

Development and Evaluation of Bilayer Gastroretentive Floating Drug Delivery System for Baclofen

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ABSTRACT

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Baclofen, related to gamma-amino butyric acid (GABA), blocks the activity of nerves within the part of the brain that controls the contraction and relaxation of skeletal muscle. The oral bioavailability of baclofen is about 40%. It is stable and well absorbed within pH range 1-4. The short half life of baclofen (2-4 h) suggests that it is a suitable drug for sustained drug delivery. The objective of this research work was to develop bilayer floating tablets of baclofen to provide an immediate release of one-third of the baclofen content to achieve an effective plasma concentration and the sustained release layer to release the drug over several hours. Immediate release layer was prepared by using the superdisintegrant sodium starch glycolate while sustained release layer was prepared using gas generating agents like sodium bicarbonate, citric acid and release retardant polymer, hydroxypropyl methylcellulose K4M (HPMC K4M) by direct compression method. The drug release rate from the bilayer tablet was sustained up to 24 h (98% release) by incorporation of HPMC K4M in the concentration of 100 mg, which showed maximum swelling up to 240 % in 12 h as compared to other formulations. Sodium bicarbonate with citric acid in the ratio 2:1 caused the floating of tablet within 60 sec and maintained so for 24 h. Conclusively, the current study attained the successful design, preparation and evaluation of floating bilayer sustained release formulation of a slightly soluble drug baclofen with initial immediate release of one third of total drug content with gastric retention for the desired period of time by the second layer.

Keywords: Bilayer tablet, Baclofen, gastro retentive, floating, immediate release, sustained release.

INTRODUCTION

Baclofen is an oral medication that relaxes the skeletal muscle. The oral bioavailability of baclofen is about 40%. It is stable and well absorbed within pH range 1-4. Currently, baclofen is administered as the immediate release (IR) tablet 10-20 mg three times a day. Also, the frequent administration of baclofen immediate release tablets leads to fluctuations in plasma concentration, producing peaks and troughs. The peaks are associated with side effects, such as drowsiness, dizziness and muscle weakness, and troughs are associated with inadequate control of muscle spasm. Further, there is noncompliance by the patients because of thrice a day dose. The noncompliance can be overcome by medication which requires a minimal number of doses suggesting once a day sustained release formulation. The short half life of baclofen (2-4 h) also suggests that it is a suitable candidate for sustained drug delivery. The high solubility, chemical and enzymatic stability and absorption profile of baclofen in acidic pH values (of stomach), points to the potential of gastro retentive dosage form.^{1,2}

Gastro retentive dosage forms can act as an alternative to parenteral therapy for all such drugs which have absorption

window in the upper part of gastro intestinal tract.³ Gastric retention of the dosage form can be brought about by various approaches like floating, mucoadhesion, high density, etc. Floating drug delivery is suitable for the drugs having absorption from the upper part of gastrointestinal tract.⁴ Combination of controlled release systems with prolonged gastric retention provides a means to utilize the entire pharmacokinetic (PK) and pharmacodynamic (PD) advantages of controlled release dosage forms for such drugs.⁵ The objective of the present research work is to develop a gastro retentive system for sustained release as well as immediate release of therapeutically active agent, in the form of a bilayer floating matrix tablet. One of the layers is an immediate release layer designed to release one-third of the baclofen content to achieve an effective plasma concentration. The other layer is a sustained release layer which releases the drug over several hours using a gastro retentive drug delivery system.

MATERIALS

Baclofen was provided as gift sample by Sun Pharmaceuticals Pvt. Ltd. Gujarat, HPMC K4M by Colorcon Asia Private Limited, Goa, India and sodium starch glycolate by Que Pharma Pvt. Ltd., Gujarat, India. sodium bicarbonate, lactose, sodium lauryl sulphate, magnesium stearate, citric acid was purchased from S.D. Fine Chemicals, Mumbai, India. All other chemicals used in the study were of analytical grade.

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METHODS

Determination of solubility:

Saturation solubility of baclofen was determined in 0.1 N HCl, pH 1.2, 4.5 and 6.8 phosphate buffer solutions. All media were prepared and baclofen was added to it and kept for shaking on mechanical shaker for 48 hrs. After 48 h of shaking, 1 ml of aliquot was taken out from each sample and filtered through Whatman filter paper. Filtrates were diluted with respective solutions (i.e. 0.1 N HCl, pH 1.2, 4.5 and 6.8 phosphate buffer). Absorbances were measured and calculations for solubility were done.

FTIR spectroscopy:

The FTIR spectrum of baclofen was recorded using FTIR spectrophotometer by KBr pellet technique.

DSC Studies:

Pure Baclofen, and a mixture of Baclofen: HPMC K4M: Sodium bicarbonate (1:1:1) were subjected to Differential Scanning Calorimetry studies to confirm the compatibility between drug and excipients. Studies were carried out using Mettler Toledo DSC in the temperature range of 30-300°C with heating rate of 10°C/min.

Preparation of bilayer floating tablets of Baclofen:

The composition of different bilayer floating formulations prepared using varying amounts of sodium starch glycolate, HPMC K4M, sodium bicarbonate, magnesium stearate, citric acid, and lactose are listed in Table No.1.

Preparation of the Immediate Release layer:

Baclofen and lactose were passed from sieve # 40 and mixed for 10 min. Magnesium stearate was then passed through

sieve # 60 and added to the above mixture. Color was added to the above mixture. The powder was then compressed to form a tablet using a 9 mm standard concave punch.

Preparation of the Sustained Release layer:

Baclofen, lactose and hydrophilic polymers were passed from sieve # 40 and mixed for 10 min. Gas generating agent was then passed through sieve # 60 and added to the above mixture. The whole bulk of powder was then mixed thoroughly for 15 min. The powder was then compressed to form a tablet using a 9 mm standard concave punch.

The bilayer tablet was compressed on a Six-Station Rotary Tableting compression machine. The hardness was maintained at 7-8 kg/cm². The bottom layer was first compressed with lower pressure, which was then followed by filling of the die cavity by the upper layer powder. The final compression was done only after both the powders occupied the die cavity one on top of the other. Both the layers were identified on the basis of color since the immediate release layer had pink color and the sustain release layer was kept white.

Optimization using 3² full factorial design:

A 3² randomized full factorial design was used in development of the dosage form⁶. In this design, 2 factors were evaluated each at 3 levels and experimental trials were performed using all possible 9 combinations. In the present study, the amount of HPMC K4M (X₁) and content of sodium bicarbonate (X₂) were selected as independent variables. The total floating time (TFT) and time required for 90% drug release (t₉₀) were selected as dependent variables. The actual formulations designed according to experimental design are shown in Table 1.

EVALUATION OF TABLETS

Physical evaluation:

Twenty tablets from each batch were evaluated for uniformity in tablet weight and thickness. Twenty tablets from each batch were examined for friability using a Roche type friabilator (Electrolab Pvt. Ltd., India) and hardness using a Monsanto type hardness tester (Lab-Hosp, India).

Uniformity of content^{7,8}

Twenty tablets were crushed and powder equivalent to weight of tablet dissolved in 0.1 N HCl. Then suitable dilutions were made and absorbance at 266 nm wavelength was taken by using a UV visible spectrophotometer. Drug content was calculated by using absorbance at wavelength 266 nm. The results obtained were compared with I. P. standards.

Buoyancy lag time⁹

This test was performed in beaker containing 200 ml 0.1 N HCl as a testing medium maintained at 37°C. The time

Table 1: Composition of baclofen tablets.

Formulation	F1	F2	F3	F4	F5	F6	F7	F8	F9
Formulation of immediate release layer									
Baclofen	10	10	10	10	10	10	10	10	10
SSG	15	15	15	15	15	15	15	15	15
Lactose	27	27	27	27	27	27	27	27	27
Mg.Stearate	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Colour	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Subtotal (mg)	55	55	55	55	55	55	55	55	55
Formulation of sustained releaselayer									
Baclofen	20	20	20	20	20	20	20	20	20
HPMCK4M	80	80	80	100	100	100	120	120	120
NaHCO ₃	20	30	40	20	30	40	20	30	40
Lactose	45	35	25	25	15	5	25	15	5
Citric Acid	15	15	15	15	15	15	15	15	15
Subtotal (mg)	180	180	180	180	180	180	200	200	200
Total (mg)	235	235	235	235	235	235	255	255	255

required for the tablet to rise to the surface and float was determined as buoyancy lag time.

Buoyancy time⁹

Buoyancy time is the total time for which the tablets float in dissolution medium (including buoyancy lag time) before getting disintegrated or settle down.

In vitro drug release studies^{9,10}

The release rate of baclofen from matrix tablets was determined using USP dissolution testing apparatus II (Paddle type). The dissolution test was performed using 900 ml of 0.1 N HCl, at $37 \pm 0.5^\circ\text{C}$ and 100 rpm. A 10 ml sample solution was withdrawn from the dissolution apparatus for 30 min, 1 hr and there after every hour for 24 hrs. Samples were replaced by its equivalent volume of dissolution medium. The samples were filtered through Whatman filter paper and solutions were analyzed at 266 nm by UV Spectrophotometer (SHIMADZU, V-1800, Japan). Cumulative percentage drug release was calculated.

Swelling behaviour⁹

Tablets were placed in the dissolution medium and their respective weight was checked at 0 h, 2 h, 4 h, 6 h, 8 h and 12 h. The tablet was taken out from the dissolution medium and the excess water was allowed to drain out and the tablet was weighed. The swelling index was calculated by using following formula.

$$\text{Swelling index} = \frac{W_1 - W_0}{W_1}$$

RESULTS AND DISCUSSION

The present research work was aimed to develop a gastro retentive system for immediate release as well as sustained release of therapeutically active agent, baclofen in upper part of gastro-intestinal tract in the form of bilayer floating matrix tablet. One of the layers is an immediate release layer designed to release one-third of the baclofen content to achieve an effective plasma concentration. The other layer is a sustained release layer which releases the drug over several hours using a gastro retentive drug delivery system.

The excipients used in this formulation are well established for floating dosage forms and are selected after performing drug excipient compatibility studies. Hydroxypropyl methylcellulose K4M was selected as release retardant for controlled drug delivery. Baclofen is poorly soluble drug and erosion can be the mechanism of drug release in case of poorly soluble drugs. Hence, the low viscosity grade HPMC K4M has been used in this study rather than higher viscosity grades. Swelling agent sodium starch glycolate used in this study is a

super disintegrant. The immediate tablet disintegration is due to the swelling and wicking nature of sodium starch glycolate. Sodium bicarbonate has been used as a gas-generating agent to induce CO_2 generation in the presence of 0.1 N HCl.

Determination of solubility:

The solubility of baclofen as observed in 0.1 N HCl and buffers of various pH values 4.5 and 6.8 are presented in Table No.2. Baclofen exhibited a pH dependent solubility phenomenon in various aqueous buffers. Very high solubility of baclofen was observed in acidic pH values, while the solubility dropped rapidly as the pH increased.

FTIR spectroscopy:

The FTIR spectrum is shown in Figure 1 and interpretation of FTIR spectra is given in Table No. 3. FTIR spectrum of baclofen showed all the peaks corresponding to the functional groups present in the structure of baclofen. Chemically baclofen is β -(Amino methyl)-4-chlorobenzenepropanoic acid. Major peaks were obtained at around 3300 cm^{-1} for amino, $700\text{-}800\text{ cm}^{-1}$ for benzene and 1700 cm^{-1} for carbonyl group, thus confirming the identity of baclofen.

Differential Scanning Calorimetry studies:

Differential Scanning Calorimetry studies indicated a sharp endothermic peak at 207°C for pure baclofen. No significant change in the position of this peak or broadening of peak in the

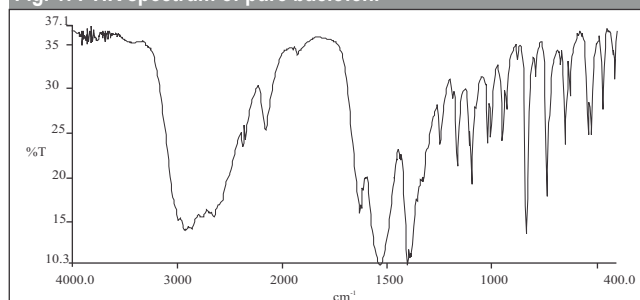
Table 2: Solubility data of baclofen.

Solvent	Solubility (mg/ml)
0.1 N Hcl	20
pH 1.2	15
pH 4.5	8
pH 6.8	5

Table 3: Interpretation of FTIR spectrum of pure baclofen.

Peak observed (cm^{-1})	Interpretation
3300	- NH_2
700-800	Benzene
3400	-OH
1700	-CO

Fig. 1: FTIR spectrum of pure baclofen.



thermogram of drug and excipient mixture was observed with respect to the thermogram of pure drug (Figure 2). So, it can be concluded that the excipients and drug do not interact with each other.

After the tablet preparation each tablet was evaluated for various physical characteristics. The shape of tablets of all formulations was circular. Further, tablet weight varied between 245 ± 4.39 mg, thickness between 5 ± 0.5 mm and hardness between 7-8 kg/cm². The friability ranged between 0.75 and 0.90 % which is within the set limits of USP. All tablets formulations showed 99.15 ± 0.87 % drug content. Tablets from each batch showed uniformity of content as per I. P. limits. Thus, all the physical parameters of the tablet were practically within control.

In the present investigation, the effect of HPMC K4M and sodium bicarbonate was studied using 3² full factorial designs. The responses studied for all 9 formulations were total floating time and time required for 90% drug release (TFT and t₉₀) Table No. 4. Based on the 3² factorial designs, the factor combinations resulted in different drug release and floating time. Various models, such as Linear, 2FI, Quadratic and Cubic, were fitted to the data for two responses simultaneously using Design Expert software and adequacy and good fit of the model was tested using analysis of variance (ANOVA). Mathematical relationships generated for the studied response variables are expressed in equations given below. Positive or negative signs before a coefficient in

quadratic models indicate a synergistic effect or an antagonistic effect for the factor.

$$\text{TFT} = +22.611 + 0.75000 X_1 - 0.750 X_2 + 0.125 X_1 X_2 - 1.16 X_{12} - 0.66 X_{22} + 0.625 X_{12} X_2 + 0.375 X_1 X_{22}$$

$$T_{90} = +20.877 + 1.00 X_1 - 1.300 X_2 + 0.375 X_1 X_2 + 0.383 X_{12} + 0.883 X_{22} + 0.975 X_{12} X_2 + 0.425 X_1 X_{22}$$

Application of two-way ANOVA based factorial analysis indicated that amount of HPMC K4M and sodium bicarbonate has a significant influence on TFT and t₉₀ (P < 0.05). Three-dimensional response surface plots are presented in Figure 3. These types of plots are useful in the study of the effects of two factors on the response at one time. Figure 3 shows that TFT increases with increasing concentrations of HPMC K4M and there is no significant difference on TFT on increasing concentration of sodium bicarbonate. T₉₀ increases with increasing concentrations of HPMC K4M and decreases with increasing concentration of sodium bicarbonate.

After generating the model polynomial equations to relate the dependent and independent variables, the formulation was optimized for all the responses. The final optimal experimental parameters were calculated, which allows the compromise among various responses and searches for a combination of factor levels that jointly optimize a set of responses by satisfying the requirements for each response in the set. Variables X₁ and X₂ were kept in the range of 0 to 1 level. Total floating time (TFT) criteria is kept in the range of 22-24 hrs and time required for more than 90% of drug release was fixed between 22-23 hrs. The optimal calculated parameters were quantity of HPMC K4M (X₁):100 mg and sodium bicarbonate (X₂):30 mg keeping all other ingredients same as other formulations. From the above results, formulation F10 was designed containing baclofen: 30 mg, HPMC K4M:100 mg, sodium starch glycolate: 15 mg, sodium bicarbonate: 30 mg, lactose: 25 mg, magnesium

Fig. 2: Overlay plot of DSC studies for drug and excipients.

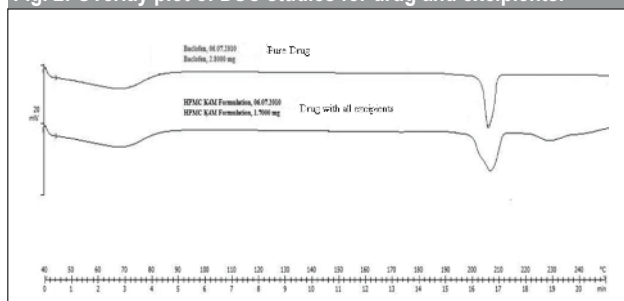
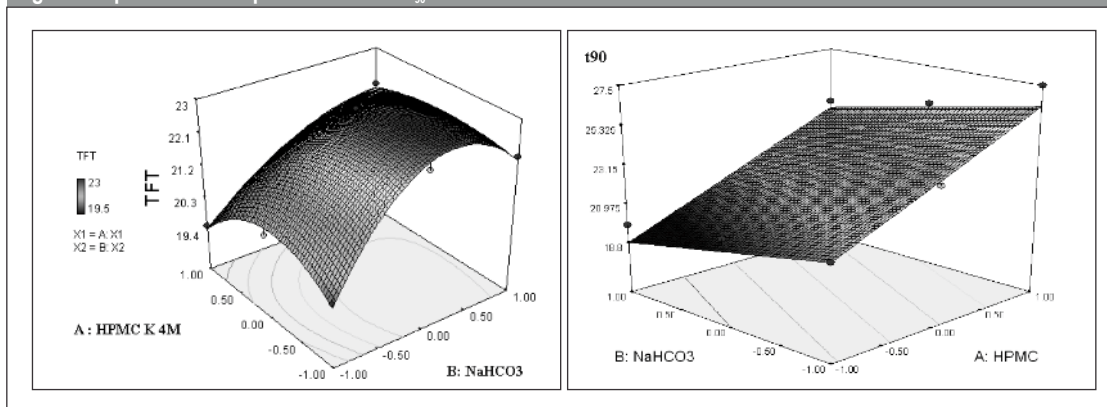


Fig. 3: Response surface plot for TFT and t₉₀.



stearate: 2.5 mg. It was evaluated for the TFT and t_{90} . The predicted values for F10 by using mathematical models are 23.5 hrs and 24 hrs for TFT and t_{90} respectively. The actual results of optimized formulation F10 are 24 h and 20.9 h respectively for TFT and t_{90} , as shown in Table No. 4. Hence, it can be concluded that the actual results are very close to the predicted values.

Buoyancy lag time:

Increasing the polymer concentration decreased the buoyancy lag time. Carbon dioxide which was liberated by the reaction of the sodium bicarbonate with the citric acid in acidic environment of the gastric contents is entrapped in the gel structure of hydrocolloid. This produced an upward motion of the dosage form and maintains its buoyancy. Buoyancy lag time for all formulations was found to be 1 min.

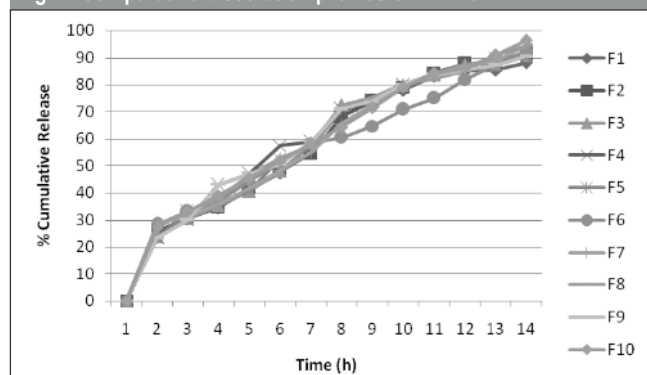
Buoyancy time:

Total time for which tablet remained floating is shown in Table No. 4.

In vitro drug release studies:

In vitro studies were performed to study the drug release from dosage form in the physiological condition and kinetics of drug release. The *in vitro* drug release profiles of F1-F10 are shown in Figure 4. Diffusion, swelling and erosion are the most important rate-controlling mechanisms of controlled drug delivery. Baclofen is poorly soluble drug and erosion can be the mechanism of drug release in case of poorly soluble drugs. Hence, the low viscosity grade HPMC K4M has been used in this study rather than higher viscosity grades. Hydroxypropyl methylcellulose is the most important hydrophilic carrier material used for the preparation of oral controlled drug delivery systems. The formulation F1 containing low level of HPMC K4M (80 mg) and low level of sodium bicarbonate (20 mg) showed desired drug release upto 24 hrs but tablet could not float for 24 hrs. Higher levels of HPMC K4M (F7-F9) results in greater amount of gel being formed. This gel increases diffusion path length of the drug.

Fig. 4: Comparative dissolution profiles of F1-F10.



HPMC swells by absorbing water and forms a swollen layer barrier for drug to diffuse through this layer. As proportion of HPMC in tablet is increased, thickness of the diffusion barrier layer increases. This results in reduced drug release initially. On the same line the formulation F5 and F6 should show relatively less drug release as high level of HPMC K4M (100 mg each) is used in these formulations. But both these formulations released more than 85% drug within 24 hours. This may be attributed to high level of sodium bicarbonate used in these formulations. As the concentration of sodium bicarbonate increases, water uptake capacity of the formulation increases. This increases the porosity of the matrix and results in increased driving force for drug release, which results in increased drug release from the matrix system. Hence, amount of drug released increases with increasing concentration of sodium bicarbonate. At low level of HPMC K4M (F1-F3) desired drug release was obtained but floating time was less. At the higher levels of HPMC K4M (F4-F9) floating time was sufficient but drug release was more retarded. Formulation F10 was found to be the optimum formulation with total floating time upto 23.5 and more than 90% drug release in 24 hrs. To analyze the mechanism of drug release from the matrix tablets, data obtained from the drug release studies was subjected to different kinetic treatments. The correlation coefficient (r^2) was used as an indicator of the best fitting for each of the models considered. The best fit model, values of release exponent (n) and release rate constant (k) are shown in Table No. 5. The value of n is about 0.45 for a Fickian release, and for an anomalous or non-Fickian release, the release is mainly by diffusion with n values > 0.45 and < 1.0 . In the present study diffusion exponent ranges from minimum 0.472 to maximum 0.694

Table 4: Data of t_{90} and total floating time obtained for formulations (F1-F10) by factorial design.

Batch Code	HPMC K4M (X_1)	NaHCO ₃ (X_2)	TFT (hrs)	t_{90} hrs
F1	-1	-1	20	21.2
F2	-1	0	20.5	20.7
F3	-1	1	19.5	19.8
F4	0	-1	22.5	23.5
F5	0	0	24	20
F6	0	1	21	20.9
F7	1	-1	22	27.5
F8	1	0	22	25.4
F9	1	1	22	24.4
F10	-0.26	1	24	20.9

Coded values	Actual values	
	X_1	X_2
-1	80	20
0	100	30
1	120	40

Table 5: Dissolution kinetics						
Formulation	%Total Cumulative Release*	Time for Release (hours)	Best Fit model	Regression Coefficient (r ²)	N	K
F1	93.45 ± 0.98	8	Matrix (Higuchi)	0.9824	0.560	6.5627
F2	97.23 ± 1.23	8.5	Korsmeyer Peppas	0.9823	0.677	7.022
F3	101.80 ± 1.56	9.7	Korsmeyer Peppas	0.9767	0.587	7.1403
F4	84.44 ± 2.34	10	Korsmeyer Peppas	0.9771	0.608	8.8824
F5	90.92 ± 2.07	12	Korsmeyer Peppas	0.9856	0.549	6.9614
F6	97.61 ± 1.34	12	Korsmeyer Peppas	0.9836	0.657	7.601
F7	69.67 ± 3.21	>24	Korsmeyer Peppas	0.9838	0.579	6.881
F8	75.24 ± 0.67	>24	Korsmeyer Peppas	0.9844	0.489	7.463
F9	82.91 ± 1.24	>24	Korsmeyer Peppas	0.9870	0.472	8.163
F10	98.98 ± 1.56	>24	Korsmeyer Peppas	0.9923	0.694	6.9178
*n=6						

therefore release of all formulations is mainly by non-fickian release. It indicates a coupling of the diffusion and erosion mechanism—so-called anomalous diffusion—and may indicate that the drug release is controlled by more than one process. The best fit model for prepared formulation follows Korsmeyer-Peppas model ($r^2=0.9923$) and n value was found to be 0.694 which signified that release pattern of optimized batch follows the non Fickian diffusion.

Swelling behavior:

The study showed that swelling increased up to 16-18 hours for all formulations but after that it decreased. In first 17-18 hours water is absorbed by the polymer and weight gain by tablet is seen. When water penetrates from outer side to the tablet core, the outer gel layer starts to erode. This erosion of polymer dominates over water sorption after 17 hours.

CONCLUSION

Conclusively, the current study attained the successful design, preparation and evaluation of floating bilayer sustained release formulation of a slightly soluble drug baclofen by gastroretentive drug delivery system which had an immediate release layer (one third of drug content) as well as sustained the release profile with gastric retention for the desired period of time by the other layer.

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