ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

Formulation and evaluation of sustained release floating tablets of diltiazem hcl using xanthan gum

P Subhash Chandra Bose*[1], P Srikanth Reddy[1], Valluru Ravi[2], D Sarita[3] and TM Pramod Kumar[2]

[1]Dept. of Pharmaceutics, MNR College of Pharmacy, Hyderabad -500074, India
[2]Department of Pharmaceutics, JSS College of Pharmacy, JSS University, Mysore -570015.
[3]Department of Pharmaceutics, Sultan Ul-Uloom College of Pharmacy, Hyderabad -500073.

ABSTRACT

The aim of the present work was to prepare floating tablets of diltiazem HCl using xanthan gum as carrier. Diltiazem HCl is a calcium channel blocker used in treatment of several diseases of the cardiovascular system, especially angina and hypertension. It has elimination half-life of about 3.5 hrs. The formulations were prepared by varying the concentrations of xanthan gum and sodium bicarbonate. The tablets were prepared by direct compression technique using PVP K-30 as a binder and sodium bicarbonate for development of CO_2. The prepared floating tablets were evaluated for tablet properties such as hardness, thickness, friability, weight variation, floating property, compatibility using DSC and FTIR. *In vitro* dissolution was carried out for 12 hrs in 0.1N HCl at 37±0.5°C using USP basket type dissolution apparatus. It was noted that, all the prepared formulations had desired floating lag time and constantly floated on dissolution medium by maintaining the matrix integrity. The drug release from prepared tablets was found to vary with varying concentration of the polymer, xanthan gum. From the study it was concluded that floating drug delivery system can be prepared by using xanthan gum as a carrier.

Key words: Floating, Diltiazem HCl, Xanthan gum, *in vitro* dissolution

Corresponding Author

ISSN: 0975-8585

INTRODUCTION

Natural polymers and their derivatives are being used widely in preparing various pharmaceutical dosage forms. Natural polysaccharides hold advantages over synthetic polymers because they are non toxic, less expensive and easily available. Natural polymers can be modified to have tailor-made materials for preparing drug delivery systems and thus can compete with synthetic biodegradable materials available in the market [1]. Oral sustained release (SR) dosage forms (DFs) are being developed for the past 3 decades due to their considerable therapeutic advantages [2-5].

Compounding narrow absorption window drugs in a unique pharmaceutical DF with gastroretentive properties would enable easy administration and such a DF would be retained in stomach for long time and release the drug in a controlled and prolonged manner, so that the drug could be supplied continuously to its absorption sites in the upper gastrointestinal tract. This mode of administration would best achieve the pharmacokinetic and pharmacodynamic advantages of SR-DFs for these drugs [6, 7]. The gastric floating drug delivery systems (GFDDS) prolong the retention time of a dosage form in the stomach, thereby improving the oral bioavailability of the drug. The influence of different viscosities of hydroxypropyl methyl cellulose (HPMC) (K4M and K100LV) and carbopol 934P on the release of calcium from the tablets using 2x3 factorial design was studied [8]. In the present study, an attempt was made to develop a GFDDS containing diltiazem HCl as a model drug and xanthan gum as the matrix polymer.

Xanthan gum is a high molecular weight extracellular polysaccharide produced by the fermentation of gram negative bacteria *Xanthomonas campestris*. It is a hydrophilic polymer, which until recently had been limited for use in thickening, suspending, and emulsifying water-based systems It appears to be gaining appreciation for the fabrication of matrices with uniform drug release characteristics [9, 10] . The interesting approach to provide floating drug delivery system is based on the formation of carbon dioxide within the device upon contact with gastric fluids. The release pattern of drug from xanthan gum matrices is preceded by polymer hydration of processing variables that might affect its hydration and would also affect its performance as a controlled release dosage form. Xanthan gum displays high degree of swelling due to water uptake and small degree of erosion due to polymer relaxation [11]. Xanthan gum offers potential utility as a drug carrier because of its inertness and biocompatibility. It is used as an effective excipient for sustained release formulations.

Combinations of xanthan gum, hydroxy propyl methyl cellulose, hydroxyl propyl cellulose and ethyl cellulose in coated tablets have been evaluated for sustained release [12]. Xanthan gum not only retards *in vitro* drug release and provides time-independent release kinetics, but also works effectively *in vitro* and establishes constant drug plasma levels as observed during *in vivo* drug release behavior [13, 14].

ISSN: 0975-8585

Diltiazem hydrochloride (DTZ) is a calcium channel blocker belonging to the benzothiazepine family. It is widely prescribed for the treatment of hypertension and angina [15, 16]. DTZ undergoes an extensive biotransformation, mainly through cytochrome P-450 CYP3A, which results in less than 4% of its oral dose being excreted unchanged in urine. Bioavailability of DTZ is ~30% to 40% owing to an important first pass metabolism. It has an elimination half-life of 3.5 hours and has an absorption zone from the upper intestinal tract. Efficacy of the administered dose may get diminished due to incomplete drug release from the device above the absorption zone. DTZ requires dosage administration in order to maintain adequate plasma concentrations. Therefore, it is a suitable model candidate for formulating into a gastroretentive tablet formulation [17, 18].

The objective of the present work was to prepare a matrix floating tablet using xanthan gum, drug and excipients. Different formulations were prepared by varying the concentration of gum in the matrix and the prepared tablets will be evaluated for hardness, thickness, friability, swelling, buoyancy, compatibility, percentage drug release and diffusion coefficient (n).

MATERIALS AND METHODS

Materials

Diltiazem Hydrochloride was received as gift sample from Divis Laboratories, Hyderabad, India. It is a white, odourless, crystalline powderfreely soluble in water and methanol. Directly compressable lactose was obtained as a gift sample from Strides Acrolab, Bangalore, India. Xantham gum was purchased from Sigma Aldrich, Mumbai, India. Sodium bicarbonate and all other chemicals used were of analytical grade and purchased from Loba Chemie, Mumbai, India.

Preparation of floating tablets

Table 1: Composition of floating diltiazem hydrochloride tablets.

Ingredients	Formulation code and weight in mg					
	F1	F2	F3	F4	F5	F6
Drug	60	60	60	60	60	60
Xanthan gum	120	150	180	120	150	180
Sodium bicarbonate	30	30	30	45	45	45
PVP K-30	9	9	9	9	9	9
Magnesium Stearate	6	6	6	6	6	6
Directly compressible lactose	75	45	15	60	30	--
Total weight of tablet (mg)	300	300	300	300	300	300

The floating tablets containing diltiazem hydrochloride were prepared by direct compression technique. The formulations were prepared by varying the concentration of polymer and sodium bicarbonate in the tablet (Table 1). Accurately weighed quantities of drug,

polymer (xanthan gum), binder (PVP K-30), sodium bicarbonate as a gas-generating agent and other diluents were blended homogeneously in a mortar and pestle and the resultant mixture was compressed into tablets using 10 station rotary tablet machine (Rimek, Mumbai, India) at 10 rpm and using 9 mm round concave punches at an optimum pressure. The prepared tablets were evaluated for tablet properties such as hardness (Irweka hardness tester), thickness (Mitotoya screw guage), weight variation (Shimadzu AW 120), percent friability (Electrolab EF-2 friabilator) and drug content (UV/Visible spectroscopy).

UV/Visible spectroscopy

The wavelength of maximum absorbance (λ_{max}) of diltiazem hydrochloride drug was determined by scanning a known concentration of sample solution in the wavelength region 200–400 nm by using Shimadzu 1601 UV/ Visible spectrophotometer. The λ_{max} was found to be 237 nm and this wavelength was used for further studies.

***In-vitro* buoyancy studies**

The *in vitro* buoyancy for the prepared formulations was characterized by floating lag time and total floating time. The test was performed in a basket type USP dissolution apparatus (Electrolab TDL-08L) using 900 ml of 0.1 N HCl buffer at a temperature of 37 $\pm$ 0.5 °C and 100 rpm. The time required for the tablet to rise to the surface of the dissolution medium and the duration till which the tablet constantly floated on the dissolution medium were noted as floating lag time and floating duration respectively The relative matrix integrity was determined on the basis of visual inspection after the floating studies.

Water uptake study

The water uptake study of the tablet was done using basket type USP dissolution tester (Electrolab TDL-08L). The study was conducted in 900 ml of 0.1 N HCl buffer, which was maintained at a temperature of 37±0.5 ºC and after a specific period of time (8 hrs) the tablets were withdrawn, blotted to remove excess water and weighed. Swelling characteristics of the prepared tablets were expressed in terms of water uptake (WU) as;

$$W\,U\,(\%) = \frac{\text{weight of the swollen tablet} - \text{Initial weight of the tablet}}{\text{Initial weight of the tablet}} \times 100 \quad (1)$$

***In-vitro* dissolution studies**

Dissolution studies were carried out in basket type USP dissolution apparatus at 100 rpm and 37±0.5°C using 900 ml of 0.1N HCl buffer for a period of 12 hrs. The samples were filtered through 0.45 µ membrane filter and diluted to a suitable concentration with 0.1N HCl buffer and the absorbance was measured at 237 nm using Shimadzu UV-Visible spectrophotometer

ISSN: 0975-8585

Peppas model fitting [19, 20]

Koresmeyer-Peppas model is one of the mathematical expression to evaluate the mechanism of drug delivery. The Koresmeyer-Peppas equation is as follows;

$$M_t / M_\infty = 1 - A (\exp^{-kt}) \quad (2)$$

$$\log (1 - M_t/M_\infty) = \log A - kt/2.303 \quad (3)$$

where, M_t/M_∞ is the fractional amount of drug released and t is the time in hrs. In this study, the release constant, k and constant, A were calculated from the slopes and intercepts of the plot of In $(1- M_t/M_\infty)$ versus time t. The interpretation of diffusional release mechanisms can be obtained by the data given in Table 2.

Table 2: Interpretation of diffusional release mechanisms.

Value of constant, A	Drug transport mechanism
<0.5	Fickian diffusion
>0.5<1.0	Non-fickian diffusion
Higher than 1.0	Super case II transport

Drug-excipients compatibility studies

For drug-excipients compatibility studies, Fourier Transform Infrared Spectroscopy (FTIR) and Differential Scanning Calorimetry (DSC) studies were carried out. In order to evaluate the integrity and compatibility of the drug in the formulations, IR spectra of the drugs and its formulations were obtained by FTIR spectrophotometer (Perkin Elmer-1,000, Japan) using potassium bromide pellet method. DSC is a fast and reliable method and provides information about the possible interaction between the drug and the polymers used in the formulation. All dynamic DSC studies were carried out on Du Pont thermal analyzer with 2010 DSC module.

Stability of the prepared tablets

The stability of the drug incorporated polymer matrix tablets was confirmed by storing the tablets at 40±0.5°C and 75% RH (relative humidity) for 6 weeks. The tablets were then evaluated for its physical properties and drug content at weekly intervals.

RESULTS AND DISCUSSION

Percentage weight variation, percent friability and content of active ingredient for all the formulations were found to be well within United States Pharmacopoeia (USP) standards and the data obtained is given in Table 3. From the table it is clear that the hardness of the prepared tablets increased as the amount of gum concentration in the tablet increased. Formulations F3 and F6 (50 and 60% w/w) showed maximum hardness among the three ratios

selected (40%, 50% and 60%). Out of F3 and F6, F3 formulation showed more hardness and this is attributed to higher concentration of directly compressable lactose in F3 when compared to F6 formulation. From the table, it was noticed that the percentage of drug content lies in the range 98.4–101.4 %.

Table 3: Evaluation data obtained for prepared tablets.

Formulation code	% weight variation*	Thickness* (mm)	Hardness* (kg/ cm^2)	Friability* (%)	% Drug content*
F1	±3.9	4.98±0.15	5.3±0.63	0.77±0.41	98.9±0.41
F2	±2.2	4.95±0.13	5.8±0.96	0.69±0.39	99.4±0.83
F3	±3.5	5.05±0.27	6.4±0.71	0.65±0.38	101.4±0.73
F4	±2.4	5.01±0.15	5.2±0.71	0.62±0.40	98.4±0.49
F5	±3.2	4.99±0.12	5.6±0.48	0.74±0.42	99.7±0.32
F6	±2.8	4.97±0.18	6.2±0.48	0.71±0.39	100.6±0.67

*mean ± SD, n = 3

In the present study, an effervescent approach using sodium bicarbonate as gas generating agent was adopted to enable the tablet float. As the dissolution medium (0.1 N HCl buffer) imbibed into the tablet matrix, the interaction of acid with sodium bicarbonate resulted in the generation of CO_2. The generated gas was entrapped and protected within the gel that was formed by hydration of xanthan gum and decreased the density of the tablet and as a result, the tablet became buoyant.

Table 4: Buoyancy results for the prepared formulations.

Formulation code	Onset of Floating* (secs)	Duration of Floating (hrs)	Water uptake* (%)
F1	40±3.4	17	220±2.8
F2	37±3.1	22	278±3.9
F3	31±2.9	>24	326±4.1
F4	35±3.0	15	219±3.7
F5	29±2.8	20	249±3.9
F6	27±3.2	>24	316±4.1

*mean ± SD, n = 3

The effect of sodium bicarbonate on floating lag time and duration of floating is given in the Table 4. From table, it is clear that the time taken by the tablet to float (onset of floating) on the dissolution medium decreased with increase in amount of gas generating agent in the formulation. It was also noted that, formulations F4-F6 floated readily when compared to formulations F1-F3. This can be attributed to the concentration of sodium bicarbonate, which is 15% w/w in F4-F6 compared to 10% in F1-F3. It can also be noted that as the polymer concentration in the formulations increased the onset of floating increased (F3 and F6 floats faster than F1 and F4 respectively). This is attributed to the fast gelation of the formulations due to an increase in polymer concentration, as a result of which the CO_2 does not escape from the matrix. The formulations F3 and F6 floated more than 24 hrs while the formulations containing lesser amount of xanthan gum floated only up to 14-16 hrs. From the table it is clear that, formulations F3 and F6 containing 60% w/w were floating better compared to

ISSN: 0975-8585

formulations containing 40 and 50% w/w of xanthan gum. The formulations F3 and F6 showed 326 and 316% increase in weight after the study period of 8 hrs. A slight increase in percent water uptake for F3 compared to F6 can be attributed to an increase in amount of lactose in F3.

The *in vitro drug* release of diltiazem hydrochloride from the prepared floating matrix tablets is given in Fig. 1. From the figure, it can be noted that the concentration of gum and sodium bicarbonate in the formulation had a remarkable influence on the drug release. Formulations F1 and F4 released more drug (80 and 82%) at the end of 6 hrs when compared to formulations F3 and F6 (61 and 55%). This decrease in amount of drug released can be attributed to the increase in the concentration of gum (60% w/w) in the formulations F3 and F6 compared to F1 and F4 (40% w/w). Increase in polymer concentration leads to the formation of thick gel barrier, causing the drug diffusion through the matrix difficult and thus decreasing the overall drug release from the matrix.

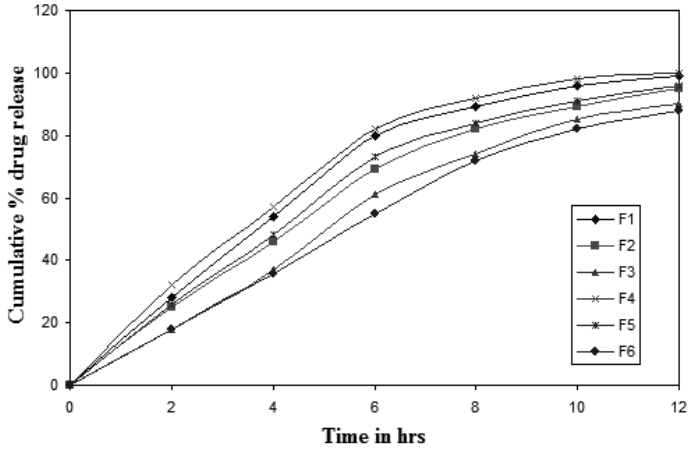

Figure 1: *In vitro* drug release profile for the prepared formulations

On the other hand, formulations F2 and F5 (50% w/w) have showed a drug release of about 69 and 73% respectively. It is noted that, formulations containing 15% of sodium bicarbonate (F4-F6) showed a marginal increase in drug release than formulations containing 10% (F1-F3). The order of drug delivery from the tablets with reference to polymer concentration is; 40 > 50 > 60%.

Table 5: Data obtained from Peppas model fitting for the formulations.

Parameters	F1	F2	F3	F4	F5	F6
Release constant (k) * 10^3	1.02	0.776	0.673	1.044	0.825	0.625
Constant (A)	1.4724	1.3257	1.3778	1.4157	1.3341	1.3507
Regression coefficient (R^2)	0.9941	0.9968	0.9935	0.9843	0.9939	0.9956

The data obtained from *in vitro* drug release studies was fit into Peppas model. From the plot of log M_t/ M_∞ versus t, the parameters such as release constant (k), constant (A) and the regression coefficient (R^2) were calculated and are given in Table 5. In all the cases the value of A were found to be more than 1. This result indicated that the release of drug from the polymer

ISSN: 0975-8585

matrix formulations was found to be super case-II transport, i.e., drug release by both diffusion and relaxation of polymer chain. From the table it can be concluded that, formulation F2 having the R^2 value of 0.9968 is the optimized formulation for 12 hr study period.

The IR spectra of diltiazem HCl and its coated formulations were found to be identical (Fig. 2). The characteristic IR absorption peaks of diltiazem at 2966 (aliphatic C–H stretch), 2837 (O–CH3 stretch), 2393 (amine HCl), 1679 (lactam C=O stretch), 839 (o-substituted aromatic C–H out of plane deformation) and 781 cm^{-1} (p-substituted aromatic C–H out of plane deformation) were obtained. The FTIR spectra obtained indicated that no chemical interaction occurred between the drug, diltiazem and the excipients used in formulating the tablet. But, a slight shift in absorption peaks position was noticed which indicated that physical interaction might have occurred between drug and the polymer.

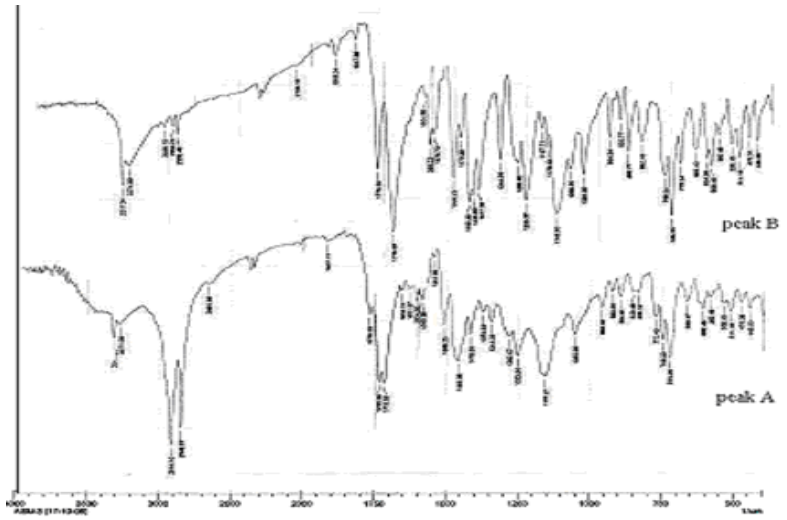

Figure 2: FTIR chromatogram for pure diltiazem hydrochloride (peak A) and formulation F2 (peak B)

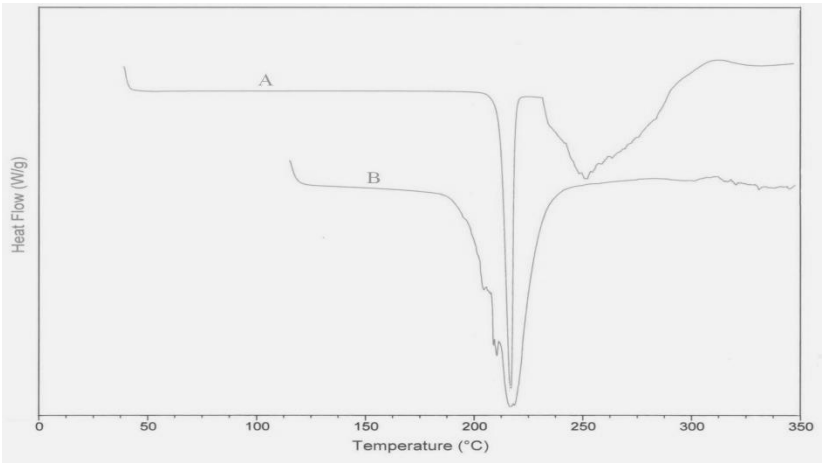

Figure 3: DSC chromatogram for pure diltiazem hydrochloride (peak A) and formulation F2 (peak B)

ISSN: 0975-8585

Table 6: Stability study data of optimized formulation F2.

Time in weeks	% Drug content in F2 mean ± SD* at 40 ± 0.5°C and 75% RH
0 (Initial)	99.27 ± 0.43
1	100.38 ± 0.83
2	99.74 ± 0.78
3	101.34 ± 0.28
4	102.92 ± 0.21
5	100.89 ± 0.31
6	98.14 ± 0.46

*Standard deviation n=3

In the present study, the optimized formulation F2 was selected for stability studies. Stability studies of the drug formulations are performed to ascertain whether the drug undergoes any degradation during its shelf life. The data obtained from the stability studies is given in Table 6. From the stability study data, it can be concluded that the drug is stable in the optimized formulation for the study period. DSC thermograms of the pure drug and its formulations after stability studies were recorded to evaluate whether the drug has undergone any degradation during the study period. From the DSC data obtained (Fig. 3), it was evident that the melting point of diltiazem hydrochloride is not changed after keeping the tablets for stability studies. Hence, it may be inferred that there is no interaction between diltiazem hydrochloride and polymers used. From DSC results it can be concluded that the drug maintained its chemical identity throughout the process.

CONCLUSION

The evaluation data for properties such as hardness, thickness, friability, weight variation, floating lag time and water uptake indicated that the prepared floating tablets were well within the specified standards. The drug release data revealed that the formulation with low amount of xanthan gum (40% w/w) showed a low release rate compared to formulation with higher concentration (60% w/w). The formulations F2 and F5 (50% w/w) showed drug release of about 95.4 and 96.7%, respectively. From the stability studies, it is clear that the formulation was stable for six weeks and the DSC thermograms and FTIR spectra obtained indicated no change in chemical identity of the drug. The data obtained from the Peppas model fitting indicates that the mechanism of drug release was by super case-II transport. From the results obtained it can be concluded that xanthan gum, a biodegradable polymer can be employed for use as a carrier in developing floating drug delivery systems.

ACKNOWLEDGEMENT

The authors are thankful to M/s Divis Laboratories, Hyderabad, India for providing gift sample of diltiazem hydrochloride.

ISSN: 0975-8585

REFERENCES

[1] IW Cottrell, KS Kang and P Kovaca. In Handbook of Water Soluble Gums and Resins (R,L.Davidson,ed.), McGraw Hill, Kingsport Press, New York, 1980, pp.24-29.
[2] A Hoffman. Adv Drug Deliv Rev 1998; 33: 185–199.
[3] Brahma N Singh and Kwon H Kim. J Control Rel 2000; 63: 235-259.
[4] Shweta Arora, Kaved Ali, Alka Ahuja, Roop K Khar and Sanjula Babota. AAPS PharmSciTech 2005; 6: 372-390.
[5] A Streubel, J Siepmann and R Bodmeier. Int J Pharm 2002; 241: 279-292.
[6] A Hoffman, D Stepensky. Crit Rev Ther Drug Carrier Syst 1999; 16 (6): 571–639.
[7] Yong-Dan Tang, SS Venkataraman, Freddy YC Boey and Li-Wei Wang. Int J Pharm 2007; 336: 159-165.
[8] Shoufeng Li, Senshang Lin, Bruce P Daggy, Haresh L Mirchandani and Yie W. Chien Int J Pharm 2003; 253:13-22.
[9] Felipe Alvarez-Mancenido, Mariana Landin and Ramon MartinezPacheco. Eu J Pharm Biopharm 2008; 69: 573-581.
[10] Alireza Shalviri, Qiang Liu, J.A. Mohammad and Xiao Yu Wu. Carbohydrate Polymers 2010; 79: 898-907.
[11] DL Munday and PJ Cox. Int J Pharm 2000; 203(1-2): 179-192.
[12] P Guley, R Deneale, and G Milosovich. U.S.Patent 4309405 (1982).
[13] E Verhoeven, C Vervaet, JP Remon. Eu J Pharm Biopharm 2006; 63 (3):320-330.
[14] Jolly MS, Mayur GS, Rajashree CM. J Contr Rel 2008; 129 (1): 49-58.
[15] ST Uday and TM Aminabhavi. J Control Rel 2004; 95: 567-577.
[16] SR Levis and PB Deasy. Int J Pharm 2003; 253: 145-157.
[17] PG Stephen, TJ Gana, LG Pascual and KS Albert. Amer Heart J 2005; 149: 1-9.
[18] F Yanagawa, Y Ishil, Y Onuki, M Morishita and K Takayama. Colloids and Surfaces B: Biointerfaces 2008; 63: 146-152.
[19] Bumsang Kim, Kristen La Flamme and Nicholas A Peppas. J Appl Polym Sci 2003; 89: 1606-1613.
[20] Valluru Ravi, Siddaramaiah Hatna and TM Pramod Kumar. J Mat Science: Materials in Medicine 2008; 19(5): 2131-2136.