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Preparation and characterization of Irbesartan solid dispersion Tablet: Melt Dispersion Technique for dissolution enhancement

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ABSTRACT

Oral bioavailability of irbesartan (IBS) is only 60% due to its poor aqueous solubility and dissolution rate. The present research work was aimed for improvement of dissolution of IBS by melt dispersion technique which is supposed to improve oral bioavailability. Solid dispersions of IBS were prepared using polymeric additives (polyvinylpyrrolidone, copovidone, polyethylene glycol and poloxamer) in different ratios. Quantitative solubility of selected formulations were evaluated after a trial of physical solubility study of all the formulations. Formulation A [IBS/PVP (1:1) + poloxamer 10%] and formulation B [IBS/PVP (1:2) + poloxamer 5%] were taken for micronization by jet milling (Cadmach, Ahmedabad, india). Formulation A and B have been characterised by instrumental study such as particle size analysis (Sympatech particle size laser analyser, GmbH, Germany); XRD (Mettler Toledo, USA); DSC (Mettler Toledo, USA). Formulation A and B have been tableted (each tablet contains 150mg IBS) using Micro Crystalline Cellulose (MCC 102), as major filler by direct compression applying 100-120 N pressure. Solubility of A and B have been improved to 4.6 (.0055mg/ml) times and 3.8 (0.046mg/ml) times respectively compared to pure drug (0.012mg/mL). IBS dissolution of tablet A has been improved to 71.76% in SGF (0.1N HCl). Micronized particle size of A (X_{90}:103μ) and B (X_{90}:69μ), and amorphization of drug in Solid dispersions (decreased intensity of XRD and is appearance of endothermic peak of crystalline drug) have brought about improved dissolution.

Keywords: Irbesartan, Melt dispersion, Polymeric additives, Poly vinyl pyrrolidone, Poloxamer and Micro crystalline cellulose.

INTRODUCTION

Irbesartan (IBS) is an angiotensin II receptor antagonist used in the treatment of hypertension. It may also delay progression of diabetic nephropathy and also indicated for the reduction of renal disease progression in patients with type II diabetes, hypertension and micro albumin urea or protein urea. According to BCS classification IBS belongs to class II. So it has poor solubility in water. [1-3]

Solubility and dissolution are the key parameters for the therapeutic effect of a drug and to achieve desired concentration of drug in systemic circulation for pharmacological response. More than 92% of the drugs cited in U.S pharmacopeia are having poor solubility. It is commonly recognized in the pharmaceutical industry that more than 40% of newly discovered drug candidates are having poor solubility. Aqueous solubility of a drug can be a critical limitation to its oral absorption. [4-6]

Lipophilic molecules, especially those belonging to the biopharmaceutical classification system (BCS) class II and IV, dissolve slowly, poorly and irregularly, and hence pose serious delivery challenges like incomplete release from the dosage form & poor bioavailability. For the enhancement of oral bioavailability of poorly soluble drugs remains one of the most challenging aspects of drug development. Although salt formation, solubilisation and particle size reduction have commonly been used to increase dissolution rate and thereby oral absorption and bioavailability of such drugs, there are some practical limitations of these techniques. [7-8]

Solid dispersion technology is the science of dispersing one or more active ingredients in an inert matrix in the solid state in order to achieve increased dissolution rate, improved solubility and stability. In case of salts, the increased dissolution rate in the gastrointestinal tract may not be achieved because of the reconversion of salts into aggregates of their respective acid (or) base forms. Further solubilisation of drugs in organic solvents or in aqueous media by the use of surfactants and co-solvents leads to liquid formulations that are usually undesirable from patient acceptability and commercialization. Solid dispersion may be obtained in different ways but there are two methods which are widely used e. g. solvent method and fusion method. [9]

The solid dispersion approach has been widely and successfully applied to improve solubility, dissolution rate and consequently the bioavailability of poorly soluble drugs. Many hydrophilic excipients like PEG 4000, PEG 8000, PVP, poloxamers, povidone can be used to enhance the dissolution of drug. In the present study, the main goal is to increase solubility and dissolution of drug (IBS) by solid dispersion technique using PEG 4000, PEG 8000, PVP, poloxamers, and povidone by physical mixing and fusion methods. [10-11]

MATERIALS AND METHODS

Material

IBS was received as a gift sample from Glenmark Laboratories Ltd, Mumbai. Poloxamer 188 and Magnesium stearate was procured from SD fine chemicals Ltd, Mumbai. Povidone (Plasdone S630) and croscarmellose was procured from Ozone International, Mumbai, PEG 4000, 8000 (poly ethylene glycol), MCC 102 (Micro Crystaline Cellulose) and Lactose was procured from Merck Speciality Ltd, SSG (sodium starch glycolate) was obtained from central drug house, New Delhi, PVP K 30 was a gift sample from Caplin point, Pondicherry and all the reagents were of analytical grade.

Method Preparation of Solid Dispersion

The solid dispersions were prepared by taking IBS as a model drug and the hydrophilic polymer in particular ratios (Table 1). The ingredients are mixed geometrically. The geometrically mixed blends were taken in metal container and co-melted at a controlled temperature of 150^0-160^0 C, with continuous stirring to get the uniform mixture.

Table 1. Formulation Ratios for solid dispersion

Excipients	Drug : Excipient
PVP K 30	1:1 & 1:2
Poloxamer	1:1, 1:2 & 1:3
Plasdone S630	1:1, 1:3 & 1:5
PEG 4000	1:1, 1:2 & 1:5
PEG 8000	1:1, 1:2 & 1:5
PVP K 30 + Poloxamer	1:1(1%), 1:1(2%), 1:1(5%), 1:1(10%), 1:2(1%), 1:2(2%), 1:2(5%) & 1:2(10%).

Table 2. Formulation compilation for solid dispersion tablets

Process	Direct compression method									
Batch no	1	Control	2	Control	3	Contro	4	Control	5	Control
Crystalline API	-	150	-	150	-	150	-	150	-	150
SDs	330	-	330	-	330	-	330	-	330	-
PVP K30	-	150	-	150	-	150	-	150	-	150
Poloxamer 188	-	30	-	30	-	30	-	30	-	30
MCC 102	40	40	190	190	173	173	162	162	162	162
Croscarmellose	15.5	15.5	15.5	15.5	-	-	-	-	55	55
lactose	60	60	60	60	-	-	-	-	-	-
Magnesium stearate	4.5	4.5	4.5	4.5	3	3	3	3	3	3
SSG	-	-	-	-	44	44	55	55	-	-
Wt of tab	450	450	600	600	550	550	550	550	550	550
hardness	100-120N	100-120N	71-171N	80-110N	120-150N	80-110N	87-98N	98-118N	96-116N	97-111N
Disintegration Time(D.T)	50 min	21 mins	46 min	19 min	43 min	16 min	48 min	21 min	26 min	9 min

The metal container was allowed to cool and the weighed surfactant was added with continuous stirring for uniformity. The half solidified mass was then quench cooled to obtain the hard mass. The resultant product was ground in mortar pestle to break up. All the resultant ground mass was passed through sieve no-60 to get the average particle size around 250 microns. The suitable ratios of solid dispersions were subjected for tablet punching (Table 2). [12]

The tablets were made by direct compression method; wet granulation method was not feasible for large scale preparation. After the tablet was formed the dissolution test was done comparing with IBS tablet.

RESULTS AND DISCUSSION

Compatibility Study

Compatibility study was carried out by employing Drug and polymer in a particular ratio meant for production of solid dispersion. For the study drug and polymer was kept in the small USP type glass vial (10 ml) in duplicate and sealed with rubber bung. A specified amount i.e. (250mg) of drug and polymer was taken, subjected for temperature and humid conditions for 30 days (Table 3). The samples were examined physically for any changes like discoloration, colour development and crystal growth.

Table 3. Compatibility Parameter

Stress factor	Condition	Duration
Temperature and Humidity	40^0c	30 days
Temperature and Humidity	40^0c + 5% Moisture	30 days

After exposing drug and polymer to pre described climatic conditions, it was found that there was no physical sign of incompatibility with model drug; hence it was selected to be formulated as solid dispersion. [13]

Solubility Study

The solubility studies were performed by physical solubility and analytical study. The physical solubility study was carried out by taking samples from each trial batch (equivalent to 150mg of model drug) and placed in the 250ml volumetric flask and in the 10ml aliquots were added up to 200 ml and shaken (rotary flask shaker) for solubilisation. The volumetric flasks were settled down for one hour and the supernatant liquid was observed for probable solubility. The best possible ratios which passed the physical solubility study were taken for analytical solubility study. In the analytical solubility study, the sample was filtered with membrane filter (0.45µ) and absorbance was taken in 244 nm using UV–visible spectrophotometer (JASCO V-630 spectrophotometer, Software: Spectra Manager). Based on the physical solubility data, suitable combinations were selected for quantitative solubility study and two suitable ratios (which have highest solubility) were selected for further study. The suitable ratios of analytical solubility study were given in Table 4. [14]

Table 4. Analytical Solubility profile of SDs

Sl .No	Batch	Solubility(mg/ml)
1	Model drug	0.012
2	Model drug + PEG (4000)(1:2)	0.013
3	Model drug + PEG (8000)(1:2)	0.041
4	Model drug +PVPK29/32(1:1) + (PX 2%)	0.031
5	Model drug +PVPK29/32(1:1) + (PX 5%)	0.019
6	Model drug +PVPK29/32(1:1) + (PX 10%)	0.046
7	Model drug PVPK29/32(1:2) + (PX 2%)	0.029
8	Model drug PVPK29/32(1:2) + (PX 5%)	0.055
9	Model drug PVPK29/32(1:2) + (PX 10%)	0.022

Micronization and Particle Size Analysis

The ratios which showed higher analytical solubility were subjected for the reduction of particle size by jet milling [Cadmach , Ahmedabad, India (air velocity-4.5 kg/cm^2)] and particle size distribution study were carried out by sympatech particle size laser analyser (GmbH, Germany). According to the solubility data, two formulations having highest solubility [sample A - IBS: PVPK29/32(1:1) + (PX 10%) & sample B- IBS:PVPK29/32(1:2)+(PX 5%)] were subjected to micronization for further enhancement of solubility and taken for particle size analysis. The particle size of sample A and B were found to be 103.22 and 69.29 µm respectively (Fig. 1 & Fig. 2). The higher reduction of particle size in case of sample B was due to higher concentration of PVP K29/32. [15]

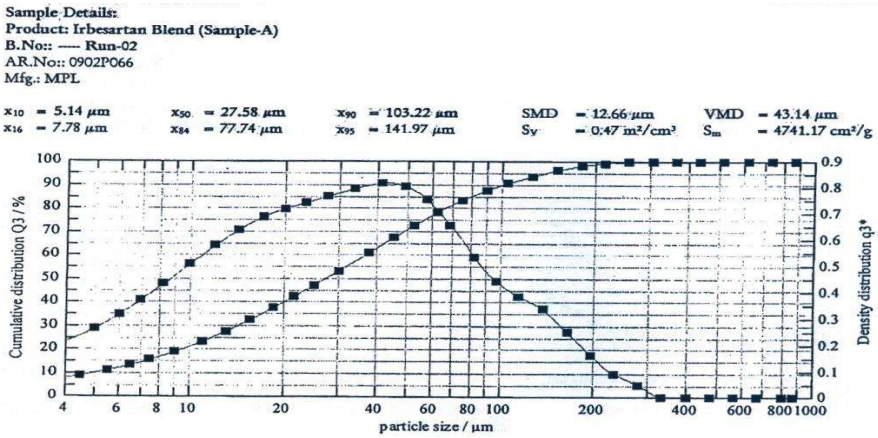

Fig. 1. Particle size analysis of sample A

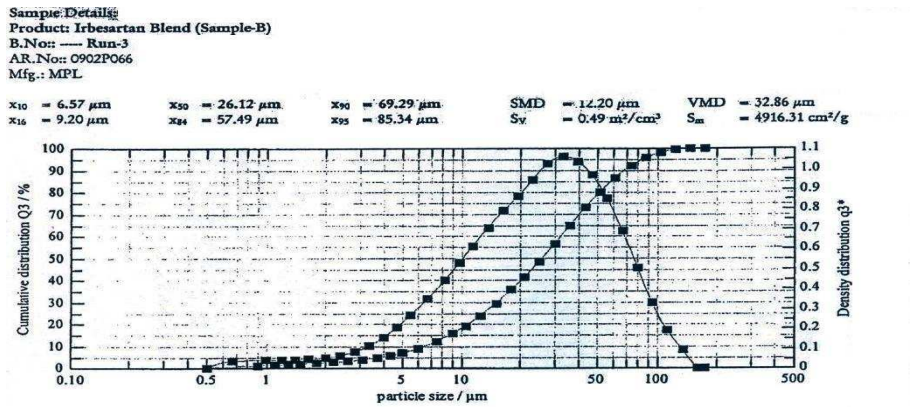

Fig. 2. Particle size analysis of sample B

XRD Analysis

XRD (X-Ray diffraction) pattern of freshly prepared powdered samples (under controlled temperature and humidity conditions) were recorded at room temperature on X-Ray diffractometer (Mettler Toledo, USA) with CuKa radiation (1.54 Å), at 45 kV, 40 mA, passing through a nickel filter with a divergence slit (0.5°), anti scattering slit (0.5°), and receiving slit (1 mm). The diffractometer was equipped with a 2q compensating slit and was calibrated for accuracy of peak positions with a silicon pellet. Samples were mounted on a 25-mm holder made of polymethyl methacrylate (PMMA) and were subjected to X-Ray powder diffraction analysis in continuous mode with a step size of 0.01° and step time of 1 second over an angular range of 3 to 40° 2q. Sample holders were rotated in a plane parallel to their surface at 30 rpm during the measurements. Obtained diffractograms is recorded using X' pert data collector and were analyzed with X'pert high score software. By a comparative defractogram analysis of model drug, physical mixture and solid disperssion sample A, it was clear that the intensity of defractogram decreased to a significant value. For model drug it was in the range of 20000, for physical mixture it was 15000 and for solid disperssion sample A, it was in 4000 range. Defractogram for sample B the range was in 2000 range. The decreased intensity showed a major transformation from crystalline to amorphous state. From the XRD plot (Fig. 3 & Fig. 4), of sample A and B, it was clear that the sample A was slightly amorphized and sample B was almost amorphized. [16]

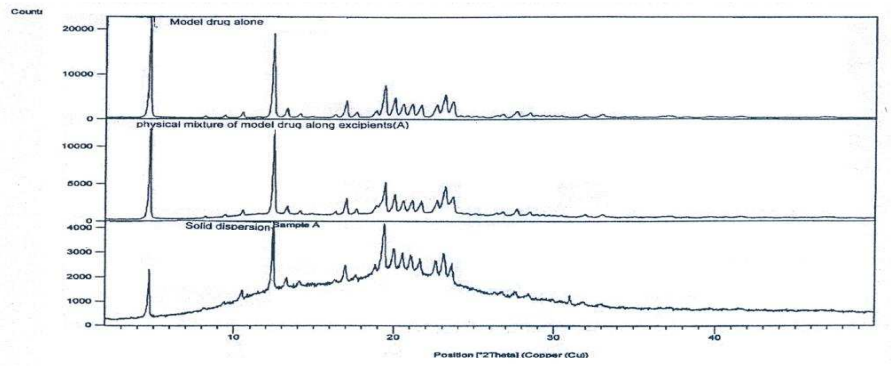

Fig. 3. XRD of Drug, physical mixture (Sample A)

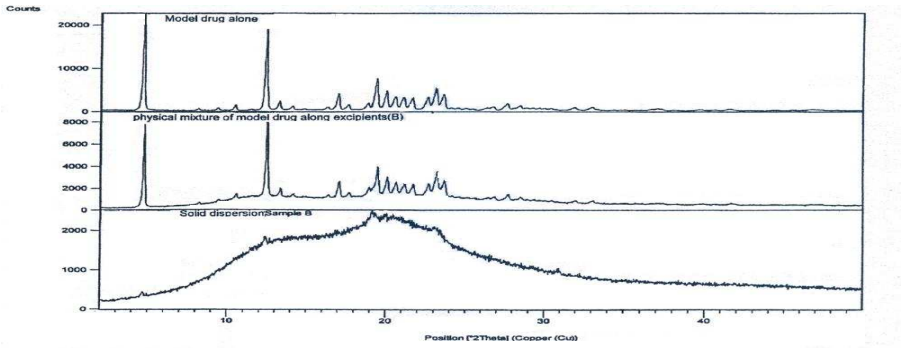

Fig. 4. XRD of Drug, physical mixture (Sample B)

DSC Analysis

Thermal transitions were determined using a Mettler Toledo 822e DSC (Mettler Toledo, USA) operating with version 8.01 of Star software using (4–6 mg) samples in aluminium pans (40µl) with pierced lids at heating rates of 20 °C min^{-1} under nitrogen purge at 60 mL min^{-1}. The initial and ending temperature were 30 and 200 centigrade respectively. The instrument was calibrated for temperature and heat flow using high purity indium and zinc standards. DSC study was performed on the pure drug, physical blend and solid dispersions samples. The thermogram of pure drug (IBS) gave a melting endotherm at 185.25ºC. But while considering the thermogram of solid dispersion gave a melting endotherm at 75-125ºC range (Fig. 5 & Fig. 6). This reduction of melting point was an indication of conversion of crystalline fraction into amorphous one. As amorphous fraction of substance are having low melting point. So we can conclude that there is positive conversion. [17]

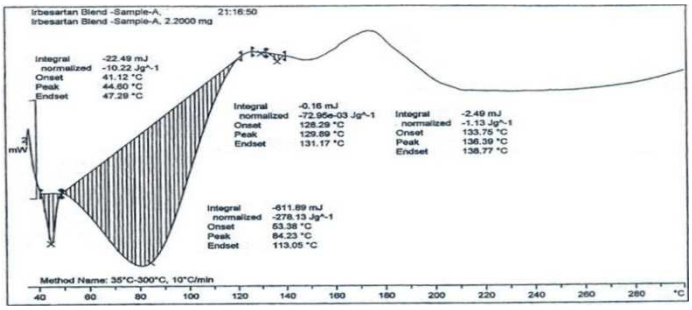

Fig.5. DSC Endotherm of Sample A

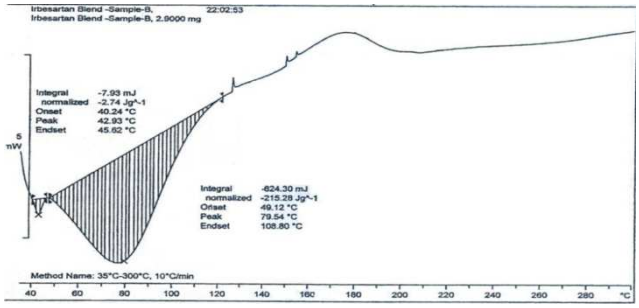

Fig.6. DSC Endotherm of Sample B

***In-vitro* Drug Release**

Dissolution experiments of crystalline, amorphous and solid disperssion samples were carried out in triplicate with a United States Pharmacopeia Apparatus II (paddle-type) (Electrolab, India), employing 900 mL of DDW water and 0.1N HCl, at a temperature of 37 ± 0.5°C, at rotational speed of 50 rpm. At predetermined intervals (30, 60, 90 and 120) samples were withdrawn (with replacement of equal volume of a pre-warmed medium into the vessel), filtered, appropriately diluted and analyzed for drug concentration using Spectrophotometer. Dissolution studies of different batches of solid dispersions were carried out in DW water and 0.1 N HCl (Fig. 7). The above mentioned batches were compred for their $Q_{50\%}$. Neither of the formulation reached $Q_{50\%}$ in water, as dissolution medium, while in 0.1 N hcl 3&5 batch succeeded to show $Q_{50\%}$. Only batch 1 &3 could not reach $Q_{50\%}$ in water and in 0.1 N hcl all the formuation reached $Q_{50\%}$ the highest percentage of realease was up to 75% in case of solid dispersion. [18]

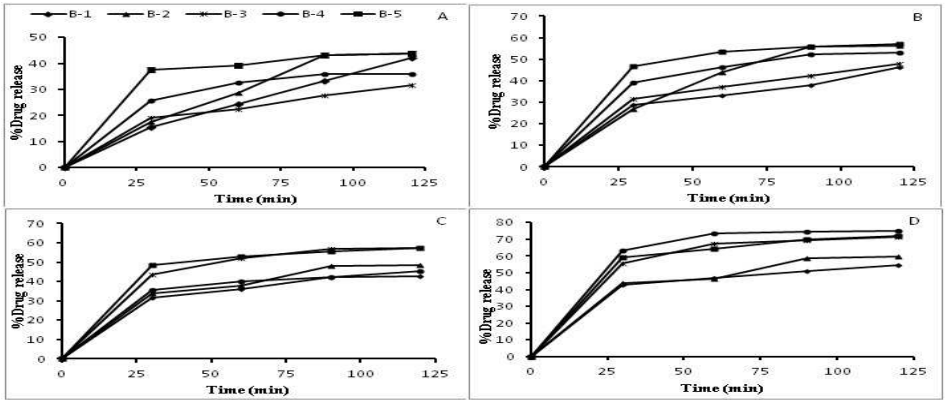

Fig. 7: In-Vitro Release comparision of model drug and Solid dispersions in water (A,C) and 0.1N Hcl (B,D)

CONCLUSION

The present study was performed to improve the dissolution rates of IBS, a poorly soluble drug using solid dispersion technique. Solid dispersion provides a practical means of further enhancing the solubility benefit, achieved using amorphous systems. IBS served as a model candidate for formation of solid solutions or dispersions of amorphous IBS into a fast dissolving matrix. The amorphous alloys generated using high molecular mass polymers like PVP K 30, PEG 4000, PEG 8000, Plasdon S 630 and poloxamer led to a significant enhancement of solubility over the crystalline form. DSC studies shows decrease of endothermic peaks of drugs in the solid dispersions prepared by PVP K30 and poloxamer indicating that the drug in amorphous form. The dissolution rates of physical mixture were higher than that of pure drug and this was possibly caused by the increase in drug wettability. Solid dispersion exhibited better dissolution rates than those of physical mixtures. The faster dissolution was obtained in case of drug: PVP K 30(1:1) and poloxamer 10%. High T*g* polymer like PVP, apart from its antiplstisization effect, increase the wettability and hydrophilicity of the system and maintain the molecules in the disordered state for a longer period. Solubility of A and B have been improved to 4.6(.0055mg/ml) times and 3.8(0.046mg/ml) times respectively compared to pure drug (0.012mg/mL). Dissolution of tablet A has been improved to 71.76% in SGF (0.1N HCl). Micronized particle size of A (X_{90}:103µ) and B (X_{90}:69µ), and amorphization of drug in solid dispersion (decreased intensity of XRD and Disappearance of endothermic peak of crystalline drug) have brought about improved dissolution.

REFERENCES

[1] N. S. Seth, *Int. J. Pharm. Sci. Res*., **2011**, 2, 3, 691.
[2] H. Karanth, V. S. Shenoy, and R. R. Murthy, *AAPS Pharm SciTech*., **2006**,7, 4, 87, E31.
[3] He. X, Pharmaceutical Theory and Practice, 1st ed., Y. Qiu, Y. Chen, and G. G. Z. Zhang, Eds., Burlington, USA: Academic Press, **2009**, 409.
[4] V. Manimaran, N. Damodharan, M. Mothilal, K. Rajkumar, and R. M. Chalackal, *Int. J. Curr. Pharm. Res*., **2010**, 2, 3, 14.
[5] K. Dua, K. Pabreja, and M. V. Ramana, *ARS Pharmaceutica*, **2010**, 51, 1, 57.
[6] A. Sayyad, and S. D. Sawant, *J. Pharm. Res*., **2010**, 3, 2494.
[7] Y. Xie, G. Li, X. Yuan, Z. Cai, and R. Rong, *AAPS Pharm Sci Tech*., **2009**, 10, 2, 631.
[8] D. K. Sharma, and S. B. Joshi, *Asian J. Pharm*., **2007**, 1, 1, 9.
[9] M. M. Patel, and D. M. Patel, *Indian J. Pharm. Sci*., **2006**, 68, 222.
[10] S. Sethia, and E. Squillante, *Int. J. Pharm*., **2004**, 272, 1, 1.
[11] S. Tasnim Jahan, M. S. Rahman Khan, M. Moniruzzaman, M. Rezowanur Rahman, S. M. Anowar Sadat, and R. Jalil, *Am. J. Sci. Ind. Res*., **2011**, 2, 1, 112.
[12] R. Mohapatra, S. Senataty, C. Sahoo, S. Mishra, A. Dinda, D. K. Sahoo, *RJPBCS*, **2013**, 4, 3, 116.
[13] A. Paradkar, A. A. Ambike, B. K. Jadhav, and K. R. Mahadik, *Int. J. Pharm*., **2004**, 271, 1-2, 281.
[14] I. Weuts, D. Kempen, G. Verreck, A. Decorte, and K. Heymans, *Eur. J. Pharm. Biopharm*., **2005**, 59, 1, 119.
[15] A. Forster, J. Hempenstall, and T. Rades, *J. Pharm. Pharmacol*., **2001**, 53, 3, 303.
[16] K. R. Bobe, C. R. Subrahmanya, S. Suresh, D. T. Gaikwad, M. D. Patil, T. S. Khade, B. B. Gavitre, V. S. VKulkarni, and U. T. Gaikwad, *Pharmacie Globale* (IJCP), **2011**, 1, 02, 1.
[17] S. Sethia, and E. Squillante, *J. Pharm. Sci.*, **2002**, 91, 9, 1948.
[18] Subrata Mallick, Saroj K. Pradhanb, Rajaram Mohapatra, *Int. J. of Biological Macromolecules*, **2013**,60, 148.