadav AV, Improvement of Solubility and Dissolution of Indomethacin by Liquisolid and Compaction Granulation Technique, J Pharm Sci & Res. 2009,44-51.
35. Alebiowu G, OA Itiola, Effects of Natural and Pregelatinized Sorghum, Plantain, and CornStarch Binders on the Compressional Characteristics of a Paracetamol Tablet Formulation Drug Delivery, A Pharm Technol. 2001, 25, 26-30.
36. Sadu S, Spireas S, Grover R, In vitro release evaluation of hydrocortisone liquisolid tablets, J Pharm Sci. 1998, 87,867–872.
37. Spireas S, Liquisolid systems and methods for preparing same, United States patent. 2002, 339 B1, 6,423.
38. Shinde AJ, Solubilization of poorly soluble drugs: A review, available at http://www.pharmainfo.net/reviews/solubilizationpoorly-soluble-drugs-review 2007.
39. Indrajeet DG, Amirit BK, Hosmani AH, Evaluation of *in vitro* dissolution profile comparison methods of sustained release Tramadol hydrochloride liquisolid compact formulations with marketed sustained release tablets, Digest Journal of Nano materials and Bio structures. 2009, 651-661.
40. Spireas S, Sadu S, Enhancement of prednisolone dissolution properties using liquisolid compacts. Int. J. Pharm. 1998, 166,177–188.
41. Javadzadeh Y, Musaalrezaei L and Nokhodchi A, Liquisolid technique as a New Approach to Sustain Propranolol Hydrochloride Release Form Tablet Matrices. Int J Pharm. 2008, 362,102-108.
42. Tayel SA, Soliman II and Louis D, Improvement of

Dissolution Properties of Carbamazepine through Application of the Liquisolid Technique. Eur J Pharm Biopharm. 2008,69,342-347.

43. Spireas, S. S, Development of a New Theory for Powdered Solution Technology and Evaluation of Amorphous (E.G.C.) and Microcrystalline (M.C.C.) Celluloses as Carriers for Prednisolone Powdered Solutions. M.S. Thesis, St. John's University, New York, 1988.
44. Spireas, S. S.; Jarowski, C. I.; Rohera, B. D, Powdered Solution Technology: Principles and Mechanism. Pharm. Res. 1992, 9, 1351-1358.
45. Fahmy RH, Kassem MA, Enhancement of famotidine dissolution rate through liquisolid tablets formulation: In vitro and In vivo evaluation. Eur J Pharm Biopham.2008, 69,993- 1003.
46. Nazzal S, Khan MA, Controlled release of a self-emulsifying formulation from a tablet dosage form: Stability assessment and optimization of some processing parameters. Int J Pharm. 2006, 315, 110-121.
47. Grover R, Spireas S, Wang T, Effect of powder substrate on the dissolution properties of Methchrothiazide liquisolid compacts. Drug Dev Ind Pharm. 1999, 25,163-168.
48. Bolton S, Spireas S, Sustained-release liquisolid compacts. In: 25th International Symposium on Controlled Release of Bioactive Materials, Nevada, USA.1998, 138-139.
49. Staniforth J, Powder flow, in: M. Aulton, Pharmaceutics: the Science of Dosage Form Design. Edinburgh. 2002, pp. 197–210.
50. Wells J, Pharmaceutical Preformulation: The physicochemical properties of drug substances. In: Aulton M, Pharmaceutics: the Science of Dosage Form Design, Edinburgh. 2002, pp.114-138.
51. Ajit S. Kulkarni, Nagesh H.Aloorkar, Madhav S, Mane and Jayashree B, Gaja Liquisolid Systems. April – June 2010, Volume 3.
52. Bindu MB, Kusum B and David Banji, Novel Strategies For Poorly Water Soluble Drugs. International Journal of Pharmaceutical Sciences Review and Research. September – October 2010, Volume 4, 14.
53. Sharma, A., Jain, C.P, Techniques to enhance solubility of poorly soluble drugs: a review. J. Global Pharm. Tech. 2010, 2, 18-28.
54. Saharan, V.A., Kukkar, V., Kataria, M., Gera, M., Choudhury, P.K. Int. J. Health Res. 2009, 2, 107-124.
55. Saharan, V.A., Kukkar, V., Kataria, M., Gera, M., Choudhury, P.K, Dissolution enhancement of drugs. Part II: effect of carriers. Int. J. Health Res. 2009, 2, 207-223.

Table 1: Requirements for Preparation of Liquisolid System.

Drug Candidate	Non Volatile Solvents	Carrier Materials	Coating Materials	Disintigrants
Digoxin, Digoxin Prednisolon, Hydrocortisone, Spironolactone, Hydrochlorothiazide, Polythiazide, Liquid Medications, such as Chlorpheniramine, Water insoluble Vitamins, Fish oil, etc.	Polyethylene Glycol 200 and 400, Glycerine, Polysorbate 80 and Propylene glycol.	Microcrystalline Cellulose such as Avicel PH 102 and 200, Lactose11, RS12 (to sustain drug delivery), etc.	Silica (Cab-O-Sil M5, Aerosil 20013, Syloid, 244FP8,9,etc)	Sodium Starch glycolate (Explotab13, Pumogel ,etc)

Table 2: Components and its characteristic of liquisolid techniques

Components	Drug Candidates	Non Volatile Solvents	Carrier Materials	Coating Materials
Properties	Low dose with BCS class ll and lV drugs	Water miscible ability to solubilise the drug. Act as binding agent	Porous. Absorption properties**.**	Fine. highly adsorptive particles
Examples	carbamazepine, famotidine, piroxicam, indomethacin, hydrocortisone, naproxen prednisolone, digoxin, digitoxin, prednisolone, hydrocortisone, spironolactone, hydrochlorothiazide, polythiazide, and other liquid medications such as chlorpheniramine, water insoluble vitamins, fish oil etc.	Polyethylene glycol 200 and 400, glycerin, polysorbate 80 and propylene glycol	grades of microcrystalline cellulose such as avicel PH 102 and avicel PH 200 20,35, lactose, eudragit Rl and eudragit RS12 (to sustain drug delivery) etc.	(Cab-O-Sil) M520,35 Aerosil 20030, Syloid, 244FP etc

Conflict of Interest: Not Declared

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