Available online at www.scholarsresearchlibrary.com

Scholars Research Library

Der Pharmacia Lettre, 2010, 2(6): 321-328
(http://scholarsresearchlibrary.com/archive.html)

ISSN 0975-5071
USA CODEN: DPLEB4

Enhancement of solubility and dissolution rate of Frusemide through liquisolid technique

Shashidher Burra*, Sandeep Kumar Galipelly

Department of pharmaceutics, University College of Pharmaceutical Sciences, Kakatiya University, Warangal, Andhra Pradesh, India

---

ABSTRACT

Frusemide is a high loop diuretic used as an adjuvant in treatment of hypertension1. However, the low aqueous solubility and poor dissolution of this molecule in gastric fluid affects its rate of absorption, resulting in a low and variable oral bioavailability. The purpose of this study was to improve frusemide dissolution through its formulation into liquisolid systems by using new mathematical model expression. All the tested frusemide liquisolid tablet formulations were tested different dissolution media such as 1.2 pH, 5.4pH, 6.8pH, 7.4pH showed higher drug dissolution rates (DR) than the conventional, directly compressed tables.

Keywords: Frusemide, Liquisolid compacts, Solubility, Dissolution rate.

INTRODUCTION

Over the years, different methods have been employed to enhance the dissolution profile and, in turn, the absorption efficiency and bioavailability of water insoluble drugs and/or liquid lipophilic medications. The use of water-soluble salts and polymorphic forms, the formation of water-soluble molecular complexes, drug micronization, solid dispersion, co-precipitation, lyophilization, micro encapsulation, and the inclusion of drug solutions or liquid drugs into soft gelatin capsules are some of the major formulation tools which have been shown to enhance the dissolution characteristics of water-insoluble drugs, however, among them, the technique of ‘‘liquisolid compacts” is one of the most promising techniques [1–19]. Generally liquisolid systems are considered as acceptably flowing and readily compressible powdered forms of liquid medications converted into a dry-looking, nonadherent, free-flowing. compressible powders by a simple admixture with selected powder excipients referred to as the carrier and coating materials. Frusemide is a high- ceiling loop diuretic which inhibits the reabsorption, used as an adjuvant in

treatment of hypertension1. However, the low aqueous solubility and poor dissolution of this molecule in gastric fluid affects its rate of absorption, resulting in a low and variable oral bioavailability. According to Bio Pharmaceutical classification it is class-IV (poor solubility and poor permeability), Frusemide is practically water insoluble, exhibits very poor solubility in acidic media (<0.012 mg/ml) slightly increased to 0.72 mg/ml at pH 5.8 [20].

In this study, frusemide was selected as a model drug, since it is a water-in soluble drug, and, thus, it establishes an ideal candidate for testing the potential of rapid-release liquisolid tablets . The flow ability and compressibility of liquisolid compacts were addressed simultaneously in the ‘‘new formulation mathematical model of liquisolid systems”, which was used to calculate the by trial and error appropriate quantities of the carrier and coating materials required to produce acceptably flowing and compressible powders.

MATERIALS AND METHODS

Materials:
Frusemide, Crospovidone, Avicel PH 102, Avicel PH 200, Avicel PH 101,Tween 80, Propylene Glycol, PEG 200, PEG 400, Tween 20, Tween 80.

Methods:
The flowability of a powder is of critical importance in the production of pharmaceutical dosage forms in order to get a uniform feed as well as reproducible filling of tablet dies, otherwise, high dose variations will occur. In order to ensure the flow properties of the liquisolid systems that will be selected to be compressed into tablets and further evaluated, angle of repose methods, Carr’s index and Hausner’s ratios were ensured [21–24]. Fixed height cone method was done in triplicate and the average angle of repose was adopted [21,22]. The bulk density procedure was calculated for each powder, fixed weight of each of the liquisolid powder prepared formulae initial volume was calculated. and then tapped at a constant velocity up to a desired volume is to reach the stable arrangement, the final bulk volume of the powder was then recorded , then the final bulk density DBmax was calculated. [21,22]

Solubility studies :
To select the best non volatile solvent for dissolving frusemide, solubility studies were carried out in seven different non volatile solvents like propylene glycol, PEG 200, PEG 400, Tween 20, Tween 80. Saturated solutions were prepared by adding excess drug to the vehicles and shaking on the shaker for 48hrs at 25^0C under constant vibration. After this period, the solutions were filtered through a 0.45 micron Millipore filterpaper, diluted with 0.1N HCl and analysed by U.V.spectrophotometer, at a wavelength of 277nm against blank sample. Six determinations were carried out for each sample to calculate the solubility of furosemide.

Preparation of drug solution: For the preparation of liquisolid compacts of Frusemide, a non-volatile solvent is choosen for dissolving the drug. From the results of solubility studies and evaluation of flow properties, liquisolid powders containing Tween 80 as the liquid medicament, Avicel PH102 as carrier and cab-o-sil as the coating material is selected for the preparation of liquisolid compacts. Various ratios of carrier to coating materials are selected. According to solubility of frusemide, desired quantities of drug and Tween 80 were accurately weighed in a

beaker and then heated to 40^0-50^0c, with constant stirring, until a homogenous drug solution was obtained. Selected amounts (W) of the resultant hot liquid medication were incorporated into calculated quantities of carrier contained in a mortar.

Mixing: The mixing procedure was conducted in three stages. During the first stage, the system was blended at an approximate mixing rate of one rotation/sec for approximately one minute in order to evenly distribute the liquid medication into the powder. In the second mixing stage, calculated quantities of coating material (cab-o-sil) was added to the system and blended for 2min. the liquid/powder admixture was evenly spread as a uniform layer on the surfaces of the mortar and left standing for approximately 5min to allow the drug solution to be absorbed in interior of the powder particles. In the third stage, the powder was scraped off the mortar surfaces by means of aluminum spatula and then blended with a calculated quantity of disintegrant (5%) for another 30sec, in a manner similar to the one used in the first stage, producing the final liquisolid formulation to be compressed.

Table: 1. Formulation of frusemide liquisolid compacts

Excipient Ratio	5:1	10:1	20:1	40:1
Drug Solution	280	280	280	280
Avicel PH 102	200	200	200	200
Aerosil PH 200	40	20	10	5
SSG	25	25	25	25
Total Tablet Wt.(mg)	545	525	515	510

Dissolution of a plain drug: Dissolution studies of plain drug 40mg were conducted in 0.1N (1.2 pH), 5.8 pH, 6.8 pH and 7.4 pH phosphate buffers.

Dissolution of marketed product: Dissolution of Lasix 40mg tablet was conducted in 0.1N (1.2 pH), 5.8 pH, 6.8 pH and 7.4 pH phosphate buffers.

RESULTS AND DISCUSSION

Calculation of loading factor:

Loading factors were calculated for different carriers, using various co-solvents. By using L_f = W/Q formula (W: Amount of liquid medication and Q: Amount of carrier material), the drug loading factors were obtained and used for calculating the amount of carrier and coating materials in each formulation. In the trial and error methods Avicel PH 102 Aerosil PH 200, choosing as a carrier and coating materials[12].

Table 2 : Solubility of frusemide in different media

S.No.	Medium	Concentration (mg/ml)
1	Distilled water	0.006mg/ml
2	5.8pH Buffer	0.72mg/ml
3	6.8pH Buffer	0.398mg/ml
4	7.4pH Buffer	0.204mg/ml

Table. 3: Solubility of frusemide in different non volatile solvents

S.No	Co solvents	Concentration (mg/ml)
1	Tween 80	201.7mg/ml
2	Tween 20	113.5mg/ml
3	PEG 400	98.69mg/ml
4	PEG 600	88.87mg/ml
5	Propylene Glycol	85.92mg/ml

Spireas et al. [9] reports that the liquisolid mechanisms suggests that drug actual form crystalline nature is converts into amorphous nature when dissolving in the liquid vehicle is incorporated into a carrier material. Initially, the liquid medication absorbed and captured into the internal particle structure, that carrier having the porous surface and closely matted fibers in its interior as cellulose, after completion of absorption saturation process and adsorption take place onto the internal and external surfaces of the porous carrier particles. High adsorptive properties and large specific surface area, desirable flow characteristics was achieved by using coating material [1,2,9].

As presented in Table 3, F7, F12, and F14 showed (h) values of 34.06^0, 36.13^0, and 36.45^0, respectively, were chosen as liquisolid systems with acceptable flowability according to the angle of repose measurements, while those having higher angles of repose were considered as non-acceptable. Powders showing Carr's index (Ci) up to 21 are considered of acceptable flow properties. Carr's index, Hausner found that the ratio DBmax/DBmin was related to the inter particle friction, that ratios 1.25 indicating good flow [21].

F7 were selected as acceptably flowing as they had average Ci of 19.61, 19.86, and 20.14, respectively, and average Hausner's ratios of 1.24, 1.23, and 1.25, in the same order. in each of the mentioned formulae, no more than one tablet is outside these limits nor one individual is outside the limits of 75–125%. Uniform distribution is achieving the good result might lead by either adsorption onto or absorption into the carrier, therefore having more homogeneous distribution throughout the batch which it is corresponding to high R-values represent higher Avicel PH 102 (carrier) concentrations. All the selected liquisolid tablets had following the acceptable friability and should met the standard USP limits and also, no tablet was cracked, split in either batches. At optimizing of the all frusemide liquisolid tablet 4-5kg hardness without applying excessive compression force, as well as achieving rapid tablet disintegration and drug dissolution and hard to resist breaking during normal handling.

Since our aim was to improve frusemide bioavailability via improving the tablets' physical characteristics, the long disintegration time (5 min) of F3 might retard the drug release and therefore bioavailability; hence, F3 was excluded from further experiments.

***Invitro* disolution studies:**

EFFECT of Excipient ratio: Comparison between the both ratios of Frusemide liquisolid tablets, 10:1 excipient ratio showing the proper flow properties, evaluation properties and also producing the 100% dissolution rate within the 25 minutes than 5:1 frusemide liquisolid tablets. So, it is eliminated further studies.

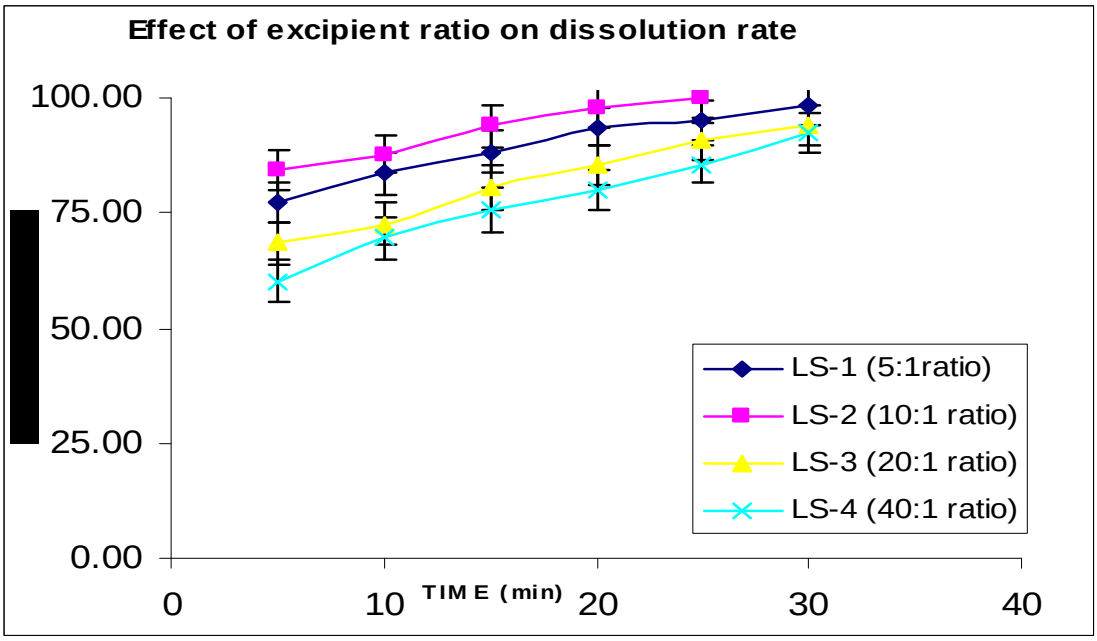

Figure:1. Dissolution profiles comparison between all excipient ratios

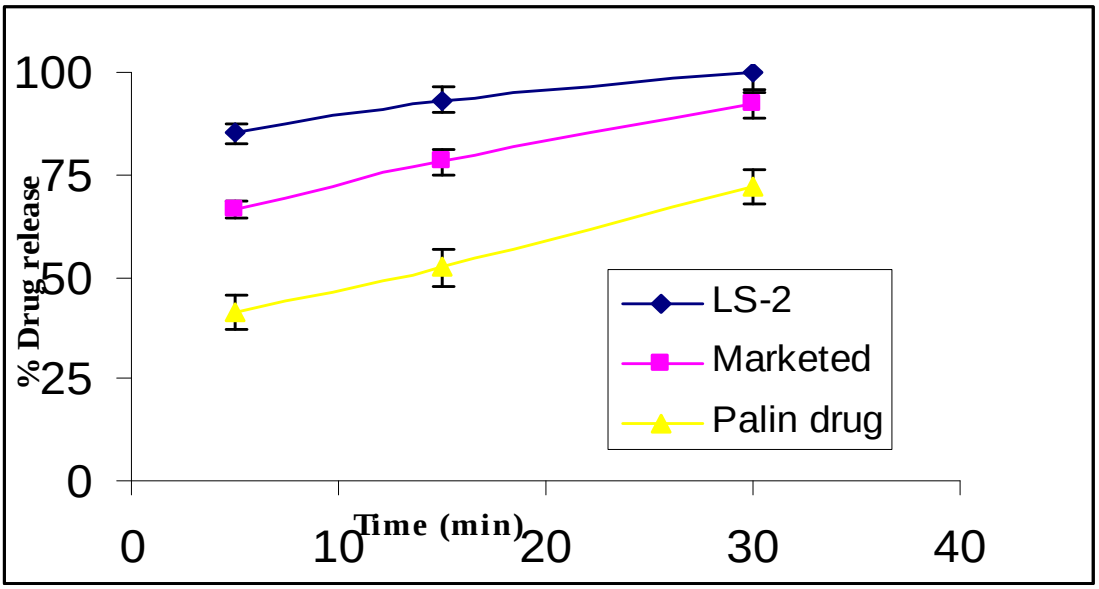

Figure:2. Dissolution profile of marketed product, plain drug and LS-2 in 5.8pH buffer

In 5.8 pH buffer solution, LSC 10:1 ratio showing the highest dissolution rate (99.95%) comparison with marketed product (91.53%) and frusemide plain drug (52.20%) showing in Figure.2.

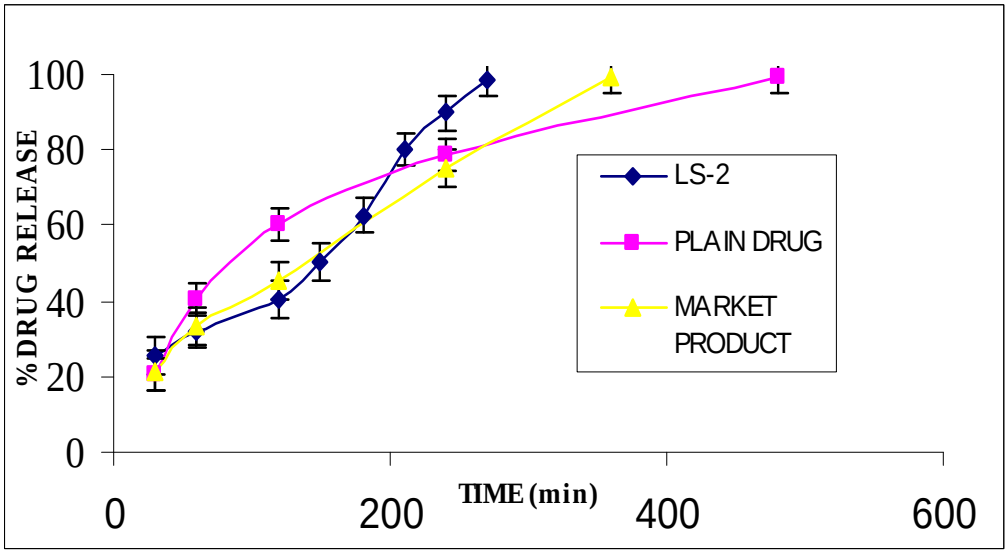

Figure: 3.Dissolution profile of marketed product, plain drug and LSC in 0.1N HCl

In Figure.3.In 0.1 N HCl , (LSC 10:1) ratio showing the highest dissolution rate(98.35%) within 270 minutes comparison with plain drug (78.80%) and marketed product (75.4%).

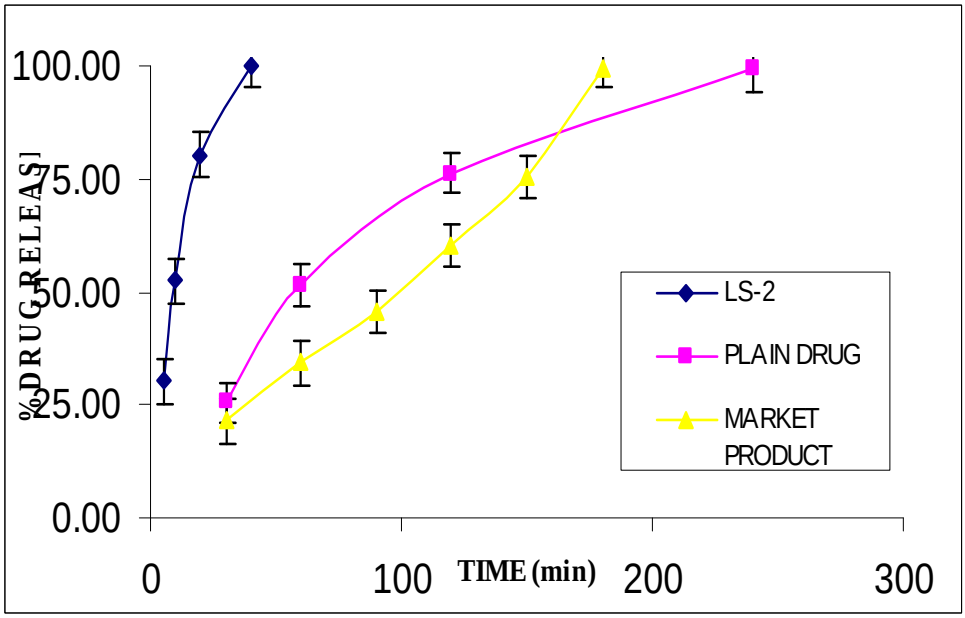

Figure: 4. Dissolution profile of marketed product, plain drug and LSC in 6.8pH buffer

In Figure. 4. LS-2 (10:1) ratio frusemide liquisolid tablets were showing the highest dissolution rate 100% within the 40 minutes in 6.8pH buffer medium and marketed product , showing the dissolution rate 99.75% in 270 minutes ,plain drug showing the dissolution rate 99.60) in 180 minutes. Improvement of dissolution rate in the frusemide liquisolid tablets mainly occurred with

the conversion of the crystalline form of the drug to amorphous nature in different dissolution mediums.

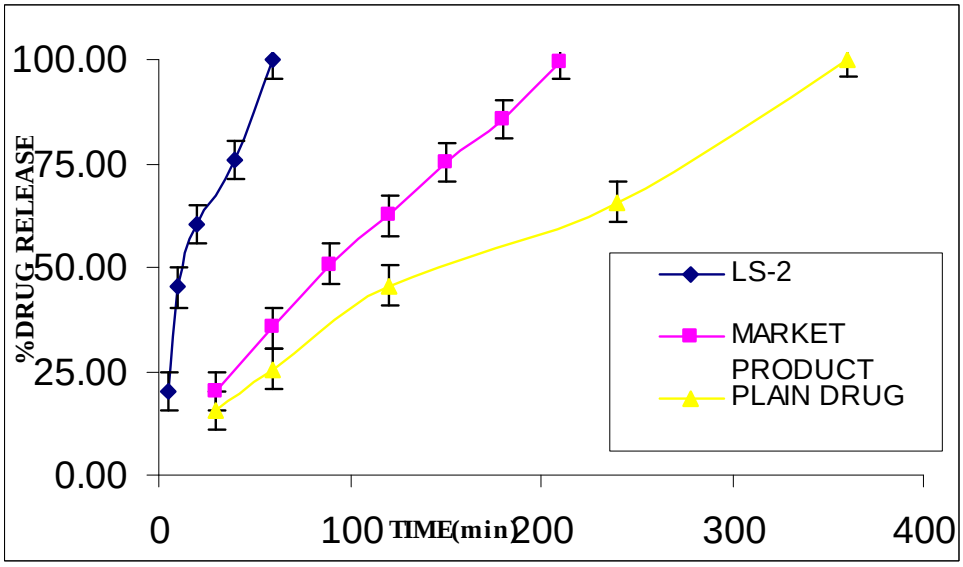

Figure: 5. Dissolution profile of marketed product, plain drug and LSC in 7.4pH buffer

Figure. 5. showing, In 7.4 pH buffer solution LS-2 (10:1 ratio) frusemide liquisolid tablets were showing the 99.72% dissolution rate within 60 min and marketed product , plain drug achieve the 100% drug release 210min, 360 min.

CONCLUSION

The solubility-dissolution behavior is the rate-limiting step to absorption from the gastrointestinal tract of poorly water soluble drugs like frusemide, needs to be enhanced. Powder solution technology is one of the promising approaches to increase dissolution rate and is confirmed by the experimental results. Rationale of the present study suggesting that the usage of Avicel ® PH 102 can provide good flow properties and hardness, invitro dissolution studies results were proving that frusemide has almost entirely converted from crystalline to amorphous state as well as all frusemide liquisolid tablets showing highest dissolution rate when compared with conventional marketed product 40mg tablets due to increase in wetting properties and surface area of drug available for dissolution media.

REFERENCES

[1] S. Spireas, M. Bolton, Liquisolid Systems and Methods of Preparing Same, U.S. Patent 5,968,550, (**1999**).
[2] S. Spireas, Liquisolid Systems and Methods of Preparing Same, U.S. Patent ,423,339 B1, (**2002**).
[3] A. Sheth, C.I. Jarowski, *Int. J. Pharm*. **1990,**16 (5) 769–777.
[4] S. Spireas, T. Wang, R. Grover, *Drug Dev. Ind. Pharm*. **1999,** 5 (2) , 163–168.
[5] A. Nokhodchi, *J. Pharm. Sci*. **2005,** 8 (1), 18–25.

[6] Y. Javadzadeh,M.R. Siahi-Shadbad, M. Barzegar-Jalali, A. Nokhodchi, *Il Farmaco*. **2005,** 60, 361–365.
[7] S. Spireas, S. Sadu, R. Grover, *J. Pharm. Sci.* 87 (7) (1998) 867–872.
[8] S. Spireas, S. Sadu, *Int. J. Pharm*. 166 (1998) 177–188.
[9] S. Spireas, C.I. Jarowski, B.D. Rohera, *Pharm. Res.* **1992**, 9 (10),1351–1358.
[10] R.H.Fahmy, MA. Kassem. *Eur J. Pharm Biopham*, **2008,**69, 993-1003,
[11] Y.Javadzadeh, B .Jafari- Navipour, A. Nokhodchi. *Int. J. Pharm*., **2007** ,341,26-34.
[12] Y.Javadzadeh , L .Mussalrezaei, A .Nokhodchi,. *Int. J. Pharm*, **2008**,362 ,102- 108,.
[13] Y.Javadzadeh , M.R.Siahi, S .Asnaashari, A .Nokhodchi. *Pharm. Dev. And Tech*., **2007**,12, 337-343.
[14] Y.Javadzadeh, H.Shariati, E.Movahhed-Danesh, A. Nokhodchi., *Drug Dev Ind. Pharm.*, **2009**,35(2), 243-51.
[15] A.Khaled, YA. Asiri, YM.El-Sayed. *Int. J. Pharm.*, **2001**.222 , 1-6.
[16] C.C. Liao, Physicochemical properties of selected powdered drug solutions, Ph.D. thesis, St.John's university, New York **1983**.
[17] A .Nokhodchi , Y.Javadzadeh, M.R Siahi, M .Barzegar-Jalali. *J.Pharm. Sci*, **2005** ,8 18-25.
[18] S.A .Tayel, I.I. Solimanlouis, D. *Eur J. Pharm Biopham*., **2007**, 69, 342-347.
[19] N.Tiong, A.A. Elkordy, *Eur J Pharm Biopharm*, **2009**, 73(3), 373-384.
[20] S.C. Sweetman, Martindale: The Complete Drug Reference, 33rd ed. The Pharmaceutical Press, London, **2002**.
[21] P.E. Luner, L.E. Kirsch, S. Majuru, E. Oh, A.B. Joshi, D.E. Wurster, M.P. Redmon, *Drug Dev. Ind. Pharm.* **2001,**27 (4) , 321–329.
[22] J. Staniforth, Powder flow, in: M. Aulton (Ed.), Pharmaceutics, the Science of Dosage Form Design, 2nd ed., (Churchill Livingstone, Longman group, Edinburgh, **2002,** 197–210.
[23] M.V. Velasco, A. Munoz-Ruiz, M.C. Monedero, M.R. Jimenez- Castellanos, *Drug Dev. Ind. Pharm*. **1995,** 21 (10), 1235–1243.
[24] G.E. Amidon, Physical and mechanical property characterization of powders, in:H.G. Brittain (Ed.), Physical Characterization of Pharmaceutical Solids, Drugs and Pharmaceutical Sciences, (70, Marcel Dekker Inc., New York, **1995**), 282–17.