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A REVIEW ON LIQUISOLID TECHNOLOGY

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ABSTRACT

Liquisolid system is a novel concept of drug delivery via oral route. Solubility is the phenomenon of dissolution of solid in liquid phase and is one of the important parameter to achieve desired concentration of drug in systemic circulation for pharmacological response. Poorly water soluble compound's oral administration often require high doses in order to reach therapeutic plasma concentrations because insufficient dissolution rate of the drug is the limiting factor in the oral bioavailability and one of the most challenging aspects of drug development. Various techniques are used for the improvement of the aqueous solubility, dissolution rate, and bioavailability of poorly water soluble drugs include micronization, chemical modification, pH adjustment, solid dispersion, complexation, co-solvency, micellar solubilization, hydrotropy etc.

A more recent technique, **"**powdered solution technology" or "Liquisolid technology", has been applied to prepare water-insoluble drugs into rapid-release solid dosage forms. 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 properties. Increase in dissolution rate and in turn improvement in bioavailability is observed in case of poorly water soluble drugs. By use of this technique, liquid medications such as solutions or suspensions of water insoluble drugs in suitable non-volatile liquid vehicles can be easily converted into powder with acceptable flow properties and compression behavior using suitable powder excipients.

KEYWORDS: Dissolution, Pharmacological response, Bioavilability,Liquisolid technology, Poorly water soluble drugs, Liquid medication.

INTRODUCTION

Dissolution is the critical parameter of pharmaceutical dosage form and used to ensure batch to batch quality contro, for the assessment of bioequivalence and sometimes to correlate *in-vitro* with *in-vivo* drug release characteristics.[1] Dissolution remains an important factor for absorption of drugs especially in case of water insoluble drugs.[2]In the oral bioavailability of poorly water soluble compounds, the insufficient dissolution rate is the limiting factor.[3]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.[4]

During the past few years many techniques have been developed such as drug micronization, solid dispersions, co-precipitation, lyophilization, micro– encapsulation, use of pro-drug and drug derivatization processes, and inclusion of drug solutions into soft gelatin capsules.[5]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.[6,7,8] The concept of powdered solutions makes it possible to convert drug solutions or liquid medications into moderately flowing powders by an admixture with selected powder excipient. Some investigators have used a similar approach to increase release profiles of several water–insoluble drugs.[9]To increase dissolution rates of drugs, salt formation, particle size reduction etc., have commonly been used but achieving desired bioavailability enhancement may not always be possible due to some practical limitations with these techniques.[10]Solid dispersion systems have shown promising results in increasing bioavailability of poorly water-soluble drugs in which the drug is dispersed in solid water-soluble matrices either molecularly or as fine particles[11,12,13]and Serajuddin et al. reported that some of the manufacturing problems with solid dispersion systems may be overcome by using surface-active and self-emulsifying carriers.

Among them, liquisolid compacts is one of the most promising and new technique which promotes dissolution rate of water insoluble drugs.[14]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.[9,15,16]Liquisolid tablets or

compacts can be defined as immediate or sustained-release tablets or capsules that are prepared using the technique of "liquisolid systems". Included are adjuvants required for tabletting or encapsulation, such as lubricants, and adjuvants required for rapid or sustained-release action, such as disintegrants or binders, respectively.[9,15]

Liquisolid compacts are acceptably flowing and compressible powder forms of liquid medications. The liquid medication is the water insoluble drugs carried in suitable non-volatile solvents. This liquid medication is converted into a free flowing powder by addition of suitable excipients. The concentrations of the carriers, coating materials, disintegrants, lubricants and glidants are optimized to get a non-sticky easily compressible blend. This technology ensures the promotion of dissolution rate of poorly water soluble drugs since the drugs are completely solubilised in the suitable solvents before converting it into free flowing mass.[17,18]

COMPONENTS

The major formulation components of liquisolid compacts are:

Carrier material

These are compression-enhancing, relatively large, preferably porous particles possessing a sufficient absorption property which contributes in liquid absorption. E.g. various grades of cellulose, starch,[9] lactose[19] ,sorbitol[20] , Avicel PH 102 and 200 , Eudragit RL and RS, amorphous cellulose etc.[21]

Coating material

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, Syloid 244FP etc.) contributes in covering the wet carrier particles and displaying a dry-looking powder by adsorbing any excess liquid.[9,15,16]

Non-volatile solvents

Inert, high boiling point, preferably water-miscible and not highly viscous organic solvent systems. Various non-volatile solvents used for the formulation of liquisolid systems include Polyethylene glycol 200 and 400, glycerin, polysorbate 80 and propylene glycol, propylene glycol, liquid polyethylene glycols, polysorbates, glycerin, N, N-dimethylacetamide, fixed oils, etc.[21]

Drug candidates

Examples of drug candidates include digoxin, digitoxin, prednisolone, hydrocortisone, spironolactone, hydrochlorothiazide, polythiazide, and other liquid medications such as chlorpheniramine, water insoluble
vitamins, fish oil, etc

Disintegrants

Most commonly used disintegrant is sodium starch glycolate (Explotab13, Pumogel, etc.)

Liquid medication includes liquid lipophilic drugs and drug suspensions or solutions of solid water insoluble drugs in suitable non-volatile solvent systems.[22]

Liquisolid systems 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 nonvolatile solvent systems, into dry, non-adherent, free-flowing and readily compressible powder admixtures by blending with selected carrier and coating materials.[22]

PREPARATION OF LIQUISOLID TABLET

Calculated quantities of drug and non-volatile solvent is accurately weighed in 20 ml glass beaker and then heated to dissolve the drug in that solvent. The resulting hot medication is incorporated into calculated quantities of carrier and coating materials. Mixing process is carried out in three steps as described by Spireas et al.[9,16]

(1)During the first stage, the system is blended at an approximate mixing rate of one rotation per second for approximately one minute in order to evenly distribute liquid medication in the powder.

(2) In the second stage, the liquid/powder admixture is evenly spread as a uniform layer on the surfaces of a mortar and left standing for approximately 5 min to allow drug solution to be absorbed in the interior of powder particle.

(3) In the third stage, the powder is scraped off the mortar surfaces by means of aluminum spatula and then blended with sodium starch glycolate for another 30 seconds in a similar way to the first stage. This gives final formulation of liquisolid tablets. Prepared liquisolid.

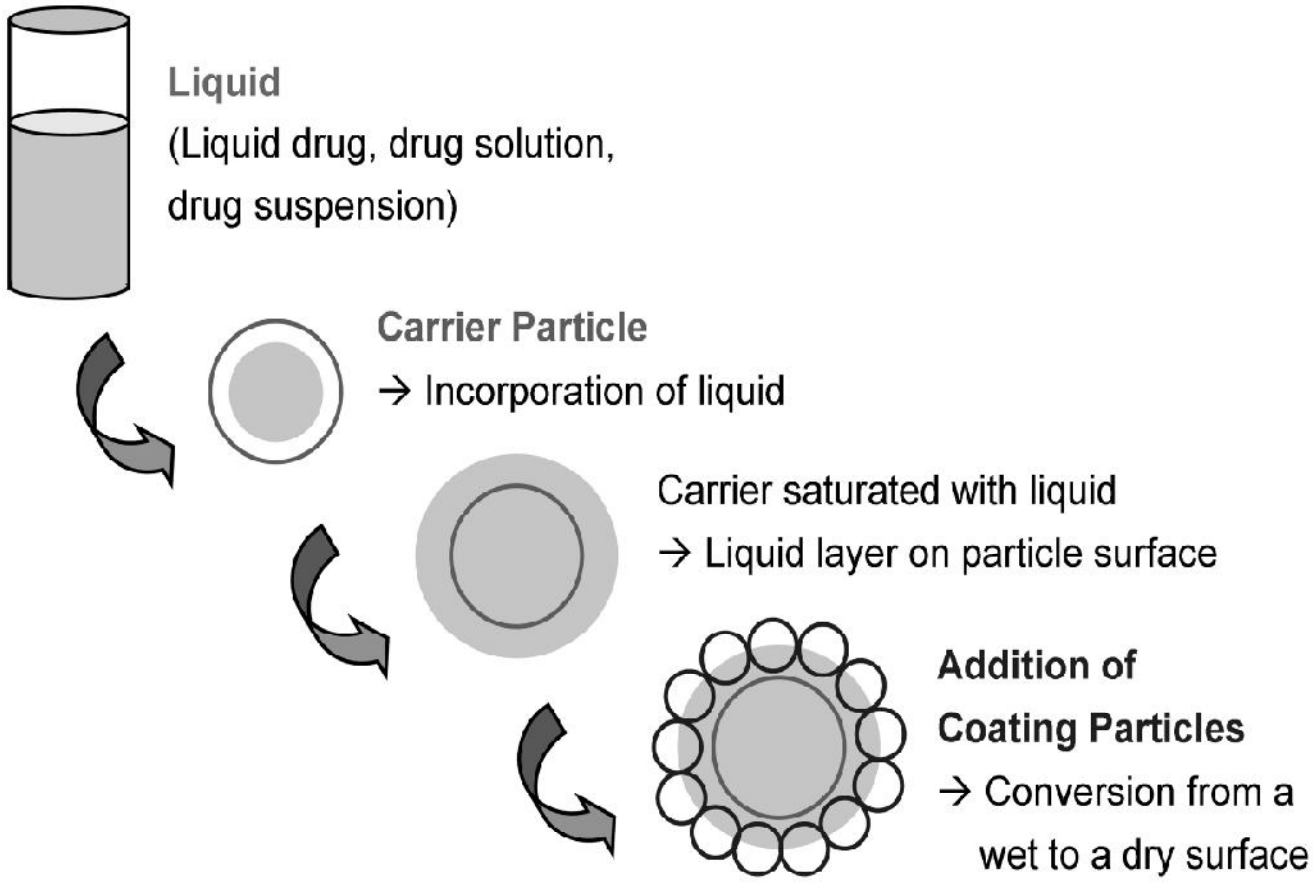

Fig. 1: Schematic representation of liquisolid systems[23]

CLASSIFICATION OF LIQUISOLID SYSTEM

A. Based on the type of liquid medication contained therein, liquisolid systems may be classified into three subgroups:

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

The first two may be produced from the conversion of drug solutions or drug suspensions and the latter from the formulation of liquid drug into liquisolid systems. Since non-volatile solvents are used to prepare the drug solution or suspension, the liquid vehicle does not evaporate and thus, the drug is carried within the liquid system which in turn is dispersed throughout the final product.

B. Based on the formulation technique used, liquisolid systems may be classified into two categories:

1. Liquisolid compacts
2. Liquisolid Microsystems [21]

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.[24]

ADVANTAGES

Liquisolid tables have many advantages. These include:

- Liquisolid systems are low cost formulations than soft gelatin capsules.
- Drug release can be modified using suitable formulation ingredients
- Drug can be molecularly dispersed in the formulation.
- Capability of industrial production is also possible.
- Enhanced bioavailability can be obtained as compared to conventional tablets.
- Several slightly and very slightly water-soluble and practically water-insoluble liquid and solid drugs, can be formulated into liquisolid systems.
- Even though the drug is in a tablet or capsule form, it is held in a solubilised liquid state, which contributes to increased drug wetting properties, thereby enhancing drug dissolution.
- Rapid release liquisolid tablets or capsules of water insoluble drugs exhibit enhanced in-vitro and in-vivo drug release when compared to their commercial counter parts, including soft gelatin capsules preparation.
- Sustained release liquisolid tablets or capsules of water insoluble drugs exhibit constant dissolution rates (zero-order release) comparable only to expensive commercial preparations that combine osmotic pump technology and laser-drilled tablets.
- Can be applied to formulate liquid medications such as oily liquid drugs.
- Better availability of an orally administered water insoluble drug.
- Production of liquisolid systems is similar to that of conventional tablets.
- Can be used for formulation of liquid oily drugs.
- Can be used in controlled drug delivery.

LIMITATIONS

- Not applicable for 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.
- Acceptable compression properties may not be achieved since during compression liquid drug may be squeezed out of the liquisolid tablet resulting in tablets of unsatisfactory hardness.
- Introduction of this method on industrial scale and to overcome the problems of mixing small quantities of viscous liquid solutions onto large amo unts of carrier material may not be feasible.
- Hydrotropy is suggested to be superior to other solubilization method, such as miscibility, micellar solubilization, cosolvency and salting in, because the solvent character is independent of pH, has high selectivity and does not require emulsification.
- It only requires mixing the drug with the hydrotrope in water.
- It does not require chemical modification of hydrophobic drugs, use of organic solvents, or preparation of emulsion system.

APPLICATIONS

- Liquisolid compact technology is a powerful tool to improve bioavailability of water insoluble drugs. Several water insoluble drugs on dissolving in different non-volatile solvents, have been formulated into liquisolid compacts.
- Literature cites different drugs successfully incorporated into liquisolid compacts.
- Rapid release rates are obtained in liquisolid formulations.
- These can be efficiently used for water insoluble solid drugs or liquid lipophilic drugs.
- Sustained Release of drugs which are water soluble drugs such as propranolol hydrochloride has been obtained by the use of this technique.
- Solubility and dissolution improvement
- Flowability and compressibility
- Designing of Controlled Release Tablets
- Bioavailability Enhancement

FUTURE PROSPECTS

Poor bioavailability is a major limitation in successful drug delivery by oral route. Lot of research work is focused on oral bioavailability enhancement of the poorly absorbed drugs. It is necessary to understand the reason behind the poor bioavailability before designing a delivery system. The positive results obtained with the use of various delivery systems or different approaches of bioavailability enhancement seem to be promising. However, the commercial development of the product demands much more research for overcoming the challenges such as scale up, cost effectiveness and instability of some of the formulations.[25]

FORMULATION DESIGN AND THEORETICAL ASPECTS

To achieve good flow behavior and compressibility of liquisolid systems a mathematical model designed by Spireas et al.was used as formulation design model for the liquisolid tablets. Prerequisites for this include suitable drug candidate, suitable non-volatile solvent, carrier and coating materials. The amounts of excipients (carrier and coating materials) used to prepare liquisolid compacts depend on the flowable liquid retention potential values (Φ-value) and the liquid loading factors (Lf) . The Φ-value of a powder is the maximum amount of a given non-volatile liquid that can be retained inside powder bulk (w/w) while maintaining acceptable flowability. Whereas, Lf is the mass ratio (w/w) of the liquid medication to the carrier powder in the liquisolid formulation, and it is given by Equation(Eq 1). Therefore, in order to calculate the required weight of excipients, we need to determine the liquid retention potential value for both carrier (ΦCA-value) and coating (ΦCO-value) materials for each non volatile liquid vehicle used, these values are constant for the given vehicle/powder system. Knowing the carrier:coating ratio (R), which is 20:1 in this study, liquid loading factor (Lf) can be calculated by the following equation:

$$Lf = \Phi CA + \Phi CO \ (1 / R) \ldots\ldots\ldots (1)$$

Once liquid loading factors were obtained for such non-volatile liquid vehicle used in this study, the optimum weight of the carrier (Q), required for the respective vehicle could be calculated by rearranging the Equation (2).

$$Lf = W / Q \ldots\ldots\ldots\ldots (2)$$

Where: W is the weight of the liquid medication (the drug + non-volatile liquid vehicle) and Q is the weight of the carrier . The weights of the liquid medications (the drug + non volatile liquid vehicle) were calculated at drug:vehicle ratios of 1:2 and 1:4. Once the values for Q

were obtained for the respective vehicle, the optimum weight of the coating material (q) could also be obtained (Equation 3).

$$R = Q / q \ldots\ldots\ldots\ldots\ldots \quad (3)$$

Where: Q and q are the weight of the carrier and coating material, respectively. By calculating Lf and W, we can calculate the amount of Q and q required for the liquisolid system.

PRECOMPRESSION SYUDIES

Flow properties of the liquisolid system

The flow properties of the liquisolid systems were estimated by determining the angle of repose, Carr's index, and Hausner's ratio. The angle of repose was measured by the fixed funnel and freestanding cone method. The Bulk density and Tap densities were determined for the calculation of Hausner's ratio and Carr's Index .[26]

Infra red spectra analysis

The infra red spectra of solid dispersions were recorded by the KBr method using a Fourier transform infrared spectrophotometer (FTIR-8400s). A base-line correction was made using dried potassium bromide and then the spectrum of the pure ATR, liquisolid system was obtained.[18]

X-ray powder diffraction

X-ray diffractograms are obtained using a Philips Analytical XRD instrument .The scanning range is from 10–70˚ 2θ. The X-ray diffraction (XRD) patterns are determined for drug, excipients used in formulation, physical mixture of drug and excipients, finally for the prepared liquisolid system.[27] Absence of constructive specific peaks of the drug in the liquisolid X-ray diffractogram indicate that drug has almost entirely converted from crystalline to amorphous or solubilized form. Such lack of crystallinity in the liquisolid system was understood to be as a result of drug solubilization in the liquid vehicle i.e., the drug has formed a solid solution within the carrier matrix. This amorphization or solubilization of drug in the liquisolid system may contribute to the consequent improvement in the apparent solubility and therefore the dissolution rate of the drug.[28]

Differential scanning calorimetry (DSC)

Thermotropic properties and thermal behavior of the samples (API, excipients, and liquisolid compacts) were recorded on a DSC. Samples (3-5 mg) were placed in aluminum pans and lids at constant heating of 15°C/min spanning a temperature range up to 30-300°C. Nitrogen was used as a purge gas through the DSC cell.[29]Complete disappearance of characteristic peaks of drug indicates the formation of drug solution in the liquisolid powdered system, i.e., the drug is molecularly dispersed within the liquisolid matrix.[28]

Scanning Electron Microscopy (SEM)

SEM study show complete disappearance of crystals of drug and confirms that drug is totally solubilized in liquisolid system.[28]

CONCLUSION

In conclusion, it is well established that the inadequate dissolution of water-insoluble drugs is the major reason for their poor and erratic bioavailability since it is the rate determining step in the absorption. The liquisolid technique could be a promising alternative technique to increase the dissolution of water insoluble drugs and thereby enhance their absorption characteristics. Liquisolid formulations are designed to contain liquid medications in powdered form, thereby possessing mechanisms of drug delivery similar to those of soft gelatin capsule preparations containing liquids. 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 ratios. The use of nonvolatile solvent in the formulation causes increased wettability of water insoluble drugs and ensures molecular dispersion of drug in the formulation. The enhanced rate of drug dissolution from liquisolid tablets is probably due to an increase in wetting properties and surface area of drug particles available for dissolution Modification of formulation by use of certain agents cause rapid disintegration rates as compared to conventional tablets and therefore, they show improved release rates and hence greater bioavailability

REFERENCES

1. Costa P, Lobo JMS. Modeling and comparison of dissolution profiles. Eur J Pharm.Sci, 2001; 13: 123-133.

2. Brahmankar DM, Jaiswal SB. Biopharmaceutics and Pharmacokinetics - A treatise. Vallabh Prakashan, Delhi, India.; 2002:19.
3. Rogers TL, Johnston KP, Williams RO. Solution-based particle formation of pharmaceutical powders by supercritical or compressed fluid CO_2 and cryogenic spray-freezing technologies. Drug Dev. Ind. Pharm, 2011;27 (10): 1003–15.
4. Walke PS, Pawar AY, Sonawane DD, Bhamber RS. Liquisolid : A novel technique to inhance solubility and dissolution rate of BSC class II pharmaceuticals. Journal of pharmacy research, 2011; 4(11):4011-14.
5. Kapsi SG, Ayreys JW, Processing factors in development of solid solution formulation of itraconazole for enhancement of drug dissolution behavior of water insoluble drugs. J. Pharm. Sci., 2001;76:744-52.
6. Aguiar AJ, Zelmer AJ, Kinkel AW. Deagglomeration behavior of relatively insoluble benzoic acid and its sodium salt. J. Pharm. Sci.,197 ;56:1243-52.
7. Finholt P, Solwang S. Dissolution kinetics of drugs in human gastric juice the role of surface tension. J. Pharm. Sci.,1968;57:1322-26.
8. Lin SL, Mewnij J, Lachman L. Interdependence of physiological surfactant and drug particle size on the dissolution behavior of water insoluble drugs. J.Pharm. Sci., 1968;57:2143-46.
9. Spireas S. Liquisolid systems and methods of preparing same. United State Patent,2002; 6423,339.
10. Serajuddin, ATM. Solid dispersion of poorly water-soluble drugs: early promises, subsequent problems and recent breakthroughs. J. Pharm. Sci.,1999; 88: 1058–66.
11. Chiou WL, Riegelman S. Pharmaceutical applications of solid dispersion systems. J. Pharm. Sci.,1971; 60:1281–1302.
12. Ford J.L. The current status of solid dispersions. Pharm. Acta Helv,1986; 61: 69–88.
13. Serajuddin, ATM, Sheen PC, Mufson D, Bernstein DF, Augustine MA.Effect of vehicle amphiphilicity on the dissolution and bioavailability of a poorly water-soluble drug from solid dispersions. J. Pharm. Sci.,1988; 77: 414–17.
14. Fahmy RH, Kassem MA. Enhancement of famotidine dissolution rate through liquisolid tablet formulation*:* In vitro and In vivo evaluation. Eur. J. Pharm. Biopharm, 2008; 69: 993-1003.
15. Spiras S, Bolton SM, Liquisolid systems and methods for preparing same. United States patent,2000; 6:096,337.

16. Spiras S, Bolton SM. Liquisolid systems and methods for preparing same, United States patent,1999; 5:968,550.
17. Babatunde A, Elkordoy AA, Esse EA, Elhagar S.Liquisolid system to improve the dissolution of furosemide. Scientia pharmaceutica, 2010; 78: 325-44.
18. Yadav AV, Shete AS, Dabke AP. Formulation and evaluation of orodispersible liquisolid compect of aceclofenac, Indian J. Pharm. Educ. Res., 2010; 44(3): 227-35.
19. Javadzadeh Y, Navimipour B, Nokhodchi A. Liquisolid technique for dissolution rate enhancement of a high dose water insoluble drug (carbamazepine).Int. J. Pharm, 2007; 341: 26-34.
20. Javadzadeh Y, Siahi MR, Asnaashri S. An investigation of physicochemical properties of piroxicam liquisolid compacts.Pharm. Dev. Tech,2007; 12: 337-34.
21. Kulkarni AS, Aloorkar NH, Mane MS, Gaja JB. Liquiosolid sysyem:A Review. Int.journal of pharmaceutical sciences and nanotechnology,2010;3(1):795-802.
22. Rao SA, Naga AT. Liquisolid technology:An overview. Int. journal of research in pharmaceutical and biomedical science, 2011;2(2):401-9.
23. Spiras S, Wang T, Grover R. Effect of powder substrate on dissolution properties of methylclothiazide Liquisolid compacts. Drug. Dev. Ind. Pharm,1999;25: 63-168.
24. Burra S, Yamsani M, Vobalaboina V.The liquisolid technique:An overview. Brazilian journal of pharmaceutical sciences, 2011;47(1):475-82.
25. Gupta AK, Sehrawat SK. Bioavilability enhancement of poorly water soluble drugs:A review. Int. journal of pharmacy and life sciences,2011;2(3):640-50.
26. Karmakar AB, Gonjari ID, Hosmani AH, Pandurang, Bhise SB.Liquisolid tablet:A novel approach for drug delivery. Int. J. of health research, 2009;2(1):93-98.
27. Javadzadeh YJ, Jafari-NB, Nokhodchi A. Liquisolid technique for dissolution rate enhancement of high dose water-insoluble drug (Carbamazepine). Int J Pharm, 2007; 34: 26-34.
28. 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.
29. Kasture SV, Gondkar SB, Darekar AB, Priyobrata D, Bhambar KV. Enhancement of dissolution rate of lansoprasole using liquisolid tablet technique. Int. J. of pharmaceutical research,2011;3(2):27-31.

30. Serajuddin ATM, Sheen PC, Augustine MA . Improved dissolution of a poorly water-soluble drug from solid dispersions in polyethylene glycol: polysorbate 80 mixtures.Int. J. Pharm. Sci,1990; 79: 463–464.
31. 25.Spireas S, Sadu S. Enhancement of prednisolone dissolution properties using liquisolid compacts. Int J Pham 1998; 166: 177-188.
32. Tayel SA, Soliman II, Louis D. Improvement of dissolution preoperties of carbamazepine through application of the liquisolid technique. Eur J Pharm Biopharm 2008; 69: 342-347.
33. Spireas S, Jarowski CI, Rohera, BD.Powdered solution technology: principles and mechanism. Pharm. Res,1992; 9: 1351-1358.
34. Patel DJ, Patel JK, Pandya VM. Improvement in the dissolution of poorly water soluble drug using media milling technique. Thai J. Pharm sci.,2010;34:155-64.
35. Karmakar AB. Effect of Ceolus KG-802 on the dissolution rate of finofibrate liquisolid tablet:Preformulation development studies. Drug discoveries and therapeutics,2010;2(6):493-98.