CODEN [USA]: IAJPBB ISSN: 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

http://doi.org/10.5281/zenodo.1408036

Available online at: http://www.iajps.com Research Article

DESIGN AND CHARACTERIZATION OF SPHERICAL AGGLOMERATED CRYSTALS LOADED FAST DISOLVING TABLETS FOR ENHANCING THE SOLUBILITY OF SIMVASTATIN

M.Suresh babu [1]* and T. E. Gopala Krishna murthy[2]

[1]Department of pharmaceutics, Acharya Nagarjuna University, Nagarjunanagar-522510.

[2] Department of pharmaceutics, Bapatla College of Pharmacy, Bapatla-522101.

Abstract:

In the present work an attempt was done to study the effect of different carriers on the solubility and dissolution rate of Simvastatin poorly water soluble drug, by spherically agglomeration using N,N-dimethylformamide, water and chloroform as good solvent, poor solvent and bridging liquid, respectively. The quasi-emulsion solvent diffusion technique was used as a method for spherical agglomeration. Spherical agglomeration of Simvastatin were prepared by using Poloxomer -F338 and Gelucire 48/16 in the ratio of 1:0.5,1:0.75,1:1. The agglomerates were subjected to various physicochemical evaluations such as practical yield, drug content, solubility, flow properities, average particle size,scanning electron microscopy and dissolution studies. The optical electron microscopy studies showed that the agglomerates posseeses a good spherical shape. This study, demonstrated that the successful development of directly compressible spherical agglomerates of Simvastatin prepared with selected carrires enhances the in-vitro dissolution property of Simvastatin, which could provide rapid onset of action and potentially increases oral bioavailability. To study the influence of co-processed superdisintegrants on performance of Simvastatin Fast dissolving tablets, a set of three formulations (F_7, F_8, F_9) were prepared using co-processed superdisintegrants (Croscarmalose sodium:Crospovidone) in three different ratios 1:1, 1:2, 1:3 respectively. The formulation prepared with co-processed superdisintegrants (Croscarmalose sodium:Crospovidone) in 1:3 ratio (F_9) was offered relatively rapid release of Simvastatin when compared with other ratios employed in this investigation.

Key words: *Simvastatin, Poloxomer -F338, Gelucire 48/16, spherically agglomeration*

***Corresponding author:**

M.Suresh babu,
Research scholor,
Department of pharmaceutics,
Deccan School of Pharmacy,
Dar-Us-Salam, Aghapura, Near Nampally,
Hyderabad, Telangana 500001
Phone: 8074479566
E-mail:msbdeccan@gmail.com

QR code

*Please cite this article in press M.Suresh babu and T. E. Gopala Krishna murthy., **Design and Characterization of Spherical Agglomerated Crystals Loaded Fast Disolving Tablets For Enhancing the Solubility of Simvastatin,** Indo Am. J. P. Sci, 2017; 04(12).*

INTRODUCTION:

Simvastatin (SIM), a crystalline compound, is practically insoluble in water and hence poorly absorbed from the GI tract. It is a potent and specific inhibitor of 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG CoA) reductase , which catalyzes the reduction of HMG CoA to mevalonate. Thus, simvastatin arrests a key step for cholesterol biosynthesis in the liver and is widely used in the treatment of hypercholesterolemia and dyslipidemia as an adjunct to diet. After oral administration, simvastatin is metabolized to its β-dihydroxy acid form (simvastatin acid) by the cytochrome-3A system in the liver, where it inhibits the rate-limiting step in cholesterol biosynthesis. This leads to up-regulation of low-density lipoprotein (LDL) receptors and an increase in catabolism of LDL cholesterol. Being a BCS Class II drug, it often shows dissolution rate-limited oral absorption and high variability in pharmacological effects. Therefore, improvement in its solubility and dissolution rate may lead to enhancement in bioavailability.

Therefore, in the present study, an attempt has been made to increase solubility of Simvastatin by spherically agglomeration technique [1,2]. The resultant crystals can be designated as spherical agglomerates. Spherical crystallization is an effective alternative to improve dissolution rate of drugs. This can be achieved by various methods such as spherical agglomeration, quasi-emulsion solvent diffusion and neutralization methods. Many of the drugs, evolving from these techniques, can be categorized as class II drugs according to Biopharmaceutical classification system.These drugs are poorly water soluble, but once they are dissolved they easily absorbed through the gastrointestinal membrane. Therefore, bioavailability after oral administration can be improved by enhancement of the dissolution rate. One of the approaches dissolution rate is use of spherical crystallizationtechnique [3-6].

MATERIALS AND METHODS:

Simvastatin was obtained from Dr.Reddy's labs, Hyderabad,India. Poloxomer -F338 and Gelucire 48/16 were purchased from SD fine Chemicals Ltd, Mumbai. All other materials used were of analytical grade.

Preparation of Spherically Agglomerates:

All spherical agglomerates were obtained by the quasi emulsion solvent diffusion method [7]. Spherical agglomerates were prepared with and without stabilizers by spherical crystallization technique. The stabilizers composition was given in Table 1. Simvastatin (1.0 g) was dissolved in good solvent N,N-dimethylformamide (25.0 mL).The bridging liquid chloroform (12.5 mL) was added to it. The resulting solution was then poured drop wise in to the poor solvent distilled water (100 mL) containing different surfactant like,. Poloxomer -F338 and Gelucire 48/16 with a stirring rate of 500 rpm using propeller type agitator (Remi Motors Ltd., Mumbai, India) at room temperature [8]. After agitating the system for 30 minutes, the prepared agglomerates were collected by filtration through whatmann filter paper no.42.

Evaluation of spherical agglomerates:

a) Particle size determination:

Particle size determination was carried out using optical microscopy with a calibrated eye piece micrometer and stage micrometer by taking a small quantity of formulation on slide[8]. About 100 spherical agglomerates size was measured individually, average was taken and their size range and mean diameter frequency was calculated.Average Particle size is calculated by the following formula, Average Particle size= £nd/ n

b)Drug Content Estimation:

The percentage drug content in spherical agglomerates was estimated by dissolving spherical agglomerates equivalent to 100 mg of Simvastatin in methanol, mixed thoroughly by shaking and the volume was made up to the mark with in 6.8 pH phosphate buffer. The solution was filtered and the filtrate was diluted suitably with 6.8 pH phosphate buffer and absorbance was measured at 372 nm using UV/Visible spectrophotometer [9].

c) Dissolution studies of agglomerates:

In-vitro dissolution studies of pure drug and spherical agglomerates were carried out for 60 minutes using USP Dissolution test apparatus type II (Lab India DISSO 2000, eight stages) at 50 rpm.Spherical agglomerates equivalent to 100 mg of Simvastatin was used for dissolution study at 37 ± 0.5^0 C in 900ml of 6.8 pH phosphate buffer as dissolution medium. Aliquot equal to 5 ml was withdrawn at regular time intervals (10, 20, 30, 40, 50, 60 min), an equal volume of fresh dissolution medium was replaced to maintain the sink condition and aliquots were measured at 238 nm UV/Visible spectrophotometer. DE_{30}%, T_{50}, T_{90} and k^{-1} values were calculated from dissolution data [10].

Preparation of Simvastatin tablets:

To study the influence of co-processed superdisintegrants on performance of SimvastatinFast dissolving tablets, a set of three formulations (F_7, F_8, F_9) were prepared using co-processed superdisintegrants (Croscarmalose sodium:Crospovidone) in three different ratios 1:1, 1:2, 1:3 respectively. Tablets were made from blends by direct compression method. All the ingredients ingredients (shown in Table 3) were mixed [11] . The resulting blend was lubricated with magnesium stearate and compressed into tablets using the Cadmach single punch (round shaped, 7mm thick) machine.

EVALUATION OF SIMVASTATIN TABLETS

a) Weight variation test [12]:

Weight variation test was done by weighing 20 tablets individually, calculating the average weight and comparing the individual tablet weight to the average weight.

b) Drug content [13]:

Twenty tablets were powdered, and powder equivalent to 100 mg of Simvastatin was accurately weighed and transferred into a 100 ml volumetric flask. Initially, 5 ml methanol was added and shaken for 10 min. Then, the volume was made up to 100 ml with 6.8 phosphate buffer. The solution in the volumetric flask was filtered, diluted suitably and analyzed spectrophotometrically at 238 nm.

c) Disintegration Time [14]:

The disintegration time was determined in distilled water at 37 ± 0.5^0 C using disintegration test apparatus USP ED-2L (Electro lab, Mumbai).

d) Friability [14]:

Roche friabilator was used to determine the friability. Pre weighed tablets were placed in friabilator and rotated at a speed of 25 rpm for 4 minutes or up to 100 revolutions. The tablets are dropped from a distance of 6 inches in each revolution. The tablets were then reweighed after removal of fines and the percentage of weight loss was calculated.

$$\% \text{ friability} = \frac{\text{Weight before friabilati on} - \text{Weight after friabilati on}}{\text{Weight before friabilati on}} X 100$$

e) Hardness [14]:

Hardness of the tablet was determined using the Monsanto hardness tester. The lower plunger was placed in contact with the tablet and a zero reading was taken. The plunger was then forced against a spring by tuning threaded bolts until the tablet fractured. Then the final reading was recorded. The hardness was computed by deducting the initial pressure from the final pressure.

f) Wetting Time [14]:

The wetting time of the tablets can be measured using a simple procedure. Five circular tissue papers of 10 cm diameter are placed in a petridish with a 10 cm diameter. 10 mL of water-containing amaranth a water soluble dye is added to petridish. A tablet is carefully placed on the surface of the tissue paper. The time required for water to reach upper surface of the tablet is noted as a wetting time.

g) In vitro dispersion time [14]:

Tablet was added to 10 ml of phosphate buffer solution pH 6.8 (pH of saliva) at 37± 0.5°C. Time required for complete dispersion of tablet was measured.

h Fineness of dispersion [14]:

This test was performed by placing two tablets in 100 ml of water and stirring it gently, untill the tablets get completely disintegrated. Then the dispersion is passed through a sieve screen with a nominal mesh aperture of 710 µm.

j) Dissolution studies [14]:

Dissolution studies for Simvastatin fast dissolving tablets were performed in pH 6.8 phosphate buffer using USP dissolution test apparatus (Electrolab, Mumbai, India) with a paddle stirrer. The paddles are allowed to rotate at speed of 100 rpm. The dissolution medium was maintained at a temperature of $37 \pm 0.5\ ^{O}$C and samples are withdrawn at an interval of every 5 min the volume of the withdrawn samples are replaced by fresh dissolution medium in order to kept the volume of the dissolution medium as constant. The withdrawn samples are filtered and absorbance was measured at absorption maxima of 238 nm using UV-visible spectrophotometer.

k) In-vitro dissolution kinetic studies [14]:

The drug release data were plotted and tested with zero order (cumulative % drug released Vs time), First order (Log % remained Vs time). The in vitro dissolution kinetic parameters, dissolution rate constants (K), correlation coefficient (r), the times (t_{50}) for 50 % drug released (half-life) and dissolution efficiency [D.E.] were calculated. From the slopes of linear plots, the dissolution rates were calculated.

l)FTIR (Fourier Transform Infra-red Spectroscopy) Studies [15]:

Infrared (IR) spectroscopy studies of Simvastatin and its optimized formulations with PVP and cross povidone were recorded in a FTIR spectrophotometer (Thermo-IR 200) Potassium bromide pellet method was employed and background spectrum was collected under identical conditions. The spectrum for each sample showed the wavelength of absorbed light which is a characteristic of the chemical bonds in the sample. Each spectrum was derived from 16 single average scans collected in the region of 400 - 4000 cm-1 at a spectral resolution of 2 cm-1.

RESULTS AND DISCUSSION:

Spherical agglomerates of Simvastatin were prepared by quasi emulsion solvent diffusion method (QESD) using a three solvent system. It involves good solvent, poor solvent and a bridging liquid. The selection of these solvents depends on the miscibility of the solvents and the solubility of drug in individual solvent. Accordingly N,N-dimethylformamide, chloroform and water were selected as a good solvent,bridging liquid, and poor solvent, respectively. Simvastatin is highly soluble in N,N-dimethylformamide, but poorly soluble in water. Also it is soluble in chloroform which is immiscible in water. Hence, this solvent system was used in the present study. In QESD method, when good solvent solution of drug plus bridging liquid were poured in the poor solvent(containing different carriers) under agitation, quasi emulsion droplets of bridging liquid and good solvent were produced. Then the good solvent diffuses gradually out of the emulsion droplet into the outer poor solvent phase. The counter-diffusion of the poor solvent into the droplets induces the crystallization of the drug within the droplet due to the decrease in solubility of the drug in the droplet containing the poor solvent. The bridging liquid wets the crystal surface to cause binding and promotes the formation of liquid bridges between the drug crystals to form spherical agglomerates. The spherically agglomerated crystals are formed by coalescence of these dispersed crystals. In the present study effect of different polymers on solubility and dissolution rate of spherical agglomerates of Simvastatin were studied. Incorporation of polymer during agglomeration significantly enhanced the dissolution. Mixing of drug with a carrier results in greater wetting and increase surface available for dissolution by reducing interfacial tension between the hydrophilic drug and dissolution media. It was noted that drug carrier system sink immediately, while pure drug keeps floating on the surface for a longer time interval. The cumulative percentage of drug released from different agglomerates was increased in the following order :Simvastatin spherical agglomerates prepared with Poloxomer -F338 > Simvastatin spherical agglomerates prepared with Gelucire 48/16.Among all the formulations prepared, spherical agglomerates prepared Simvastatin and Poloxomer -F338 in 1:1 ratio showed highest drug release in 60 minutes.

To study the influence of co-processed superdisintegrants on performance of SimvastatinFast dissolving tablets, a set of three formulations (F_7, F_8, F_9) were prepared using co-processed superdisintegrants (Croscarmalose sodium:Crospovidone) in three different ratios 1:1, 1:2, 1:3 respectively. . The dissolution rate followed first-order kinetics as the graphs drawn between log % drug unreleased vs time were found to be linear. The dissolution rate of Simvastatin was found to be effected by nature of the superdisintegrant used in the preparation of tablets. The formulation prepared with co-processed superdisintegrants (Croscarmalose sodium:Crospovidone) in 1:3 ratio (F_9) was offered relatively rapid release of Simvastatin when compared with other ratios employed in this investigation.

Table 1: Composition of Simvastatin Spherical Agglomerates

Ingredients	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**
Simvastatin(g)	1	1	1	1	1	1
Poloxomer -F338 (g)	0.5	0.75	1			
Gelucire 48/16 (g)				0.5	0.75	1
N,N-dimethylformamide	25	25	25	25	25	25
Dichloromethane(ml)	12.5	12.5	12.5	12.5	12.5	12.5
Water (ml)	62.5	62.5	62.5	62.5	62.5	62.5

Table 2: Particle size and % of Drug content of Simvastatin spherical agglomerates

Formulation	**Particle size(µm)**	**% of Drug content**
FI	215	98.18
F2	247	97.63
F3	267	97.23
F4	276	98.44
F5	293	97.14
F6	312	96.27

Table 3: *In-vitro* dissolution kinetics of Simvastatin spherical crystals prepared with different carriers.

S.No.	Formulation	T_{50} (min)	T_{90} (min)	DE_{30} (%)	K (min^{-1})	Correlation coefficient values	
						Zero Order	First order
1	F_1	21.9	72.7	30.55	0.0317	0.9724	0.9814
2	F_2	18.7	62.1	34.29	0.0371	0.9582	0.9774
3	F_3	16.3	54.1	37.24	0.0426	0.9463	0.9704
4	F_4	25.1	83.5	27.16	0.0317	0.9816	0.9839
5	F_5	21.8	72.3	30.84	0.0371	0.9703	0.9817
6	F_6	19.5	64.6	33.44	0.0426	0.9620	0.9818

Table 4: Composition of ingredients for Simvastatin fast dissolving tablets

S.No	Ingredients	F_7	F_8	F_9
1	Simvastatin crystals prepared with Poloxomer -F338 in 1:1 ratio	40	40	40
2	Croscarmalose sodium+ Crospovidone	10	10	10
3	Manitol	70	70	70
4	Micro crystaline cellulose	76	76	76
5	Talc	2	2	2
6	Magnesium streate	2	2	2
	Total weight	200	200	200

Table 5: Physical parameters of Simvastatin fast dissolving tablets

S.No.	Parameters	F_7	F_8	F_9
1	**Average weight (mg)**	199$\pm$0.3	199$\pm$0.2	200$\pm$0.1
2	**Drug content(%)**	98.4	99.5	99.8
3	**Disintegration time (sec)**	152	143	111
4	**Friability(%)**	0.23	0.46	0.41
5	**Hardness(kg/sqcm)**	4.2	4.2	3.8
6	**Wetting time (sec)**	130	121	95
7	***In-vitro* dispersion time (min)**	254	212	161
8	**Fineness of dispersion**	pass	pass	pass

Table 6: *In-vitro* dissolution kinetics of Simvastatin fast dissolving tablets

S.No.	Formulation	T_{50} (min)	T_{90} (min)	DE_{15} (%)	K (min^{-1})	Correlation coefficient values	
						Zero Order	First order
1	F_7	6.0	20.1	48.80	0.11	0.8493	0.9778
2	F_8	4.9	16.2	56.54	0.14	0.8206	0.9825
3	F_9	3.2	10.7	66.50	0.21	0.8007	0.9908

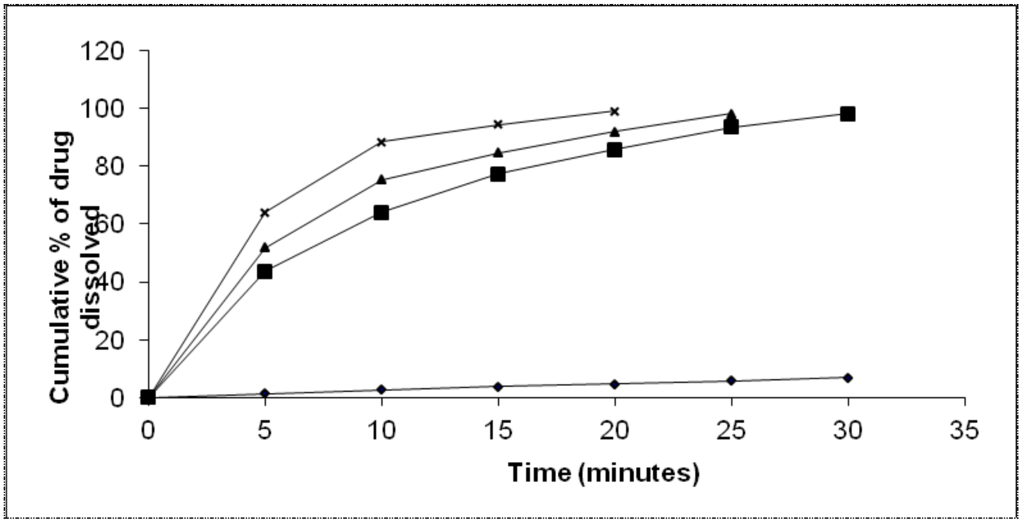

Figure 1: ***In-vitro*** **dissolution profile of Simvastatin fast dissolving tablets with coprocessed superdisintegrants**
(-♦-) Simvastatin pure drug
(-■-) Simvastatin tablets prepared with crospovidone and croscarmalosesodium in 1:1 ratio by coprocessing technique
(-▲-)Simvastatin tablets prepared with crospovidone and croscarmalosesodium in 1:2 ratio by coprocessing technique
(-×-) Simvastatin tablets prepared with crospovidone and croscarmalosesodium in 1:3 ratio by coprocessing technique

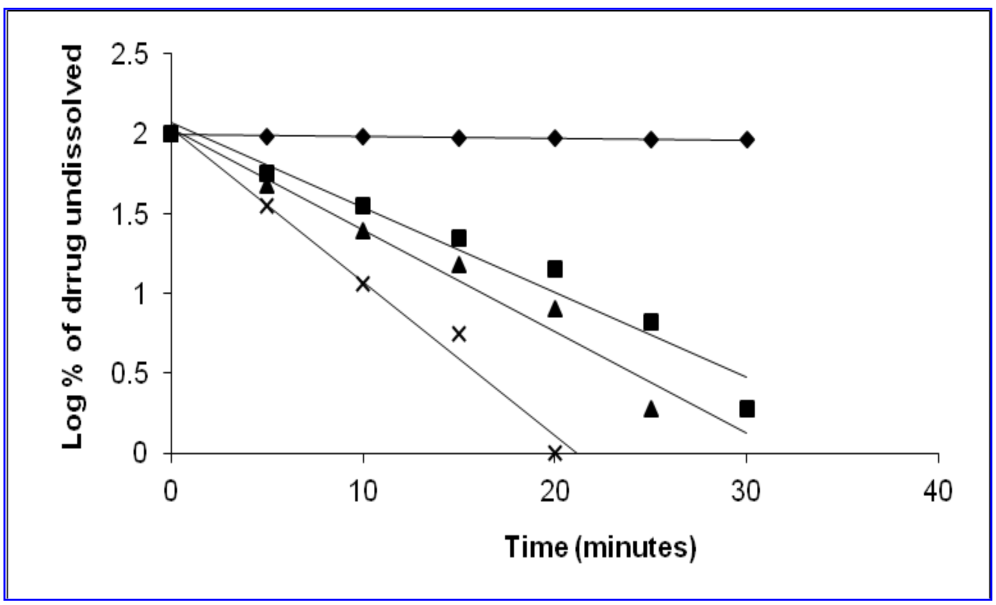

Figure 2: First order plots of Simvastatin tablets with coprocessed superdisintegrants

(-♦-) Simvastatin pure drug
(-■-) Simvastatintablets prepared with crospovidone and croscarmalosesodium in 1:1 ratio by coprocessing technique
(-▲-)Simvastatin tablets prepared with crospovidone and croscarmalosesodium in 1:2 ratio by coprocessing technique
(-×-) Simvastatintablets prepared with crospovidone and croscarmalosesodium in 1:3 ratio by coprocessing technique

CONCLUSION:

Present study concluded that spherical agglomerates prepared by the quasi emulsion solvent diffusion method showed an improvement in the solubility, dissolution rate, compactibility, wettability, flowability and bioavilability.These spherical agglomerates also showed excellent physico-chemical characters as compared with plain drug which indicates that the spherical agglomerates can suitable for directly compressible tablet process .

REFERENCES:

1. Patel R, Patel M. Preparation, characterization, and dissolution behavior of a solid dispersion of simvastatin with polyethylene glycol 4000 and polyvinylpyrrolidone K30. J Disper Sci Technol.2008;2:193–204.
2. Rao M, Mandage Y, Khole I, Munjapara G. Characterization of solid dispersions of simvastatin with PVP K30 . Ind J Pharm Educ Res. 2011;45:145–52.
3. Guillaume F., Guyot-Hermann A.M., Guyot J.C., Spherical crystallization of meprobamate, Il Farmaco., 1993; 48: 73–485.
4. Di Martino P., Barthelemy C., Piva F., Joiris E., Palmieri G.F., Martelli S., Improved dissolution behavior of fenbufen by spherical crystallization, Drug Dev.Ind.Pharm.,1999; 25:1073–081.
5. Akbuga J., Preparation and evaluation of controlled releasefurosemide microspheres by spherical crystallization, Int. J.Pharm.,1989; 53:99–105.
6. Ribardie`re A., Tchoreloff P., Couarraze G., Puisieux F., Modification of ketoprofen bead structure produced by the spherical crystallization technique with a two-solvent system,Int. J. Pharm.,1996; 144: 195–207.
7. Sanjeev Kumar , Pradeep Kumar, Chanderparkash, Shailendra K Singh. Evaluation of Some Novel Techniques For Dissolution Enhancement of Poorly Water Soluble Drug Nimodipine.International Journal of PharmTech Research. 2010 ;2(1): 950-959.
8. Tapan Kumar Giri, Hemant Badwaik, Amit Alexander , Dulal Krishna Tripathi . Solubility enhancement of Simvastatin in the presence of hydrophilic polymer and surfactant. Int j applied Biology and Pharmaceutical Technology 2009; 2(2):119-130.
9. Ranjit Dash, Ajit Kumar Acharya, Sanysi Swain, Mayank Barg, Hemant Kumar Choudhary, Khageswar Meher. Formulation and Evaluation of Spherical Crystal of Etoricoxib. International Journal of Pharmaceutical & Biological Archives 2011; 2(4):1123-1129.
10. Goczo H, Szabo-Revesz P, Farkas B, Hasznos-Nezdei M, Serwanis SF, Pintye-Hodi AK., Development of spherical crystals of Acetyl salicylic acid for direct tablet making, Chem.Pharm. Bull., 2000, 48, 1877-81.
11. Di Martino P, Barthélémy C, Piva F, Joiris E, Palmieri GF, Martelli S., Improved dissolution behavior of fenbufen by spherical crystallization, Drug Dev. Ind. Pharm., 1999, 25, 1073-81.
12. Battue S K,Repay M.A, Maunder S , Rio M Y. Formulation and evaluation of rapidly disintegrating tablet Fenoverine tablets: Effect of superdisintegrants. Drug. Dev. Ind. Pharm 2007;33: 1225-1232.
13. Sunada H , Yonezawa Y, Danjo K, Otsuka A , Iida K . Preparation and evaluation of a compressed tablet rapidly disintegrating in the oral cavity. Chem Pharm Bull (Tokyo) 1996 ; 44: 2121-2127 .
14. Gohel.M.C, Bansal.G, Bhatt.N, Formulation and evaluation of orodispersible taste masked tablets of Famotidine. Pharma Boil world 2005;3: 75-80.
15. Sunil Kumar J, Meenakshi S, Vivek S. Development and in Vitro Evaluation of Simvastatin Mouth DissolvingTablets Using Solid Dispersion Technique**.** Chem. Pharm. Bull. 2010; 58(8): 1037—1042.