Liquisolid Dosage System: A Novel Approach for Dosage formulation

Sudarshan B. Aher*[1], Dattatraya M. Shinkar[1], Ravindra B. Saudagar[1].

1.Department of pharmaceutics, KCT'S RGS College of pharmacy, Anjaneri, Nashik.422213. Maharashtra, India.
2. Department of pharmaceutical Chemistry, KCT'S RGS College of pharmacy, Anjaneri, Nashik.422213.Maharashtra, India.
Email: sudarshanaher321@gmail.com
Contact. No 9545454165.

Abstract:

In the drug development enhancement of oral bioavailability of poorly water soluble drugs is one of the most challenging aspects of drug. The pharmaceutical industry face the problem poor dissolution characteristics of water insoluble drug. these problem solve by applying recent techniques "powdered solution technology" or "liquisolid technology", for prepare water-insoluble drugs into rapid-release solid dosage forms. Design and formulation of this approach is prescribed according to new mathematical model given by spires et al. the solubility is Increasing by using a non-volatile solvent which is suitable for drug, their by dissolving the drug in the non volatile solvent it is termed as liquid medicament. This case, the drug is in a solid dosage form, it is held within the powder substrate in solution or, in a solubilized, almost 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.

Keywords : liquisolid compact ,poorly water soluble drugs, carriers, bioavailability.

Introduction

The oral course is the most favored method for medication organization because of the straightforwardness, high patient agreeability, and minimal effort of creation. The medication must be introduced in solution form for retention through gastrointestinal tract (GIT) when given orally [1]. It has been made that the dynamic fixing in a strong measurement structure must experience disintegration before it is accessible for retention from the gastrointestinal tract. The rate of absorption of an poorly water-dissolvable medication, formulated as an orally managed solid dosage form, is controlled by its dissolution rate in the liquid present at the absorption site, i.e. the disintegration rate is regularly the rate-determination step in drug absorption[2].

This system is for the most part used to form the medications of BCS class II and IV . Inadequately water solvent medications are hard to figure utilizing conventional strategies. Diverse methods have been accounted for in the writing to accomplish better medication disintegration rates, to be specific: (a) decrease of molecule size by means of micronization or nanonization to expand the surface region; (b) utilization of surfactants[4] ; (c) inclusion with cyclodextrins [5] ; (d) utilization of pro-drug and derivatisation; (e) development amorphous solid ; (f) microencapsulation and incorporation of medication arrangements or fluid medications into delicate gelatin cases or uniquely fixed hard shell capsules[6,7] Amongst different strategies to conquer the solvency issue, a few scientists reported that the plan of liquisolid tablets is a standout amongst the most guaranteeing strategies for advancing medication disintegration [8].

Historical Development

Truly, liquisolid frameworks are relatives of "powdered arrangements", a more established strategy which was focused around the transformation of an answer of a medication in a non-unstable dissolvable into a dry-looking, non-disciple powder by for the most part adsorbing the fluid onto silica of extensive particular surfaces. In later studies on powder arrangement, pressure enhancers, for example, microcrystalline cellulose were included such scatterings to expand the compressibility of the system. Particularly when such adjusted powdered arrangements were layered into tablets, they exhibited critical "fluid crushing out" sensation and inadmissibly delicate tablets, in this manner hampering the modern application of such frameworks [9].

The liquisolid compacts are acceptably streaming and compressible powdered manifestations of fluid meds. The term „liquid prescription alludes to fluid lipophilic (oily) medications or water- insoluble solid medications broke up in suitable water-miscible non-unstable dissolvable frameworks termed as the fluid vehicle. The fluid solution is incorporated into the permeable transporter material. As the transporter is soaked with fluid, a fluid layer is shaped on the molecule surface which is quickly adsorbed by the fine covering particles. Such fluid

solution may be changed over into a dry- looking, nonadherent, free flowing and promptly compressible powders by a basic admixture with chose powder excipients alluded to as the transporter and covering materials [10-11].

Benefits Of Liquisolid Systems

•Number of water-insoluble strong medication can be planned into liquisolid frameworks.

•Can be connected to figure fluid medicine, for example, slick fluid medications.

•Simplicity.

•Better accessibility of an orally controlled water- insoluble medication.

•Lower generation cost than that of delicate gelatin capsules.

•Production of liquisolid framework is like that of customary tablets.

•Can be utilized for definition of fluid slick medications.

•Exhibits improved in-vitro medication discharge as contrasted with business partners, including delicat gelatin case arrangements.

•Can be utilized as a part of controlled medication conveyance.

•Optimized managed discharge, liquisolid tablets or cases of water insoluble medications exhibit consistent disintegration rates (zero request discharge).

•Drug can be molecularly scattered in the definition.

Bad Marks Of Liquisolid Systems

•formulation of high dosage lipophilic medications the liquisolid tablet is one of the limits of this procedure.

•due to the high surface charge on discrete little paricles, there is a solid propensity

Rundown of Drugs that can be joined into liquisolid frameworks

•antihistaminic: chlorpheniramine

•antiarrthymic: digoxin, digitoxin

•antihypertensive: nifedipine

•antilipidemics: clofibrate, gemfibrozi

•antiepileptic: Carbamazepine, valproic corrosive.

•chemotherapeutic operators: etoposide.

•diuretics: Hydrochlorothiazide, methylchlorthiazide, polythiazide, spironolactone.

•glucocorticoids: prednisolone, hydrocortisone, prednisone.

•NSAIDS: piroxicam, indomethacin, ibuprofen.

•water-insoluble vitamins: vitamin A, D, E, and K

Prerequisites For Liquisolid Systems

Drug candidates

Examples of medication hopefuls incorporate digoxin, digitoxin, prednisolone, hydrocortisone, spironolactone, hydrochlorothiazide, polythiazide, and other fluid solutions, for example, chlorpheniramine, water insoluble vitamins, fish oil, and so on.[12,13]

Non-volatile solvents

Different non-unpredictable solvents utilized for the plan of liquisolid frameworks incorporate Polyethylene glycol 200 and 400, glycerin, polysorbate 80 and propylene glycol .[14]

Carrier materials

It refers to an ideally permeable material having sufficient ingestion properties, for example, microcrystalline and indistinct cellulose, which helps in fluid assimilation. for example, Avicel PH 102 and 200, Lactose, Eudragit RL and RS (to manage drug conveyance), etc[15]

Covering materials

It Refers to a material having fine and profoundly adsorptive particles, for example, different sorts of silica, which helps in covering the wet transporter particles and showing a dry looking powder by adsorbing any overabundance fluid. With the liquisolid innovation, a fluid may be changed into a free streaming, promptly compressible and clearly dry powder by straightforward physical mixing with chose excipients named the bearer and covering material. The fluid parcel, which can be a fluid medication, a medication suspension or a medication arrangement in suitable nonvolatile fluid vehicles, is consolidated into the permeable bearer material (Fig. 1) .[16]

Disintegrants

Most ordinarily utilized disintegrant is sodium starch glycolate (Explo

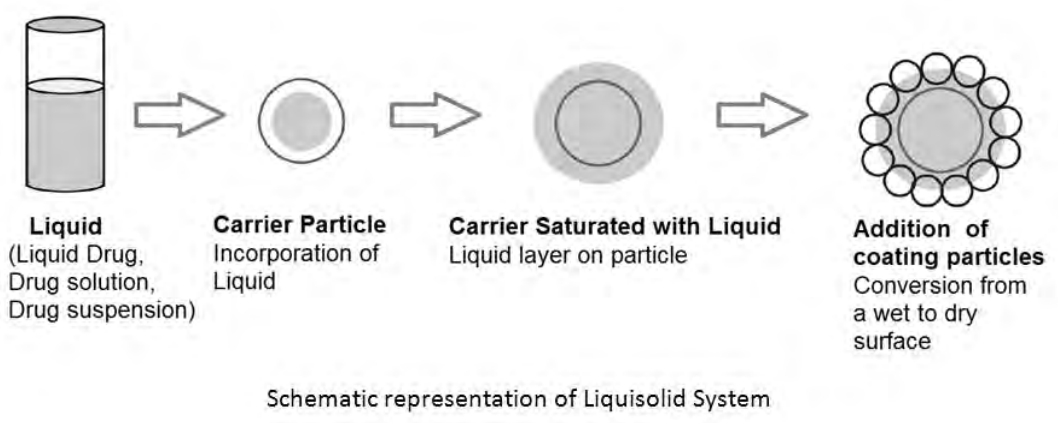

Fig.no:1 schematic representation of liquisolid system

Classification Of Liquisolid Systems

Taking into account the sort of fluid medicine contained in that, liquisolid frameworks may be grouped into three sub-bunches . [17]

- powdered drug arrangements
- powdered drug suspensions
- powdered liquid drug

Powdered medication arrangements and suspensions may be delivered from the change of medication arrangements or medication suspensions into liquisolid frameworks and powdered fluid medications are created from the detailing of fluid medications into liquisolid frameworks. At the same time, taking into account the detailing method utilized, liquisolid frameworks may be grouped into two classes specifically,

- Liquisolid compacts
- Liquisolid Microsystems

The expression "Liquisolid compacts" alludes to prompt or supported discharge tablets or capsules, consolidated with the consideration of fitting adjuvants needed for tabletting or encapsulation, for example, lubricants, and for quick or maintained discharge activity, for example, disintegrants or binder, separately . [10] The expression "liquisolid Microsystems" alludes to capsul arranged by joining the medication with carrier and coating materials, combin with consideration of an added substance e.g., PVP in the fluid prescription wherein the ensuing unit size may be as much as five times that of liquisolid compacts .[18-23]

Plan of Liquisolid Compact

The plan piece of liquisolid minimized chiefly incorporates Pre- foemulation studies and Formulation of liquisolid compact system.

Preformulation Studies

Preformulation Studies incorporates:

1. Determination solvency of medication in diverse 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) [24-25]

Solvency (solubility) studies

Solvency studies are completed by get ready immersed arrangements of medication in non-volatile dissolvable and examining them spectrophotometrically [26] . Immersed arrangements are arranged by adding overabundance of medication to non unpredictable dissolvable and shaking them on shaker for particular time period under consistent vibration. After this, the arrangements are sifted and dissected spectrophotometrically.[27]

Determination of angle of slide

Point of slide is utilized as an issue of the flow properties of powders. Determination of angle of slide is carried out by weighing the obliged measure of carrier material and set toward one side of a metal plate with a polish surface. The end is step by step raised till the plate gets to be precise to the flat at which powder is going to slide. This plot is known as angle of slide. Point of 33o is viewed as ideal [28].

Determination of flowable fluid maintenance potential (Φ esteem) :

The expression "flowable fluid retential potential" (Φ-quality) of a powder material portrays its capacity to hold a particular measure of fluid while keeping up great stream properties.The Φ-worth is characterized as the greatest weight of fluid that can be held every unit weight of the powder material to create an acceptably streaming liquid/powder admixture. The Φ qualities are ascertained as indicated by mathematical statement

Φ esteem = weight of fluid/ weight of strong ... (1)

Calculation of liquid load factor (Lf)

Different concentration of non- volatile solvents are taken and the medication is disintegrated. Such liquid medication is added to the carrier coating material admixture and mixed. Utilizing mathematical statement (2) medication Loading factor are determine and used for calculating the amount carrier and coating materials in every detailing.

Lf = weight of liquid medicament / weight of carrier material.

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 .[29-32]

Procedure :

As shown in figure 2, a liquid lipophilic drug (eg. carvedilol, clofibrate, etc.) is formulated, it should be initially dissolved or suspended in a suitable non-volatile solvent system to produce a drug solution or drug suspension of desired concentration. Next, a certain amount of the prepared drug solution or suspension, or the liquid drug itself, is incorporated into a specific quantity of carrier material which should be preferably of a porous nature and possessing sufficient absorption properties, such as powder and granular grades of microcrystalline and amorphous cellulose are most preferred as carriers. The resulting wet mixture is then converted into a dry-looking, non adherent ,free-flowing and readily compressible powder by the simple addition and mixing of a calculated amount of coating material. 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 adjuvants such as lubricants and disintegrants (immediate) or binders (sustained-release) may be mixed with the finished liquisolid systems to produce liquisolid compacts i.e. tablets or capsules . [33]

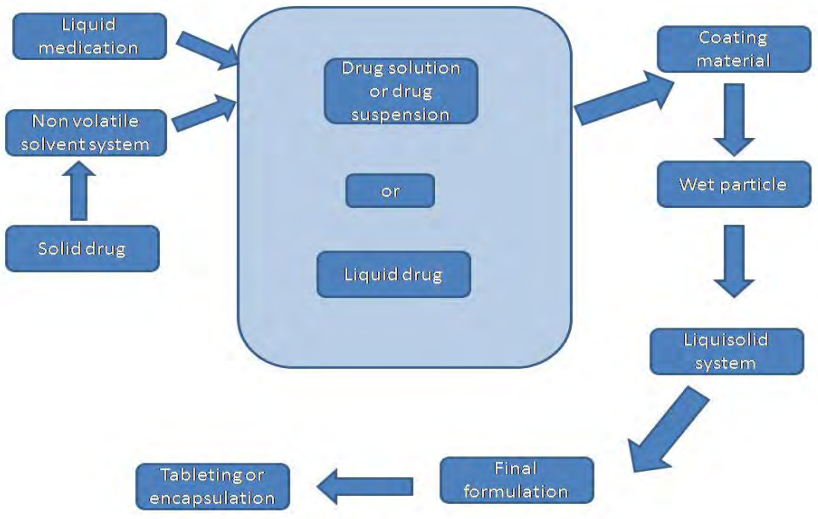

Figure. 2: Schematic outline of the steps involved in the preparation of liquisolid compacts.

Evaluation of liquisolid system

Flow behavior: The flowability of a powder is of basic imperativeness in the generation of pharmaceutical measurements structures keeping in mind the end goal to decrease high measurement varieties.[34] Angle of repose, Carr's index and Hausner's ratio were utilized as a part of request to guarantee the flow behavior of the liquisolid frameworks.

Precompression studies of the prepare Liquisolid Powder system:

Keeping in mind the end goal to guarantee the suitability of the chose excipients, Fourier Transform Infra Red Spectroscopy, Differential scanning Calorimetry, X-ray Diffraction and Scanning Electron Microscope studies are to be performed. Furthermore, flowability studies are likewise to be done to choose the ideal formulae for compression, before the compression of the powders the measurements structures, for example, into tablets and capsules.

Fourier Transform Infra Red Spectroscopy (FT-IR):

FT-IR spectra of arranged melt granules are recorded on FTIR-8400 spectrophotometer. Potassium bromide (Kbr) pellet strategy is utilized and foundation range is gathered under indistinguishable circumstance. Every range is gotten from single normal outputs gathered in the locale 400 - 4000^{cm-1} at otherworldly determination of 2^{cm-2} and proportion against foundation interfereogram. Spectra are broke down by programming. [35]

Differential scanning calorimetry (DSC) :

Differential scanning calorimetry (DSC) is performed to evaluate the thermotropic properties and the warm practices of the medication, excipients utilized as a part of the plan of the liquisolid framework. Complete vanishing of characteristics peaks of medication demonstrates the development of medication arrangement in the liquisolid powdered framework, i.e., the medication is molecularly scattered inside the liquisolid matrix. [35-37]

X-ray diffraction (XRD):

For the characterization of crystalline state, X-ray diffraction (XRD) examples are dead set for physical mixture of medication and excipients utilized as a part of definition and for the arranged liquisolid compacts.[38] Absence of constructive specific peaks of the medication in the liquisolid compacts in X-ray diffractogram determine that medication has just about completely changed over from crystalline to formless or solubilized structure. Such absence of crystallinity in the liquisolid framework was comprehended to be as an issue of medication solubilization in the fluid vehicle i.e., the medication has structured a strong arrangement inside the transporter network. This amorphization or solubilization of medication in the liquisolid compacts it may help the ensuing change in the obvious dissolvability and improvement of dissolution rate of the medication. [39]

Scanning electron microscopy (SEM) :

Scanning electron microscopy (SEM) is used to survey the morphological qualities of the crude materials and the medication transporter frameworks. [39]

Contact angle measurement :

For appraisal of wettability, contact plot of liquisolid tablets is measured as per the imaging technique. The ordinarily utilized strategy is to gauge contact edge straightforwardly for a drop of fluid resting on a plane surface of the robust, the purported imaging technique. An immersed arrangement of the drug in dissolution media is readied and a drop of this arrangement is put on the surface of tablets. The contact angle are calcutation by measuring the hight and daimeter of spher drop on the tablet.[38]

In Vitro Dissolution Studies :

Works of numerous analysts uncovered that technique of liquisolid compacts could be a guaranteeing option for definition of water-insoluble medications. This strategy of liquisolid compacts has been effectively utilized to enhance the in-vitro arrival of ineffectively water dissolvable medications as Carbamazepine[37] Piroxicam[37,38]. Additionally a few water insoluble medications nifedipine, gemfibrozil, and ibuprofen, have indicated higher bioavailability in rats as contrasted with their business partners.

In vivo evaluation of liquisolid system:

his liquisolid innovation is a guaranteeing instrument for the improvement of medication arrival of ineffectively dissolvable medications. The ingestion attributes of Hydroclorothiazide liquisolid compacts in correlation with

business tablets were examined in beagle dogs. Huge contrasts in the zone under the plasma focus time bend, the top plasma fixation and unquestionably the bioavailability of the liquisolid and the business tablets were watched. Nonetheless, for the mean home time, the mean retention time, and the rate of ingestion no huge contrasts were found. Indisputably the bioavailability of the medication from liquisolid compacts was 15% higher than that from the business definition .[39]

References :

[1] 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 Pharma 2006; 317:61–68.
[2] Amidon GL, Lennernas H, Shah VP, Crison JR. A theoretical basis for biopharmaceutic drug classification: The co-relation of in-vitro drug product dissolution and in-vivo bioavailability. Pharma Res 1995;12: 413-420.
[3] Blagden N, Matas M, Gavan P, York P. Crystal engineering of active pharmaceutical ingredients to improve solubility and dissolution rates. Adv Drug Deliv Rev 2007; 59:617–30.
[4] Sonoda R, Horibe M, Oshima T, Iwasaki T, Watano S. Improvement of dissolution property of poorly water soluble drug by novel dry coating method using planetary ball mill. Chem Pharm Bull 2008; 56:1243–7.
[5] Jin X, Zhang Z, Sun E, Li S, Jia X. Statistically designed enzymatic hydrolysis of anicariin /b- cyclodextrin inclusion complex optimized for production of icaritin. Acta Pharma 2012; 2: 83–89.
[6] Gursoy RN, Benita S. Self emulsifying drug delivery systems (SEDDS) for improved oral delivery of lipophilic drugs. Biomed Pharmacotherapy 2004; 58: 173–82.
[7] Ahuja G, Pathak K. Porous carriers for controlled or modulated delivery. Indian J Pharm Sci 2009; 71: 599–607.
[8] Spireas S, Bolton SM. Liquisolid systems and method of preparing same. United States patent US6096337. 2000 Aug 1.
[9] Setty CM, Prasad DVK, Gupta RM. Development of fast dispersible aceclofenac tablet: effect of functionality of super disintegrants. Indian J Pharm Sci. 2008; 70:180-185.
[10] Yadav VB, Nighuk AB, Yadav AV, Bhise SB. Aceclofenac size enlargement by non-aqueous granulation with improved solubility and dissolution. Arch Pharm Sci Res 2009; 1:115-122
[11] Gubbi SR, Jarag R. Formulation and characterization of atorvastatin calcium liquisolid compacts. Asian J Pharm Sci 2010; 2:50-60.
[12] S. Spireas, US Patent, US 6,423,339 B1.strial Pharmacy, 3rd edition, 295-303.
[13] Spireas S, Bolton M. Liquisolid Systems and Methods of Preparing Same. U.S. Patent5,968,550, 1999.
[14] Spireas S. Liquisolid Systems and Methods of Preparing Same. U.S. Patent 6,423,339 B1,2002.
[15] 15.Javadzadeh YJ, Jafari-Navimipour B, Nokhodchi A. Liquisolid technique for dissolution rate enhancement of high dose water-insoluble drug (Carbamazepine). Int J Pharm 2007; 34: 26- 34.
[16] 16.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
[17] Spireas S., US Patent, US 6,423,339 B1.
[18] Karmarkar AB, Gonjari ID, Hosmani AH, Dhabale PN, Bhise SB. Dissolution Rate Enhancement of Fenofibrate Using Liquisolid Tablet Technique. Part II: Evaluation of in- vitro dissolution profile comparison methods. Lat Am J Pharm 2009; 28 (4): 538-43.
[19] 19. Akinlade B, S Elkordy. Liquisolid system to improve the dissolution of furosemide. Sci Pharm 2010; 78: 325-344.
[20] 20. Darwish IAE, El-Kama AH. Dissolution enhancement of glibenclamide using liquisolid tablet technology. Act Pharm 2001; 51: 173-181.
[21] Elkordy AA, Essa EA, Dhuppad S, Jammigumpula P. Liquisolid technique to enhance and to sustain griseofulvin dissolution: Effect of choice of non-volatile liquid vehicles. Int J Pharma 2012; 434: 122– 132.
[22] Patel VP, Patel NM. Dissolution enhancement of glipizide using liquisolid tablet technology. Ind Drugs 2008; 45(4): 318-323.
[23] Khaled KA, Asiri YA, El-Sayed YM. In-vivo evaluation of hydrochlorothiazide liquisolid tablet in beagle dogs. Int J Pharm. 2001; 222: 1-6.
[24] 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.
[25] Furer R, Geiger M. A simple method of determining the aqueous solubility of organic substances. J Pharm Sci. 1976; 8(4):337-344.
[26] Spireas S, Sadu S, Enhancement of prednisolone dissolution properties using liquisoli compacts. Int. J. Pharm. 1998, 166,177–188.
[27] 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.
[28] Tayel SA, Soliman II and Louis D, Improvement ofDissolution Properties of Carbamazepine through Application of the Liquisolid Technique. Eur J Pharm Biopharm. 2008,69,342-347.
[29] Gavali SM, Pacharane SS, Sankpal SV, Jadhav KR and Kadam VJ. Liquisolid Compact: A New Technique for Enhancement of Drug Dissolution. Int J Res Pharm Chem. 2011; 1(3): 705-713.
[30] Spireas S and Bolton SM. Liquisolid systems and methods for preparing same, United States patent. 1999; 5:968,550.
[31] Kumar SK, Suria PK, Satish K, Satyanarayana K and Kumar RH. Solubility Enhancement of a Drug by Liquisolid Technique. Int J Pharma Bio Sci. 2010; 1(3): 1-5.
[32] Rajesh K, Rajalakshmi R, Umamaheswari J and Kumar CKA. Liquisolid Technique a Novel Approach to Enhance Solubility and Bioavailability. Int J Biopharma. 2011; 2(1):8-13.
[33] piras S., Bolton sm. Liquisolid system and method for preparing same, united states patent 6,096,337, (2000).
[34] Bhise SB, Nighute AB, Yadav AV, Yadav VB, Aceclofenac 1 size enlargement by non aqueous granulation with improved solubility and dissolution. Arch Pharm Sci & Res. 2009; 1:115-122.
[35] 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
[36] Asnaashari S, Javadzadeh Y, Siahi MR., A. Nokhodchi, An investigation of physicochemical properties of piroxicam liquisolid compacts. Pharm Develop Tech. 2007; 12: 337–343.
[37] Rakshit P, Ridhish P, Moinuddin S. Formulation and evaluation of liquisolid compacts of piroxicam. Ind drugs. 2007; 44: 967- 972.
[38] Martindale, The Complete Drug Reference, 6 Edn, The Pharmaceutical Press, London, 1999, pp. 937.
[39] Khaled KA, Asiri YA, El-Sayed YM. In-vivo evaluation of hydrochlorothiazide liquisolid tablet in beagles dogs. Int J Pharm. 2001; 222: 1-6.