Available on line at : www.eijppr.com

International Journal of Pharmaceutical and Phytopharmacological Research

(ICV-5.09)

ISSN (Online) 2249 – 6084

ISSN (Print) 2250 – 1029

Int.J.Pharm.Phytopharmacol.Res. 2012, 2(2): 116-121

(Review Article)

A Review on Liquid Solid Compacts

V.N.L. Sirisha*, B. Sruthi, M. Namrata, I. Bhavani Harika, P.Kirankumar, Y. Kiran Kumar Rao, K. Pranavi, S. Sindhura, N.Vamsi Krishna, O. Uma Maheshwar Rao

Anurag Pharmacy College, Affiliated to JNTUH, Kodad, Nalgonda Dist., Andhra Pradesh, India.

Received on: 16/09/2012 ***Accepted on:*** 04/10/2012

ABSTRACT

At present 40% of the drugs in the development pipelines, and approximately 60% of the drugs coming directly from synthesis are poorly soluble. The limited solubility of drugs is a challenging issue for industry, during the development of the ideal solid dosage form unit. Liqui-solid compacts technique is a new and promising approach to overcome this consequence and that can change the dissolution rate of water insoluble drugs and increase the bioavailability of the drugs. According to the new formulation method of liqui-solid compacts, liquid medications such as solutions or suspensions of water insoluble drugs in suitable non-volatile liquid vehicles can be converted into acceptably flowing and compressible powders by blending with selected powder excipients. It has been speculated that such systems exhibit enhanced release profiles. In this case, even though the drug is in a solid dosage form, it is held within the powder substratin solution or, in a solubilized, almost molecularly dispersed state, which contributes to the enhanced drug dissolution properties.

Key Words: Liquid solid compact**,** Liquid medications, Non-volatile Vehicles, Dissolution rate.

INTRODUCTION

Solubility of drugs is a major factor in the design of pharmaceutical formulations lead to variable oral bioavailability. Dissolution is an important factor for absorption of drugs especially in case of water insoluble or poorly soluble drugs [1].The rate limiting step for most of the pharmaceuticalformulations is dissolution. Various methods used to increase the solubility of poorly water soluble drugs are solid dispersions[2], inclusioncomplexes with β-cyclodextrins[3], micronization[4], eutectic mixtures[5] and spray-drying technique[6].

The new developed technique by Spireas[7] liqui-solid system improves the dissolution properties of water insoluble or poorly soluble drugs. The term 'liqui-solid systems' (LS) is a powdered form of liquid drug formulated by converting liquid lipophilic drug or drug suspension or solution of water-insoluble solid drug in suitable non-volatile solvent systems, into dry looking, non-adherent, free-flowing and readily compressible powdered mixtures by blending with selected carrier and coating materials.Various grades of cellulose, starch, lactose, etc. are used as the carriers, whereas very fine silica powder is used as the coating (or covering) material[8].

The good flow and compression properties of Liqui-solid may be attributed due to large surface area of silica and fine particle size of avicel. Hence, Liqui-solid compacts containing water-insoluble drugs expected to display enhanced dissolution characteristics and consequently improved oral bioavailability. The *in vitro* drug dissolution rates of such preparations were compared to those ofconventionally prepared directly compressed tablets using a USP-II apparatus[9].

Liquid lipophilic drugs (e.g. Chlorpheniramine and Clofibrate) or solid drugs (e.g., prednisone, prednisolone, hydrocortisone, theophylline, Polythiazide and Spiranolactone) dissolved in non volatile, high-boiling point solvent systems (e.g., polyethylene and polypropylene glycols ,glycerin, N,N-dimethylacetamide, various oils) have been formulated in powdered solutions by admixture with various carriers (e.g., cellulose) and coating materials (e.g., silica). This technique has been reported to produce improved dissolution profiles as compared to the commercially available products[10].

Liao[11] proposed mathematical expressions for the calculation of the amount of excipients needed for powdered solution formulations. The major drawback of this approach was that the final product exhibited poor and erratic flow ability due to the inadequacy of the proposed model to calculate the appropriate amount of excipients required to produce powder admixtures of acceptable and consistent flow properties. Mathematical model expressions based on powder properties and the fundamentals principles and mechanisms of powdered solutions are derived.

THEORY OF LIQUID SOLID SYSTEMS

A powder can retain only limited amounts of liquid while maintaining acceptable flow and compression properties. To calculate the required amounts of powder excipients (carrier

and coating materials) a mathematical approach for the formulation of liqui-solid systems has been developed by Spireas[12,13]. This approach is based on the flowable (Φ-value) and compressible (Ψ-number) liquid retention potential introducing constants for each powder/liquid combination.

The Φ-value of a powder represents the maximum amount of a given non-volatile liquid that can be retained inside its bulk [w/w] while maintaining an acceptable flowability. The flowability may be determined from the powder flow or by measurement of the angle of repose. The Ψ-number of a powder is defined as the maximum amount of liquid the powder can retain inside its bulk [w/w] while maintaining acceptable compactability resulting in compacts of sufficient hardness with no liquid leaking out during compression[14]. The compactability may be determined by the so-called "pactisity" which describes the maximum (plateau) crushing strength of a one-gram tablet compacted at sufficiently high compression forces. The terms "acceptable flow and compression properties" imply the desired and thus preselected flow and compaction properties which must be met by the final liqui-solid formulation.

Depending on the excipient ratio (*R*) of the powder substrate an acceptably flowing and compressible liqui-solid system can be obtained only if a maximum liquid load on the carrier material is not exceeded. This liquid/carrier ratio is termed "liquid load factor Lf [w/w] and is defined as the weight ratio of the liquid formulation (*W*) and the carrier material (*Q*) in the system:

$$Lf = W/Q \text{------ (1)}$$

'R' represents the ratio between the weights of the carrier (*Q*) and the coating (*q*) material present in the formulation:

$$R = Q/q \text{------ (2)}$$

The liquid load factor that ensures acceptable flowability (Lf) can be determined by:

$$Lf = \Phi + \varphi.(1/R) \text{ ----- (3)}$$

Where Φ and φ are the Φ-values of the carrier and coating material, respectively. Similarly, the liquid load factor for production of liqui-solid systems with acceptable compactability (Ψ*Lf)* can be determined by:

$$^{\Psi}L_f = \Psi + \psi.(1/R \text{ ------- (4)}$$

Where Ψ and ψ are the Ψ-numbers of the carrier and coating material, respectively. In Table-1 examples of liqui-solid formulation parameters of various powder excipients with commonly used liquid vehicles are listed.

Table 1: Liqui-solid formulation parameters of various powder excipients with commonly used liquid vehicles

Powder Excipient or System	Φ-values		Ψ-numbers	
	Propylene glycol	PEG-400	Propylene glycol	PEG-400
Avicel pH 102	0.16	0.005	0.224	0.242
Avicel pH 200	0.26	0.02	0.209	0.232
Cab-O-Sil M5(silica)* With Avicel pH 102	3.31	3.26	0.560	0.653
Cab-O-SilM5(silica)* With Avicel pH 200	2.57	2.44	0.712	0.717

***Included as coating material in carrier/coating powder systems.**

Therefore, the optimum liquid load factor (Lo) required to obtain acceptably flowing and compressible liqui-solid systems are equal to either *ΦLf*or*ΨLf,* whichever represents the lower value.

As soon as the optimum liquid load factor is determined, the appropriate quantities of carrier (*Qo*) and coating (*qo*) material required to convert a given amount of liquid formulation (*W*) into an acceptably flowing and compressible liqui-solid system may be calculated as follows:

$$\mathbf{Q0 = W/Lo} \text{-----(5)} \quad \mathbf{And\ q0 = Q0/R} \text{-------(6)}$$

The validity and applicability of the above mentioned principles have been tested and verified by producing liqui-solid compacts possessing acceptable flow and compaction properties[12].

MECHANISMS OF ENHANCED DRUG RELEASE FROM LIQUID-SOLID SYSTEMS

Several mechanisms of enhanced drug release have been postulated for liqui-solid systems. The three main suggested mechanisms include an increased surface area of drug available for release, an increased aqueous solubility of the drug, and an improved wettability of the drug particles. Formation of a complex between the drug and excipients or any changes in crystallinity of the drug could be ruled out using DSC and XRPD measurements[14].

a. Increased Drug Surface Area

If the drug within the liqui-solid system is completely dissolved in the liquid vehicle it is located in the powder substrate still in a solubilized, molecularly dispersed state. Therefore, the surface area of drug available for release is much greater than that of drug particles within directly compressed tablets[13].

b. Increased Aqueous Solubility of the Drug

In addition to the first mechanism of drug release enhancement it is expected that*Cs*, the solubility of the drug, might be increased with liqui-solid systems. In fact, the relatively small amount of liquid vehicle in a liqui-solid 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 liqui-solid primary particle and the release medium it is possible that in this microenvironment the amount of liquid vehicle diffusing out of a single liqui-solid particle together with the drug molecules might be sufficient to increase the aqueous solubility of the drug if the liquid vehicle acts as a co-solvent[13].

c. Improved Wetting Properties

Due to the fact that the liquid vehicle can either act as surface active agent or has a low surface tension, wetting of the liqui-solid primary particles is improved (Fig-3). Wettability of these systems has been demonstrated by measurement of contact angles and water rising times [15].

Many poorly soluble drugs have been formulated as liqui-solid systems showing enhanced drug release. Different liquid vehicles, carrier and coating materials were used to formulate these drug delivery systems.

APPLICATIONS OF LIQUID-SOLID COMPACTS

Following are few important applications of liquid-solid compacts[16-20]:

- Rapid release rates are obtained in liqui-solid 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 enhancement.
- Designing of controlled release tablets.
- Application in probiotics.

ADVANTAGES OF LIQUID-SOLID COMPACT

- Several slightly and very slightly water-soluble and practically water-insoluble liquid and solid drugs can be formulated into liqui-solid systems.
- Even though the drug is in a tablet or capsuleform, it is held in a solubilized liquid state, which contributes to increased drug wetting properties, thereby enhancing drug dissolution.
- Production cost is lower than soft gelatin capsules[21].

LIMITATIONS

- Not applicable for the formulation of high dose insoluble drugs.
- If more amount of carrier is added to produce free-flowing powder, the tablet weight increases to more than one gram which is difficult to swallow.
- Acceptable compression properties may not beachieved since during compression liquid drug may be squeezed out of the liquid-solid tablet resulting in tablets of unsatisfactory hardness[21]
- Introduction of this method on industrial scale and to overcome the problems of mixing smalll quantities of viscous liquid solutions onto large amounts of carrier material may not be feasible.

CLASSIFICATION OF LIQUI-SOLID SYSTEMS

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

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

The first two may be produced from the conversion ofdrug solutions or (e.g. prednisolone solution inpropylene glycol) or drug suspensions (e.g. Gemfibrozil suspension in Polysorbate 80), and the latter from the formulation of liquid drugs (e.g. Clofibrate, liquid vitamins, etc.), into liqui-solid 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, liqui-solid systems may be classified into two categories:

- Liqui-solid compacts
- Liqui-solid Microsystems

Liqui-solid compacts are prepared using the previously outlined method to produce tablets or capsules, whereas the liqui-solid microsystems are based on a new concept which employs similar methodology combined with the inclusion of an additive, e.g., Polyvinylpyrrolidone (PVP), in the liquid medication which is incorporated into the carrier and coating materials to produce anacceptably flowing admixture for encapsulation. The advantage stemming from this new technique is that the resulting unit size of liqui-solid microsystems may be as much as five times less than that of liqui-solid compacts [21- 23].

PREPARATION OF LIQUID SOLID COMPACTS

As shown in figure, a liquid lipophilic drug (e.g.Chlorpheniramine, Clofibrate, etc.) can be converted into a liqui-solid system without being further modified. On the other hand, if a solid water-insoluble drug (e.g. Hydrochlorothiazide, Prednisone, 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.

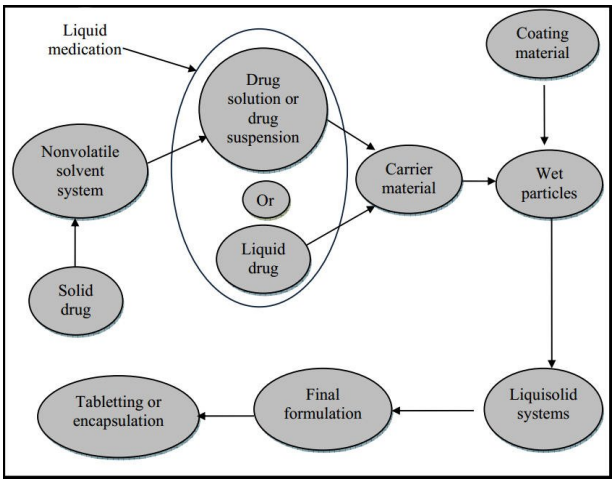

Fig.1: Steps involved in the preparation of liquid solid systems

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 disintegrates (immediate) or binders (sustained-release) may be mixed with the finished liqui-solid systems to produce liqui-solid compacts i.e. tablets or capsules [22,23,24].

FORMULATION COMPONENTS

The major formulation components of liqui-solid 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[22], lactose[25], sorbitol[26] etc.

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 [22, 23, 24].

Non-volatile Solvents

Inert, high boiling point, preferably water-miscible and not highly viscous organic solvent systems e.g., propylene glycol, liquid polyethylene glycols, polysorbates, glycerin, N, N-dimethylacetamide, fixed oils, etc. are most suitable as vehicles.

Disintegrants

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

Examples of drugs that can be incorporated into liqui-solid systems[22, 23]:

- Chlorpheniramine
- Digoxin
- Nifedipine
- Clofibrate
- Gemfibrozil
- Etoposide
- Carbamazepine
- Hydrochlorothiazide
- Methyclothiazide
- Spironolactone
- Hydrocortisone
- Piroxicam
- Indomethacin
- Ibuprofen

PRE-COMPRESSION STUDIES OF THE LIQUID SOLID SYSTEM

Flow Properties of the Liqui-Solid System

The flow properties of the liqui-solid systems wereestimated by determining the angle of repose, Carr'sindex, and Hausner's ratio. The angle of reposewas measured by the fixed funnel and freestanding conemethod. The Bulk density and Tap densities were determined for the calculation of Hausner's ratio andCarr's Index.

Angle of repose

The angle of repose physical mixtures of liqui-solid compacts were determined by fixed funnel method. The accurately weighed physical mixtures of liqui-solid compacts were taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touches the apex of the heap of the powder. The powder was allowed to flow through the funnel freely into the surface. The height and diameter of the powder cone was measured and angle of repose was calculated.

$$\mathbf{Tan\ \theta = h/r}$$

Where, θ is the angle of repose
h is the height in cms
r is the radius in cms

Values for angle of repose $\leq 30^0$ usually indicate a free flowing material and angles $\geq 40^0$ suggest a poorly flowing material. 25- 30 showing excellent flow properties,31-35 showing good flow properties, 36-40 showing fair flow properties, 41-45 showing passable flow properties.

Bulk Density

The loose bulk density and tapped density were determined by using bulk density apparatus. Apparent bulk density was determined by pouring the blend into a graduated cylinder. The bulk volume (V_b) and weight of the powder (M) was determined. The bulk density was calculated using the formula:

$$\mathbf{D_b = M/V_b}$$

where, M is the mass of powder
V_b is bulk volume of powder

Tapped Density

The measuring cylinder containing a known mass of blend was tapped for a fixed time. The minimum volume (V_t) occupied in the cylinder and the weight (M) of the blend was measured. The tapped density was calculated using the formula:

$$\mathbf{D_t = M/V_t}$$

Where, M is the mass of powder
V_t is tapped volume of powder

Carr's Index (%)

The compressibility index has been proposed as an indirect measure of bulk density, size and shape, surface area, moisture content and cohesiveness of material because all of these ca influence the observed compressibility index.

The simplest way for measurement of free flow of powder is Carr's Index, a indication of the ease with which a material can be induced to flow is given by Carr's index (CI) which is calculated as follows:

CI (%) = [(Tapped density – Bulk density) / Tapped density] x 100

The value below 15% indicates a powder with usually gives rise to good flow characteristics, where as above 25% indicates poor flowability. 1-10 showing excellent flow properties, 11-25 showing good flow properties 16-20 showing fair to passable, 21-25 showing passable.

Hausner's Ratio

Hausner's ratio is an indirect index of ease of powder flow. It is calculated by the following formula.

Hausner's Ratio=Tapped density (ρ_t) / Bulk density (ρ_b)

Where ρ_t is tapped density and ρ_b is bulk density. Lower Hausner's ratio (<1.25) indicates better flow properties than higher ones, between 1.25 to 1.5 showing moderate flow properties and more than 1.5 poor flow.

POST COMPRESSION STUDIES OF LIQUI-SOLID COMPACTS

Weight Variation

Twenty tablets were randomly selected from each batch and individually weighed . The average weight and standard deviation three batches were calculated. It passes the test for weight variation test if not more than two of the individual tablet weights deviate from the average weight by more than the allowed percentage deviation and none deviate by more than twice the percentage shown. It was calculated on an electronic weighing balance.

Thickness

The thickness of liqui-solid tablets was determined by using Digital micrometer. Ten individual tablets from each batch were used and the results averaged.

Hardness

The hardness of the tablets was determined by using Monsanto hardness tester. Five individual tablets from each batch were and results averaged.

Friability

The friability values of the tablets were determined using a Roche-type friabilator. Accurately weighed six tablets were placed in Roche friabilator and rotated at 25 rpm for 4 min.
Percentage friability was calculated using the following equation.

$$\text{Friability} = ([W_O - W] / W_O) \times 100$$

Where,
W_O = Weight of the tablet at time zero before revolution.
W = Weight of the tablet after 100 revolutions.

Disintegration Test

Six tablets were taken randomly from each batch and placed in USP disintegration apparatus baskets Apparatus was run for 10 minutes and the basket was lift from the fluid, observe whether all of the tablets have disintegrated.

In-vitro Release

Drug release from liqui-solid tablets was determined by using dissolution test United States Pharmacopoeia (USP) 24 type II (paddle).
5ml aliquots of dissolution media were withdrawn each time at suitable time intervals (5, 10, 15, 20, 25, 30, 45 and 60 minutes.) and replaced with fresh medium. After withdrawing, samples were filtered and analyzed after appropriate dilution by appropriate analytical method. The concentration was calculated using standard calibration curve.

CONCLUSION

Liquid solid compacts are improved beneficial technology to overcome the low bioavailability of the drug. The improvement in the dissolution characteristics of a liqui-solid technique changes the properties of drug release by simply dispersed the drug particles in a non volatile liquid vehicle, which in turn increase the wetting properties and surface area of drug particles, and hence improve the dissolution profiles and might be oral bioavailability of the drug.

REFERENCES

1) Sahil M. Gavali, Sharad S. Pacharane, Shirish V. Sankpal, Kisan R. Jadhav and Vilasrao J. Kadam,Liquisolid compact: a new technique for Enhancement of drug dissolution, *IJRPC*, 2011, 1(3) :705-713.
2) Shinde SS, Patil SS, Mevekari FI, Satpute AS. An approach for solubility enhancement: solid dispersion. *International Journal of Advances in Pharmaceutical Sciences*.2010; 299-308.
3) Hiremath SN, Raghavendra RK, Sunil F, Danki LS, Rampure MV, Swamy PV, Bhosale UV. Dissolution enhancement of gliclazide by preparation of inclusion complexes with β-cyclodextrin .*Asian J Pharm*. 2008; 2: 73-76.
4) Kornblum S, Hirschorn J., Dissolution of poorly water-soluble drugs I: Some physical parameters related to method of micronization and tablet manufacture of a quinazolinone compound. *J. Pharm Sci*. 1970; 59: 607-609.
5) Sekiguchi K, Obi N. Studies on absorption of eutectic mixtures. I. A comparison of the behavior of eutectic mixtures of sulphathiazole and that of ordinary sulphathiazole in man. *Chem. Pharm. Bull*. 1961; 9: 866-872.
6) Rajarajan S, Beny Baby, K Ramesh, Dhananjaysingh. Preparation and evaluation of ternary mixingItraconazole solid dispersions by spray drying method. *J. Pharm. Sci. and Res*. 2009; 1(1): 22-25.
7) Spireas S. Liqui-solid Systems and Methods of Preparing Same. U.S. Patent 6,423,339 B1, 2002.
8) Patents: S. Spireas ,United State Patent., 423,339B1, 2002
9) Dinesh M. Pardhi*, Umesh D. Shivhare, Vijay B. Mathur, Kishor P. Bhusari,Liquisolid Technique for Enhancement of Dissolution Properties of Carvedilol,*Der Pharmacia Lettre*, 2010, 2(5): 412-427
10) Spireas SS, Jarowski CI, Rohera BD. Powder Solution technology: Principles and Mechanism.*Pharma Research.*1992; 9:1351 – 1358.
11) Liao CC. Physicochemical properties of selected powdered drug solutions, Ph.D. thesis, St.John's university, Jamaica, NY. 1983.
12) Spireas, S. Liqui-solid systems and methods of preparing same. U.S. Patent 6423339B1 (2002)
13) Spireas, S., Sadu, S.Enhancement of prednisolone dissolution properties using liqui- Solid compacts.*Int. J. Pharm.* 1998,166: 177-188.
14) Spireas, S., Sadu, S. Enhancement of prednisolone dissolution properties using liqui-solid compacts. *Int. J. Pharm.* 1998, 166: 177-188.
15) Yadav, V.B., Nighute, A.B., Yadav, A.V., Bhise, S.B. Aceclofenac size enlargement by non aqueous granulation with improved solubility and dissolution. *Arch. Pharm. Sci. and Res.* 2009,1: 115-122.
16) Kulkarni Ajit S., Aloorkar Nagesh H., Mane Madhav S. and Gaja Jayashree B., Liqui-solid Systems. *International Journal of Pharmaceutical Sciences and Nanotechnology*,2010,3(1),795-802.
17) Bindu MB, Kusum B and David Banji, Novel Strategies for Poorly Water Soluble Drugs, *International Journal of Pharmaceutical Sciences Review and Research*,2010,4(3),1-5.

18) Sharma, A., Jain, C.P. Techniques to enhance solubility of poorly soluble drugs: a review. *J.Global Pharm. Tech.* 2010,2: 18-28.
19) Saharan, V.A.,Kukkar, V., Kataria, M., Gera, M., Choudhury, P.K. Dissolution enhancement of drugs. Part I: technologies and effect of carriers. *Int. J. Health Res*. 2009,2: 107-124.
20) 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.
21) S.Spireas, US Patent, US 6,423,339 B1.
22) SpirasS.Liqui-solid systems and methods for preparing same, *United States patent6,423,339 B1,* (2002).
23) Spiras S, Bolton SM. Liqui-solid systems and methods for preparing same, *United States patent 6,096,337,* 2000.
24) Spiras S, Wang T, Grover R. Effect of powder substrate on dissolution properties of methylclothiazideLiqui-solid compacts, *Drug. Dev. Ind. Pharm.* 1999,25: 63-168.
25) JavadzadehY,Navimipour B, Nokhodchi A. Liqui-solid technique for dissolution rate enhancement of a high dose water insoluble drug (carbamazepine), *Int. J. Pharm*., 2007, 341: 26-34.
26) Javadzadeh Y, Siahi MR, Asnaashri S, et al., An investigation of physicochemical properties of piroxicamliqui-solid compacts, *Pharm. Dev. Tech.* 2007, 12: 337-34.
27) Brahmankar DM, Jaiswal SB. Biopharmaceutics and Pharmacokinetics - A treatise.VallabhPrakashan, Delhi, India. 2002.

Corresponding Author:
Sirisha.V.N.L,
M.pharm, (Ph.D),
Anurag Pharmacy College, Affliated to JNTUH, Kodad, Nalgonda Dist., Andhra Pradesh, India,
Email: sirishaphd2011@gmail.com