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LIQUISOLID TECHNIQUE: AN OVERVIEW ON ENHANCED SOLUBILITY AND BIOAVAILABILITY

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ABSTRACT

One of the most innovative dosage form used for enhancing dissolution rate and improving *in vivo* bioavailability of poorly soluble drugs is "liquisolid technology" Liquisolid systems essentially relate to formulations prepared by converting a liquid drug or a drug in liquid state (solutions, suspensions, or emulsions) into dry, non-adherent, free-flowing, and readily compressible powder mixtures by blending a liquid dispersion onto specific powder carriers and coating materials. Hence, liquisolid technique is also known as "powder solution technology. As these days there are many drugs in the market with poor solubility which results in poor dissolution and bioavailability, so solubility is becoming rate limiting factor in the development of new drugs. To succeed in dealing with this problem of solubility, there are many techniques but liquisolid technique is most promising technique which is discussed in this article. Drug, non-volatile solvent, carrier material, coating material, and disintegrants are the main components of liquisolid technique. In liquisolid technique carrier and coating material is mixed into the non-volatile solvent and then disintegrants is added and for tablet formulation final material is compressed. Therefore, the liquisolid technology allows the conversion of liquid systems into solid drug delivery systems. The main objective of this article, to explain about the liquisolid technique like method, classification, optimization, advantages, disadvantages, applications, pre-formulation studies, characterisation, formulation of tablet, post-compression studies, evaluation.

KEYWORDS: Liquisolid, bioavailability, dissolution, carrier material, emulsion, coating material.

INTRODUCTION

Oral bioavailability of drugs relies on various factors (circumstances) for example; aqueous solubility, permeability of drug, disintegration rate, first-pass and solvency and low permeability (penetrability) speak to the most vital parameter for orally administered drugs which empower them to accomplish the required concentration in systemic circulation necessary for the desired (optimum) pharmacological response.[1] Therapeutic effectiveness of a drug depends on the bioavailability which is subject to the solubility of drug particle. Almost 40% of new APIs are poorly water- soluble and lower dissolution rate hence lower solubility of compact solid dosage form is their principle constraint. Poorly water-soluble drugs require additional amount of time to dissolve in the gastrointestinal fluid under normal conditions that may delay the entry and ultimately absorption of the drug to systemic circulation. Throughout the years, formulation strategies targeted at dissolution improvement of poorly soluble substances by several techniques have been utilized to plan the formulation of oral drug delivery system that would upgrade the dissolution profile and in turn, the absorption efficiency of water- insoluble drugs, for example, reducing particle size via micronization, solid dispersion, lyophilisation, use of complexing, agents, preparation of self-emulsifying drug delivery systems are some of the methods which have been used to increase dissolution.[1,2]

Liquisolid technique is one of the most promising, encouraging and novel technique to improve the dissolution rates of poorly water soluble drugs. The concept of liquisolid technique enables one to convert a liquid drug or poorly water soluble solid drug dissolved in a suitable non-volatile solvent into a dry, non- adherent, free-flowing and readily compressible powder by its simple admixtures with selected carrier and coating materials. The compression can be processed by direct compression and slugging method.[1–3]

Preparation of Liquisolid

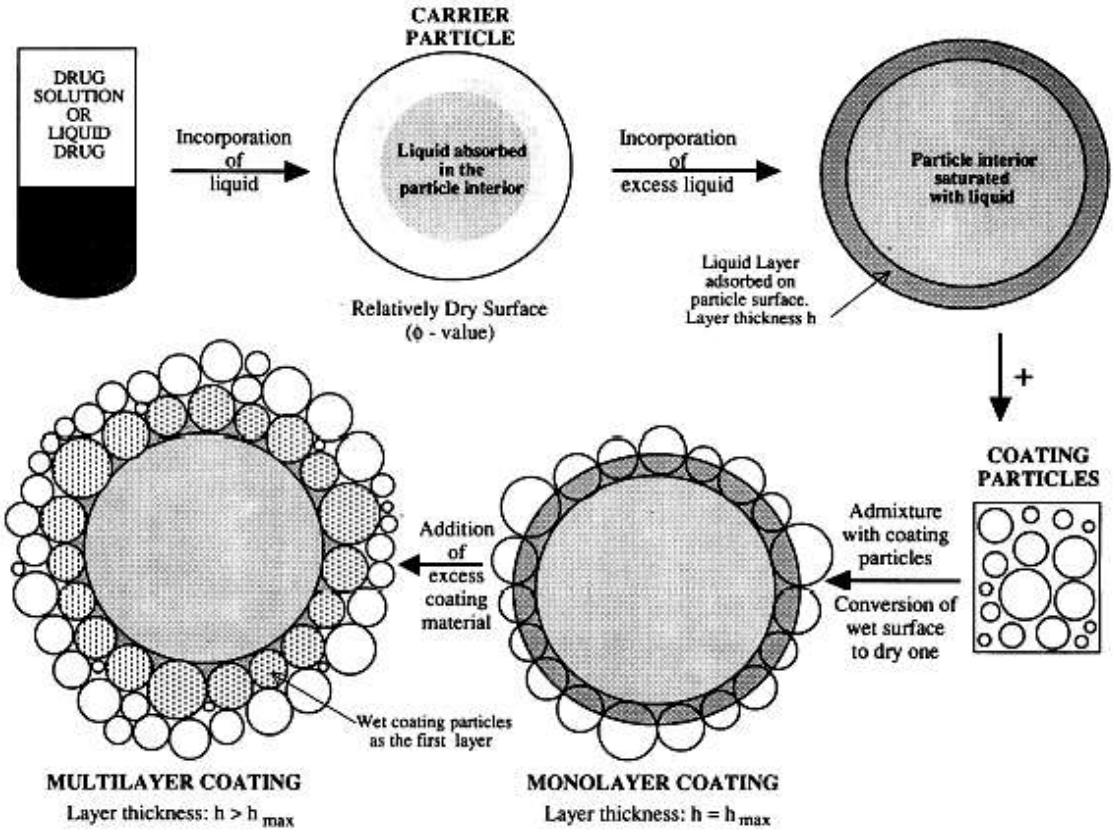

Fig: Theoretical model of powdered solutions.

The technology involved in preparation of Liquisolid compact is simple yet novel. As shown in figure a liquid lipophilic drug or solid drug is formulated, it should be initially dissolved or suspended in a suitable non-volatile solvent for production of a drug solution or drug suspension of desired concentration.[3]

1. A specific measured amount of the prepared drug solution or suspension, or the liquid drug itself, is taken into a particular amount of carrier material which ough to be ideally of porous nature and having possessing sufficient absorption properties, for example powder and granular grades of microcrystalline and amorphous cellulose are most favoured as carriers.[4]
2. The resulting wet blend is then converted into a dry looking, non-adherent, free flowing and easily compressible powder by the simple addition and mixing of a deliberate amount of coating material. Excipients having fine and highly adsorptive particles, for example various types of amorphous silicon dioxide (silica) are most suitable for this step.[5]
3. Before compression or encapsulation, different kinds of adjuvants such as lubricants and disintegrants (in case of immediate release compact) or binders (in case of sustained –

release compacts) might be blended with the finished Liquisolid systems for produce Liquisolid compacts i.e. tablets or capsules.[3,6]

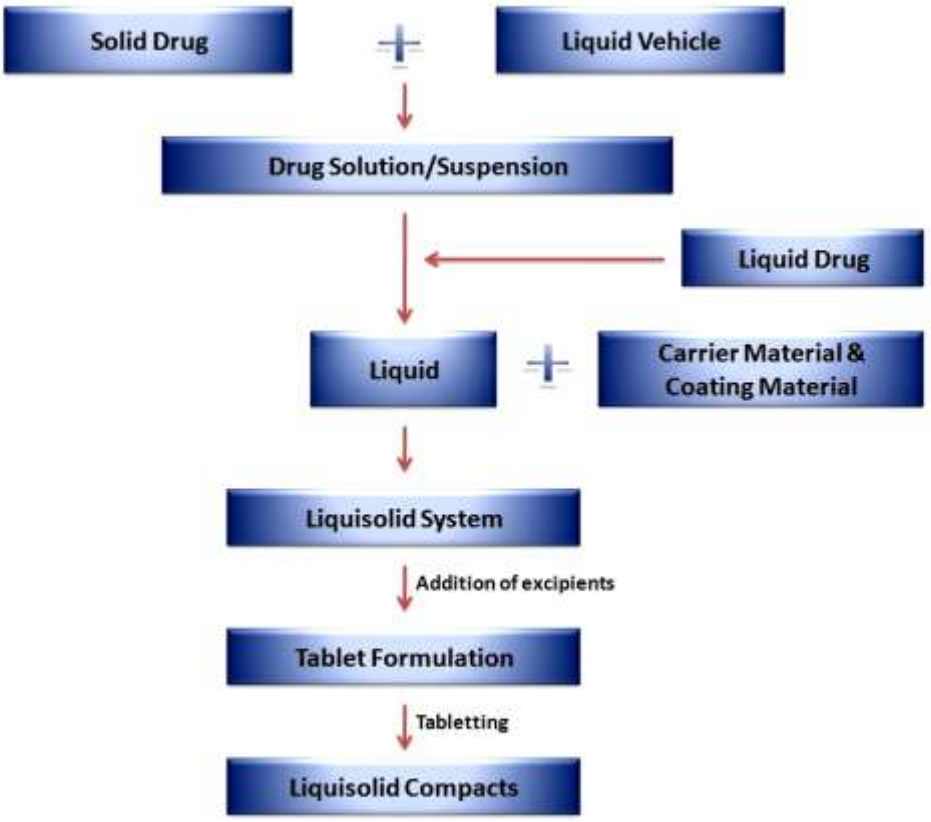

Fig: Flow chart of the steps involved in the preparation of liquisolid compacts.

The mathematical model for designing the Liquisolid systems

A powder has capacity to retain only limited amount of measured liquid while providing acceptable flow and compression properties. To compute the required amounts of powder excipients (carrier and coating material) a mathematical approach for the planning of formulation of Liquisolid systems has been developed by Spireas, this approach depends on the flowable(Φ-value) and compressible(Ψ-number) liquid retention potential.[7]

The flowable liquid retention potential (Φ) of a powder defined as the utmost amount of a given non-volatile liquid the powder can held inside the mass (w/w) while enabling acceptable flowability.

The compressible liquid(Ψ) retention potential of a powder defined as the utmost amount of liquid that can be retained inside its mass (w/w) while keeping up acceptable compactibility in order to produce compacts of suitable hardness & friability with no liquid squeezing out occurring during compression procedure.

The flowable liquid retention potential (Φ) of powders might be resolved using a new strategy the liquidsolid flowability (LSF) test. The compressible liquid retention potential (Ψ) of a powder might be determined using a new procedure termed the liquisolid compressibility (LSC) test which utilizes the 'pactisity theories' to evaluate compaction properties of liquid/ powders admixtures.[7–10]

According to this theory carrier 'pactisity theories' and coating material can hold certain amount of liquid while keeping up acceptable flow and compaction properties).

Depending on the excipients ratio (R) or carrier: coating ratio.[11,12]

Where,

R= Q/q…….. (1)

R= ratio between carrier & coating materials

Q=weight of carrier

q= weight of coating material

An adequately flowing and compressible liquisolid systems can be produced if a maximum if the liquid on the carrier is not exceed such characteristic amount of liquid is termed as the liquid load factor. Liquid load factor (Lf) defined as the ratio of liquid medication (W) and weight of carrier powder (Q) in the formulation, which must be compelled to an adequate (acceptable) flowing and compressible liquisolid system.[13–15]

Lf = W/Q…… (2)

Where,

W = weight of liquid medication

Q = weight of carrier.

Advantage[16,17]

1. Optimized rapid-release. Liquisolid tablets or capsules of water insoluble drugs exhibit enhanced in- vitro and in-vivo drug release as compared to their conventional counterparts.

2. Lower production cost than that of soft gelatin capsules.
3. Production of liquisolid system is similar to that of conventional tablets.
4. Capability of industrial production is also possible.
5. Enhanced bioavailability can be obtained as compared to conventional tablets.
6. Differentiate the dosage form by admixture of colour into liquid vehicle
7. Omit the process approaches like nanonisation, micronization techniques
8. Drug release can be modified using suitable formulation ingredients.

Disadvantage[16,17]

1. The liquisolid systems have low drug loading limits and they need high solubility of drug in non-volatile liquid vehicles.
2. Remembering the objective to accomplish acceptable flowability and compactibility for liquisolid powder formulation, high levels of carrier material and coating materials ought to add. This will increase the heaviness of tablets to above one gram which makes them hard to swallow. Thus, it is impossible with conventional tablet methods to convert high dose to liquisolid tablets with a tablet weight of less than 50mg.
3. Acceptable compression properties may not be accomplished since during the step of compression process liquid drug might be squeezed out of the liquisolid table bringing about tablets of inadmissible hardness.
4. Introduction of this strategy 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.

Classification of Liquisolid Systems[18,19]

Liquisolid compact are adequately flowable and compressible powdered forms of liquid medications, and is having industrial application. Additionally, the term ‘liquid medication’ does not just imply drug solutions, as in powdered solutions, but also include drug suspensions, emulsions, or liquid oily drugs.

A) Based on the formulation of powdered drug in liquid vehicle these ‘liquisolid compacts’ are four distinctive formulation systems namely

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

Since the non-volatile solvents are utilized to provide the drug solution or suspension, the liquid vehicle does not evaporate and hence, the drug is carried within the liquid system which thus is dispersed throughout the final product.[20]

B) depending on the formulation method used, liquisolid systems might be categorised into two categories which include.

- Liquisolid compacts
- Liquisolid microsystems.
- The term "liquisolid compacts" refers to immediate or sustained release tablets or capsules prepared, combined with the inclusion of appropriate adjuvant required for tableting or encapsulation, such as lubricants, and for fast 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 substance e.g., PVP in the liquid medication wherein the resulting unit size may be five times that of liquisolid compacts.

Mechanisms of Enhanced Drug Release from Liquisolid Systems[11,13,14,17,18,20]

There are several mechanisms of improved drug release have been proposed for liquisolid systems. The three primary proposed mechanisms comprises of an expanded surface area of drug accessible for release, an enhanced aqueous solubility of the drug, and a better developed wettability of the drug particles.

1. Increased surface area of the drug

As long as the medication inside the liquisolid system is totally dissolved in the liquid vehicle, it is situated in the powder substrate still in a solubilized, molecularly dispersed state. Consequently, the drug's surface area accessible for release is much prominent as compared to drug particles in directly compressed tablets.

2. Increased aqueous solubility

Moreover, in the first mechanism of drug released increment expectancy is that *Cs*, the drug solubility, may be increased with liquisolid systems. Actually, 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 essential molecule and the release medium in this microenvironment it is possible that the quantity of liquid vehicle that is diffusing out of a single liquisolid particle

together with the drug molecules might be enough to improve the aqueous solubility of the drug if the liquid vehicle behaves as a co-solvent.

3. Improved wetting properties

Because of the action of the liquid vehicle as surface active agent or having a low surface tension, wetting of the liquisolid important particles is improved.

Estimation of contact angles and water rising times are used for showing wettability of the liquisolid system. By decreasing interfacial tension between dissolution medium and tablet surface the non- volatile solvent present in the liquisolid system increases the wetting of drug particles, demonstrating lowering of contact angle of liquisolid compacts when compared to conventional tablets and hence increases wettability.

Components

The major components of liquisolid compacts include Drug, Nonvolatile solvent, Carrier materials, Coating materials, Disintegrants and Lubricants.

Drug

The drug must be poorly water soluble and having biopharmaceutical classification system II and IV.

Nonvolatile solvent

It should be inert, high boiling point, preferably water- miscible and less viscous organic solvent systems. Examples include propylene glycol, liquid polyethylene glycols, polysorbates, glycerin, N, N-dimethyl acetamide, fixed oils, PEG 560 and 370, Tween80 and 19, Span80 and 19, Glycerin.

Carrier material

It should be of materials with porous surface, closely matted fibers in their interior, sufficient absorption properties and high surface area. Examples include microcrystalline and amorphous cellulose, Starch, Lactose, MCC (Avicel PH 102), DCP (dibasic calcium phosphate), Eudragit RL and RS.

Coating materials

Fine and highly adsorptive particles contributes in covering the wet carrier particles and displaying a dry-looking powder. Particle size range of about 10 nm to 4560 nm in diameter.

Examples includes amorphous silicon dioxide (silica 2), silica (Cab-O-Sil M5), Syloid.

Disintegrants

Disintegrants is added to tablet formulation to facilitate a breakup or disintegrantion of tablet when it contacts water in the gastrointestinal tract. Disintegrants may function by drawing water into the tablet, swelling and causing the tablet to burt apart. Most commonly used Sodium starch glycolate, Cross carmelose sodium, Cross povidine, Explotab, Pregelatinized Starch etc.

Lubricants

During tablet ejection between the walls of the tablet and the walls used to reduce the of the die cavity in which the tablet was formed, lubricants are used to reduce friction. Example include: calcium stearate, magnesium stearate, talc etc.

Table no: Components of Liquisolid Technique.

Drug Candidates	Hydrochlorothiazide, Digitoxin, Prednisolone Hydrocortisone, Spironolactone, Digoxin etc.
Non Volatile Liquids	Poly Ethylene Glycol 200, Poly Ethylene Glycol 300, Poly Ethylene Glycol 400, Glycerine, Propylene Glycol, fixed oils.
Carrier Materials	Microcrystalline Cellulose PH 101, Microcrystalline Cellulose PH 200, Lactose, Methyl Cellulose, Ethyl Cellulose, Starch1500, Ethocel, Eudragit RL, Eudragit RS 12, Hydroxy Propyl Methyl Cellulose K4M, Hydroxy Propyl Methyl Cellulose K100M, Xanthum Gum, Guargum.
Coating Materials	Aerosil 200, Silica (Cab-O-Sil M5), Syloid 244FP, and Colloidal Silicon Dioxide.
Disintegrants	Sodium Starch Glycolate (Explotab, Primogel), Croscarmellose Sodium, Cross Polyvinyl Pyrrolidine, Pregelatized Starch.
Glidant	Talc
Lubricant	Magnesium Stearate
Release retardant material	Eudragit RS, RL, Hydroxy Propyl Methyl Cellulose K100M, K15M, K4M.

Optimization of Liquisolid Formulations[12,16]

The liquisolid technology has been effectively implemented to poorly water soluble drugs and drugs having lower doses. The formulation of a high dose, poorly soluble drug is one of the limitations of the liquisolid technology is the formulation of poorly water soluble drug, having high dose recommendation. In the liquid formulation the release rate of the drug is

directly proportional to the fraction of molecularly dispersed drug, as a higher drug dose will require higher liquid amounts for a desired release profile. Additionally to obtain liquisolid systems having acceptable flowability and compatibility carrier and coating materials having high level properties are required. Although, this results in an increase in weight of the tablet, eventually leading too difficult to swallow formulation of tablet sizes. Accordingly, to successfully overcome this, different issues of the liquisolid technology, several formulation parameters may be optimized shown in Table.

Formulation parameter	Optimization	Effect
liquid vehicle	high drug solubility in the vehicle	increased fraction of the molecularly dispersed drug (FM)
carrier and coating materials	high specific surface area	increased liquid load factor (Lf)
addition of excipients	Polyvinyl pyrrolidone (PVP)	increased liquid load factor (Lf), increased viscosity of liquid vehicle, inhibition of precipitation
excipient ratio (R)	high *R*-value	fast disintegration, inhibition of precipitation

Evaluation of liquisolid compact

***Flow behaviour*[9,18]**

For reducing the high dose difference In the production of the pharmaceutical dosages forms the flowability of a powder is of explanatory importance.

Angle of repose, Carr's index and Hausner's ratio were used in order to ensure the flow properties of the liquisolid systems.

Bulk density (sb) = Mass / Poured volume

Tap density (st) = Mass / Tapped volume

Carr's Index = [(st – sb) / st] x 100

Hausner ratio = (st / (sb)

Angle of repose (Fixed funnel and free standing cone method): A funnel with the end of the stem cut perpendicular to the axis of symmetry is secured with its tip 2.5 cm height (h) above graph paper placed on a flat horizontal surface. The powder sample to be analyzed is carefully poured through the funnel until the apex of the conical pile so formed just reached the tip of the funnel (h). The mean diameter (d) of the powder cone is determined and the tangent of the angle of repose is given by the equation.

Tan ɵ = h/r,

ɵ = tan –1 (h/r), Tan ɵ = h/0.5d,

Where,

ɵ = Angle of repose,

h = height of the tip of funnel from horizontal plane, r = radius of the pile made by powder,

d = diameter of cone.

Values for angle of repose = 29^0 usually indicate free flowing material and angle = 37^0 suggested a poor flowing material.

Solubility studies

Solubility studies are carried out by preparing saturated solutions of drug by adding excess of drug to non-volatile solvent and shaking them for 24 hrs. on orbital shaker under constant shaking. After this, the solutions are filtered and analyzed spectrophotometrically.[2]

Dissolution studies of liquisolid tablet

Generally Dissolution studies of Liquisolid tablet are carried out using dissolution apparatus USP II at 36ºC ± 0.5ºC. Many researchers revealed that at low drug concentrations in liquid medication, more rapid release rates are observed. The steady and higher dissolution rate displayed by liquisolid compacts will enhance the drug absorption from gastrointestinal tract.[1–3]

Characterization of Liquisolid

S. No.	Characterization	Purpose
1	UV/HPLC	Assay & uniformity content
2	Infrared Spectroscopy	Interaction studies
3	Powder X-Ray Diffraction Analysis (XRD)	Crystalline Properties
4	Differential Scanning colorimetry (DSC)	Interaction studies, polymorphism
5	HPLC/TLC	Purity, interaction/degradation
6	*In vitro* Dissolution studies	Release Properties of drug

Differential Scanning Calorimetry (DSC)

Thermal properties of the untreated drug and prepared samples are analyzed by DSC. It is necessary to determine any possible interaction between excipients used in the formulation. This will also indicate success of stability studies. If the characteristic peak for the drug is absent in the DSC thermogram, there is an indication that the drug is in the form of solution

in liquisolid formulation and hence it is molecularly dispersed within the system.[21,22]

Fourier Transform Infrared spectroscopy (FTIR)

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

Powder X-ray diffraction (PXRD)

Disappearance of characteristic peaks of drug in the liquisolid formulation and retaining peaks of carrier material is usually observed. This is an indication of conversion of drug to it's that drug to amorphous form or to solubilized form in the liquisolid formulation

Stability Studies

The result of storage on the release profile and the crushing strength of liquisolid compacts were examined for securing information on the stability of liquisolid system. Study on stability of liquisolid systems containing polythiazide (37˚C/ 38 and 75 % R.H., 12 weeks), hydrocortisone (ambient conditions, 10 month, carbamazepine (24˚C/ 75 % R.H., 6 months), indomethacin (24˚C/ 75 % R.H., 12 months)[35], piroxicam (24˚C/ 75 % R.H., 6 and 9 months, respectively) naproxen (19˚C/ 76 % R.H., 4 weeks) demonstrated that storage at various conditions neither had an effect on the hardness nor on the release profiles of liquisolid compacts. This is an indication that this technology is a promising technique to increase the release rate without having any physical stability issues.[8,23]

CONCLUSION

For improving in vitro dissolution rate and enhancing in vivo bioavailability of poorly water soluble drugs preparation of liquisolid systems is among one of the most promising and innovative techniques. A liquisolid system can be prepared by incorporating a certain drug in liquid state (liquid drug; drug solution, suspension, or emulsion) onto a specific carrier and coating material while forming a dry, free-flowing, and readily compressible powdered blend. Liquisolid systems are unique medical forms which require specific evaluation for their quality assurance. The presented work was aimed at the modern evaluation of liquisolid systems and the evaluation of differences among liquisolid tablets and conventional tablet. It could be stated from the obtained results, that all liquisolid tablets had very fast disintegration times connected to enhanced dissolution profiles.

REFERENCES

1. Sri LDS. A LATEST REVIEW ON LIQUISOLID, 2017; 1-3.
2. Guidelines A. Journal of drug delivery and therapeutics (jddt), 2014; 4(5): 69-73.
3. Spireas S, Sadu S, Grover R. In vitro evaluation of hydrocortisone liquisolid tablets. *J Pharm Sci*, 1998; 87(7): 867-872. doi:10.1021/js970346g.
4. No CAS, Manufacturers C, Compan AY. DialB2B, 2016; 298: 4-9.
5. *Www.pharmatechbd.blogspot.com*.
6. Komala DR, Janga KY, Jukanti R, Bandari S, Vijayagopal M. Competence of raloxifene hydrochloride loaded liquisolid compacts for improved dissolution and intestinal permeation. *J Drug Deliv Sci Technol*, 2015; 30: 232-241. doi:10.1016/j.jddst.2015.10.020.
7. Vijay kumar Nagabandi K.N.Jayaveera TR. LIQUISOLID Compacts: A Novel Approach to Enhance Bioavailability of Poorly\rSoluble Drugs. *Int J Pharm Biol Sci (eISSN 2230-7605)*, 2011; 1(3): 89-102.
8. Al-Sarraf MA, Hussein AA, Abdul Jabbar AS. Dissolution enhancement of telmisartan by liquisolid compacts. *Int J Pharm Pharm Sci*, 2014; 6(SUPPL. 2): 743-749.
9. Pavani E, Noman S, Syed IA. Liquisolid technique based sustained release tablet of trimetazidine dihydrochloride. *Drug Invent Today*, 2013; 5(4): 302-310. doi:10.1016/j.dit.2013.08.006.
10. Pezzini BR, Beringhs AO, Ferraz HG, Silva MAS, Stulzer HK, Sonaglio D. Liquisolid technology applied to pellets: Evaluation of the feasibility and dissolution performance using felodipine as a model drug. *Chem Eng Res Des*, 2016; 110: 62-69. doi:10.1016/j.cherd.2016.01.037.
11. Sanjay PD, Deepak M, Bhanudas SR. Liquisolid Technology: Technique for Formulation With Enhanced Bioavailability. *World J Pharm Pharm Sci*, 2013; 3(1): 368-387. http://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=1&ved=0CCYQFjAA&url=http%3A%2F%2Fwww.wjpps.com%2Fdownload%2Farticle%2F1388592691.pdf&ei=jv10VYKBLbGOsQTt4YGACg&usg=AFQjCNGyNkEeqQWBJNUyGIs7-kLMsBEPDg&sig2=CXXKltGfHZTB_3j83bTKSw&bvm=bv.95039771,.
12. Azharshekoufeh B. L, Shokri J, Adibkia K, Javadzadeh Y. Liquisolid technology: What it can do for NSAIDs delivery? *Colloids Surfaces B Biointerfaces*, 2015; 136: 185-191. doi:10.1016/j.colsurfb.2015.09.014.
13. Bhowmik D, Harish G, Duraivel S, Kumar BP, Raghuvanshi V, Sampath KP. Nanosuspension -A Novel Approaches In Drug Delivery System. *Pharma J*, 2012; 1(12):

50-63.

14. No CAS, Manufacturers N, Compan AY. DialB2B, 2016; (21829): 4-9.
15. Suliman AS, Anderson RJ, Elkordy AA. Norfloxacin as a model hydrophobic drug with unique release from liquisolid formulations prepared with PEG200 and Synperonic PE/L-61 non-volatile liquid vehicles. *Powder Technol*, 2014; 257: 156-167. doi:10.1016/j.powtec.2014.02.048.
16. Sowmya C, Reddy CS, Anilkumar D, Amrutha V, Anusha AL. Liquisolid technique: A novel approach to enhance solubility and bioavailability of BCS-II drugs. *Int Res J Pharm*, 2012; 3(7): 108-115. http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L365873163%5Cnhttp://www.irjponline.com/admin/php/uploads/1220_pdf.pdf.
17. Balaji A, Umashankar MS, Kavitha B. Liquisolid technology- A latest review. *Int J Appl Pharm*, 2014; 6(1): 11-19.
18. Chella N, Shastri N, Tadikonda RR. Use of the liquisolid compact technique for improvement of the dissolution rate of valsartan. *Acta Pharm Sin B*, 2012; 2(5): 502-508. doi:10.1016/j.apsb.2012.07.005.
19. Chella N, Shastri N, Tadikonda RR. Use of the liquisolid compact technique for improvement of the dissolution rate of valsartan. *Acta Pharm Sin B*, 2012; 2(5): 502-508. doi:10.1016/j.apsb.2012.07.005.
20. Savjani KT, Gajjar AK, Savjani JK. Drug Solubility: Importance and Enhancement Techniques. *ISRN Pharm*, 2012; 2012: 1-10. doi:10.5402/2012/195727.
21. Vraníková B, Gajdziok J, Vetchý D. Modern evaluation of liquisolid systems with varying amounts of liquid phase prepared using two different methods. *Biomed Res Int*, 2015; 2015. doi:10.1155/2015/608435.
22. Vajir S. Enhancement Of Dissolution Rate of Poorly Water Soluble Diclofenac Sodium By Liquisolid Technique, 2012; 1(3): 989-1000.
23. Prajapati ST, Bulchandani HH, Patel DM, Dumaniya SK, Patel CN. Formulation and Evaluation of Liquisolid Compacts for Olmesartan Medoxomil. *J Drug Deliv*, 2013; 2013(5): 1-9. doi:10.1155/2013/870579.