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Development and *In-Vitro* Evaluation of Baclofen Floating Tablets Using Different Natural Polymers

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ABSTRACT

Background and the purpose of the study: Baclofen, a centrally acting skeletal muscle relaxant, is indicated in the long-term treatment of spasticity. It is difficult to formulate baclofen sustained release dosage forms because its absorption on arrival to the colon (or even before) is low or non-existent. In the present investigation, efforts were made to improve the bioavailability of baclofen by increasing the residence time of the drug through gastro-retentive mechanism. **Materials and Methods:** Baclofen floating tablets were prepared by the dry granulation technique using guar gum and xanthan gum as polymers, PVP as a binding agent, sodium bicarbonate as an effervescent agent, Dicalcium phosphate as diluents, Cross povidone as a swelling agent and magnesium stearate as a lubricant. **Results:** Drug-excipient interaction studies were conducted by FTIR and DSC. The results suggested that there was no incompatibility between the drug and polymers. The prepared tablets were evaluated for their physical characteristics. All the parameters were within the pharmacopoeial limits. Further, tablets were also studied for their floating properties and *in vitro* drug release characteristics. The tablets exhibited controlled and prolonged drug release profiles. Drug release kinetic studies showed Fickian diffusion. The developed formulation was found to be stable. **Conclusion:** The developed floating tablets of baclofen exhibit prolonged release up to 12 h, and thus may improve bioavailability and minimize fluctuations in plasma drug concentrations.

INTRODUCTION

Baclofen is a structural analog of gamma-aminobutyric acid is a centrally acting skeletal muscle relaxant, which is widely used in the treatment of spasticity resulting from multiple sclerosis, muscle spasms, muscular rigidity and spinal cord injuries.

The oral bioavailability of baclofen is about 40%. It is stable and well absorbed within pH range 1-4.The half-life of the drug is ~2.5 to 4 hrs in plasma [1]. Baclofen has an absorption window in upper G.I. tract, and as a result, it shows low bioavailability [2]. It has good solubility in acidic pH, but solubility reduces when it enters into alkaline pH. Based on the above factors, we made an attempt to increase the residence time of baclofen at or above the absorption window through the preparation of gastro-retentive formulations for baclofen, as it is stable under gastric condition [3].

MATERIALS AND METHODS

Baclofen was purchased from Yarrow chem. Products, Mumbai, India. Guar gum, xanthan gums were obtained from Colorcon Asia Private Limited (India). Sodium bicarbonate, Crospovidone, Dicalcium phosphate, Magnesium stearate and PVP k-30 were purchased from S.D. Fine-Chem. Ltd., Mumbai, India.

Procedure for Preparation of Baclofen floating tablets:

Accurately weighed quantities (Table1) of polymer and dicalcium phosphate, crospovidone were taken in a mortar and mixed geometrically. To this required quantity of baclofen was added and mixed slightly with a pestle. Accurately weighed the quantity of sodium bicarbonate was taken separately in a mortar and powdered with a pestle. The powder was passed through sieve no.40 and mixed with the drug blend which was also passed through sieve no. 40. The whole mixture was collected in a plastic bag and mixed for three minutes. To this PVP K30 was added and mixed for two minutes. The mixture equivalent to 200 mg was compressed into tablets with 8 mm flat punches at a hardness of 6 kg/cm$^{2.}$ The composition of the different formulations is shown in table 1.

Solubility studies:

The equilibrium solubility of baclofen was measured in 0.1M hydrochloric acid (pH of 1.2), phosphate buffer of pH 6.8, and pH 7.4 respectively in order to determine its solubility.

Excess amounts of the drug were added to 50 ml-stoppered conical flasks (n=3). The flasks were shaken mechanically at 37°C±0.5°C for 24 hrs, in a horizontal shaker (HS 501 Digital, IKA-Labortechnik,and Staufen, Germany). After 2 days of equilibrium, aliquots were withdrawn and filtered (0.22 μm pore syringe filter). Then, the filtered samples were diluted with an appropriate amount of dissolution medium and assayed by UV-spectrophotometer at 220nm for baclofen.

Drug-Excipient interaction study:

Differential scanning calorimetry

The physicochemical compatibilities of the drug and the excipients were tested by differential scanning calorimetric (DSC) analysis. DSC thermograms of the drug alone, drug-excipient physical mixture and tablets were derived from DSC (2-C, Perkin-Elmer, New York, NY). The instrument was calibrated with an indium standard. The samples (2-4 mg) were heated (20-300 °C) at a constant scanning speed (10 °C/min) in sealed aluminum pans, using nitrogen purged gas.

FTIR spectroscopy:

Compatibility studies were carried out to know the possible interactions between Baclofen and excipients used in the formulation. Physical mixtures of drug and excipients were prepared to study the compatibility. Drug-polymer compatibility studies were carried out using FTIR spectrophotometer (Schimadzu) by KBr pellet technique. IR spectrum of pure drug and polymers were seen in between 4000-400 $cm^{-1.}$

Evaluation of physicochemical properties:

Hardness test: Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablets was determined using Monsanto hardness tester (Campbell Electronics, India). For each formulation, the hardness of 6 tablets was determined. Hardness values are reported in kg/cm^2. Mean and SD values were also calculated.

Wight variation: To study weight variation, twenty tablets of each formulation were weighed using an electronic balance (Schimadzu BL-22OH, Japan). Values are reported in milligrams. Mean and SD value were also calculated

Thickness: The thickness of the tablets was determined by using vernier calipers (Mitutoyo, Japan). Ten tablets from each batch were used. Thickness values are reported in millimeters. Mean and SD values were also calculated.

Friability: Friability test was carried out using Roche friabilator (Erection instrument & engineering, Ahmedabad, India). Ten tablets were weighed and subjected to the combined effect of attrition and shock by utilizing a plastic chamber. The friabilator was operated for 100 revolutions (4 min, 25 rpm). The tablets were dedusted and re-weighed to calculate the percentage of friability.

Drug Content: Ten tablets for each batch was taken and triturated. Powder equivalent to the average mass was weighed and was transferred into a 100 mL volumetric flask. To this 50 ml of 0.1N HCl was added and it was then shaken for 5 minutes and finally 0.1N HCl was added to make the volume up to 100 ml and solution was then sonicated for 15 minutes and filtered through Whatman filter paper. Finally, a solution was diluted suitably and the absorbance of the resultant solution was measured to determine the drug content spectrophotometrically at 220nm using UV/Visible spectrophotometer (Elico, SL 159, India) against 0.1N HCl blank.

Floating behavior: The *in vitro* buoyancy was determined by the floating lag time. The tablet was placed in a 250 ml beaker containing 0.1N HCl. The time required for the tablet to rise to the surface for floating was determined as the floating lag time (FLT) and the duration of the tablet remaining buoyant was determined as total floating time (TFT) and was observed visually.

***In vitro* dissolution studies:** *In vitro* drug release studies for the prepared baclofen floating tablets were conducted for a period of 12 hrs using USP XXIV type-II (Paddle) dissolution apparatus (Labindia, India) at 37±0.5^{o}C at 50 rpm using 900 ml of 0.1N HCl as dissolution medium. At a predetermined interval of time, 5 ml of sample was withdrawn from the dissolution medium and replaced with fresh medium to maintain the sink condition. After filtration and appropriate dilution, the samples were analyzed for baclofen by UV/Visible spectrophotometer (Elico, SL 159, India) at 220 nm.

Dissolution profile modeling: There are several linear and non-linear kinetic models to describe release mechanisms and to compare test and reference dissolution profiles are as follows:

Zero order kinetics

Drug dissolution from pharmaceutical dosage forms that do not disaggregate and release the drug slowly (assuming that area does not change and no equilibrium conditions are obtained) can be represented by the following equation:

$$W0 – Wt = K0t$$

Where W0 is the initial amount of drug in the pharmaceutical dosage form, Wt is the amount of drug in the pharmaceutical dosage form at time t and k is proportionality constant.

Dividing this equation by W0 and simplifying:

$$ft = k0t$$

Where ft = 1 – (Wt / W0) and ft represents the fraction of drug dissolved in time t and k0 the apparent dissolution rate constant or zero order release constant [4].

First order kinetics

This type of model to analyze drug dissolution study was first proposed by Gibaldi and Feldman and later by Wagner. The relation expressing this model:

$$Log\ Qt = Log\ Q0 + K1t/2.303$$

Where Qt is the amount of drug released in time t, Q0 is initial amount of drug in the solution and K1 is the first order release rate constant [5-6].

Korsmeyer Peppas model

Korsmeyer developed a simple semi empirical model, relating exponentially the drug release to the elapsed time (t).

$$Qt/Q\alpha = Kktn$$

Where Kk is a constant incorporating structural and geometric characteristic of the drug dosage form and is the release exponent, indicative of the drug release mechanisms. The Release exponent can be obtained from the slope and the Constant (Kk) obtained from the intercept of the graphical relation between logarithmic versions of left side of the equation versus log t.

Higuchi Model

$$Qt = KHt1/2$$

Where Qt = the amount of drug released at time t and
KH = the Higuchi release rate;

This is the most widely used model to describe drug release from pharmaceutical matrices. A linear relationship between the square root of time versus the concentration indicates that the drug release follows strict Fickian diffusion [7-9].

Physical stability studies: Physical stability studies were conducted according to International Conference on Harmonization (ICH) guidelines [10]. One of the optimized formulations F4 was enclosed in polyethylene bottle and placed in a desiccator containing saturated sodium chloride solution (75% RH). The desiccator was stored at 40°C for 3 months. At predetermined time intervals, the tablets were examined for hardness, FLT, TFT, drug content and drug release.

RESULTS AND DISCUSSION

Baclofen exhibited a pH dependent solubility phenomenon in different buffers. Solubility of baclofen in different buffer solutions of pH of 1.2, 6.8, 7.4 and water at 37°C was 25, 5.8 and 5.1, 4.3 mg/ml, respectively (Table 2). It shows maximum solubility in 0.1 N HCl, while the solubility dropped rapidly as the pH increased.

Drug-Excipients interaction study: Differential scanning calorimetry studies indicated a sharp endothermic peak at 210°C corresponding to its melting point, for pure baclofen (Fig.1). No significant change in the position of this peak or broadening of peak in the thermogram of drug and excipient mixture was observed with respect to the thermogram of pure drug (fig.2). So, it can be concluded that the drug and excipients do not interact with each other.

The drug-excipient compatibility study was done by Fourier transform infrared (FT-IR) spectroscopy study. The prominent peaks of Baclofen pure drug (Fig. 3) were shown at 1100cm^{-1} (due to –C-Cl), 1530 cm^{-1} (due to -COOH), and 1610 cm^{-1} (due to $–NH_2$). These prominent peaks of drug were also observed in the IR spectrum of physical mixture of drug

(Fig. 4) with various excipients, which indicates that, the drug was not interacted with the polymers used in the study which confirms the stability of the drug.

Physical properties of tablets: The tablets of baclofen were prepared by direct compression method using natural polymers like xanthan gum, guar gum. The data of physical parameters was presented in table 3. All the tablet formulations showed acceptable physicochemical properties and complied with the pharmacopoeial specifications for weight variation, drug content and friability [11]. All the tablets with different proportion of polymer composition were within the weight range of 197.6 mg to 201 mg with SD values 0.42-2.41. Tablets of all the batches passes the weight variation test as the % weight variation was within the standard pharmacopoeial limits. The weights of all the tablets were found to be uniform with low standard deviation values. The mean thickness of the tablets was uniform in all the batches and was found to be in the range of 3.5mm to 3.6 with SD values 0.01-0.08. The hardness of tablets of each batch ranged between 6.01 to 6.3 kg/cm^2. This ensures good handling characteristics for all batches. The Percentage friability for all formulations was found to be less than 1% in all the formulations ensuring that the tablets were mechanically stable. The percentages of drug content for all the batches were found to be in the range of 98.28% to 101.06 % of Baclofen, it complies with official specifications.

Floating lag time and total floating time: In this study, sodium bicarbonate was used as a gas-generating agent in order to aid floating of tablets. The *in vitro* testing revealed the ability of most formulations to maintain buoyant for more than 12 h (Table 4 and fig 5). This suggested that the gel layers formed by the investigated polymers enabled efficient entrapment of the generated gas bubbles. The possible increase in tablet porosity made it to float on the test medium (0.1 N HCl) for extended period of time. The sodium bicarbonate induced CO_2 generation in the presence of dissolution medium. The generated gas was entrapped and protected within the gel formed by hydration of the polymer. This, decreased the density of the tablet below 1 gm/ml, and the tablet became buoyant [4]. As shown in Table 4, all the formulations floated with a lag time of less than 1 min.

***In vitro* release studies:** *In vitro* dissolution studies of all the formulations of baclofen tablets were carried out in 0.1 N HCl (pH 1.2). The study was performed for 12 h and cumulative drug release was calculated. Formulations F1-F5, were prepared with varying concentrations of guar gum and formulations F6-F10 were prepared with varying concentrations of xanthan gum. The *in vitro* drug release studies revealed that formulations F1, F2 and F3 showed a

release of 92.4, 95.2 and 96.7 %, respectively, in 8 h (Fig 6). Formulation F4 showed maximum drug release of 98.5 % in 12 h. The variation in drug release was due to different polymer concentrations in all the formulations. Formulations F1-F3 was unable to sustain the drug release desired period of time. Formulation F4 met the needed theoretical drug release profile and floated with a lag time of 18s. Formulation F5 failed to release the required drug profile. For these reasons, F4 was considered as the best formulation among all the five formulations of this series. The results were shown in fig 6.

Drug release profiles of formulations F6-F10, composed of xanthane gum, are shown in Fig.7. The percentage of drug released from formulations F6, F7 and F8 was 66.8, 74.3 and 77.3, respectively, in 8 h. This variation was considered to be due to different polymer concentrations in formulations. Further, these three formulations failed to meet the required theoretical drug release profile. Formulation F9 met the needed theoretical drug release profile and floated with a lag time of 37s. Formulation F10 failed to release the required drug profile. For these reasons, F9 was considered as the best formulation among all the five formulations of this series. The results were shown in (fig 7).

Data of the *in vitro* release of optimized formulation was fit into kinetic models to explain the release kinetics of baclofen from the floating tablets. The kinetic models used were zero order equation, first order equation, Higuchi and Koresmeyer-Peppas models. The cumulative amount of drug released from the tablets, when plotted against square root of time, the release profiles of the drug seem to follow the Higuchi model compared to all other models which are used in the release kinetic study (Table 5).

The prepared baclofen floating tablets (F4) was selected for stability study based on physical characters and in vitro drug release. The stability study was conducted for 3 months. No significant change was observed in the tablet hardness, FLT, TFT, drug content or *in vitro* dissolution (Table 6). Thus, the formulation F4 was stable for 3 months under these storage conditions.

Table 1: Composition (in mg) of baclofen floating tablets

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Baclofen	20	20	20	20	20	20	20	20	20	20
Guar gum	100	80	60	40	20	-	-	-	-	-
Xanthan gum	-	-	-	-	-	100	80	60	40	20
$NaHCO_3$	40	40	40	40	40	40	40	40	40	40
DCP	90	70	50	30	10	90	70	50	30	10
Crospovidone	20	20	20	20	20	20	20	20	20	20
Mg.Stearate	5	5	5	5	5	5	5	5	5	5
PVP K-30	5	5	5	5	5	5	5	5	5	5
Total tablet weight	200	200	200	200	200	200	200	200	200	200

Table 2: Solubility data of baclofen in different pH buffers

Medium	Solubility (mg/ml)
0.1 N HCl	25
6.8 pH phosphate buffer	5.8
7.4 pH phosphate buffer	5.1
Water	4.6

Table 3: Physical evaluation parameters

FORMULATION	WEIGHT VARIATION (mg)	THICKNESS (mm)	HARDNESS (kg/cm^2)	FRIABILITY (%)	CONTENT UNIFORMITY
F1	199.3±1.52	3.5±0.05	6.1±0.115	0.22	98.28
F2	200.6±1.15	3.5±0.08	6.3±0.2	0.36	99.52
F3	198.3±0.57	3.5±0.05	6.2±0.305	0.25	99.04
F4	200±1.17	3.5±0.08	6.0±0.230	0.33	99.56
F5	198.6±1.52	3.5±0.05	6.1±0.115	0.26	99.41
F6	200±1.73	3.5±0.05	6.0 ±0.23	0.37	99.84
F7	201± 0.42	3.5±0.01	6.0±0.101	0.12	98.28
F8	199±1.18	3.5±0.03	6.1±0.2	0.14	99.52
F9	200.4±1.45	3.5±0.04	6.3±0.215	0.19	99.04
F10	198.3±2.41	3.5±0.08	6.2±0.130	0.28	98.56

Table 4: Floating properties of prepared Baclofen Tablets

Formulations	Floating lag time (sec)	Total floating time (hrs)
F1	35 ± 1	23.65 ± 0.25
F2	27 ± 3	24.05 ± 0.30
F3	23 ± 5	23.30 ± 0.22
F4	18 ± 4	24.45 ± 0.16
F5	35 ± 2	24.25 ± 0.15
F6	45 ± 7	24.45 ± 0.35
F7	47 ± 8	23.35 ± 0.19
F8	62± 2	23.35 ± 0.27
F9	37 ± 4	23.37 ± 0.29
F10	49 ± 9	23.35 ± 0.15

Table 5: The correlation coefficient (R2) values for optimized formula

Zero order	First order	Higuchi	Peppas
0.9885	0.6087	0.9953	0.9928

Table 6: Stability studies optimized batch

Parameters	Storage conditions		
	At 2-8°C	Room temperature (RT)	At 40°C
% Cumulative Drug Release After 8 hrs	91.34%	92.18%	90.30%
Drug Content Uniformity	99.23%	99.52%	99.10%
Colour Change	No	No	No

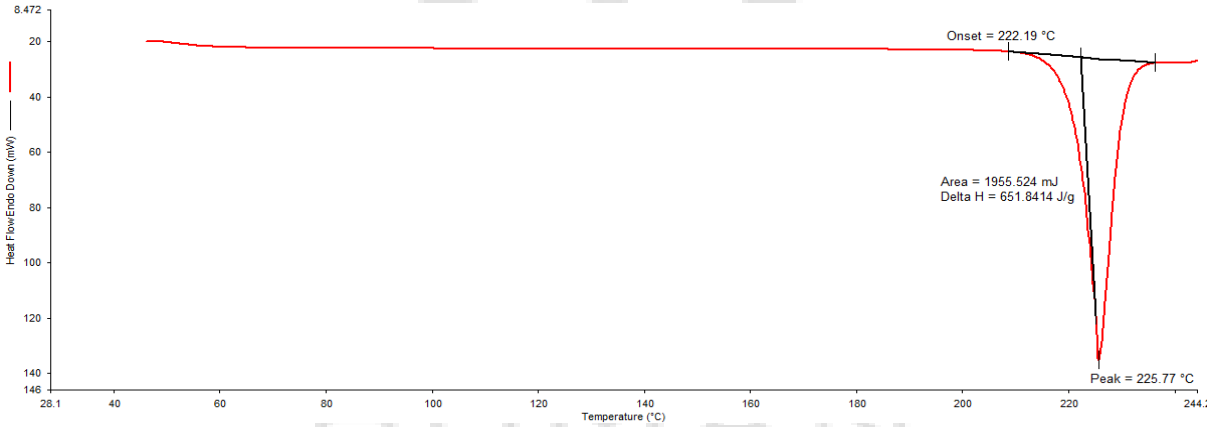

Fig 1: DSC thermogram of Pure drug Baclofen

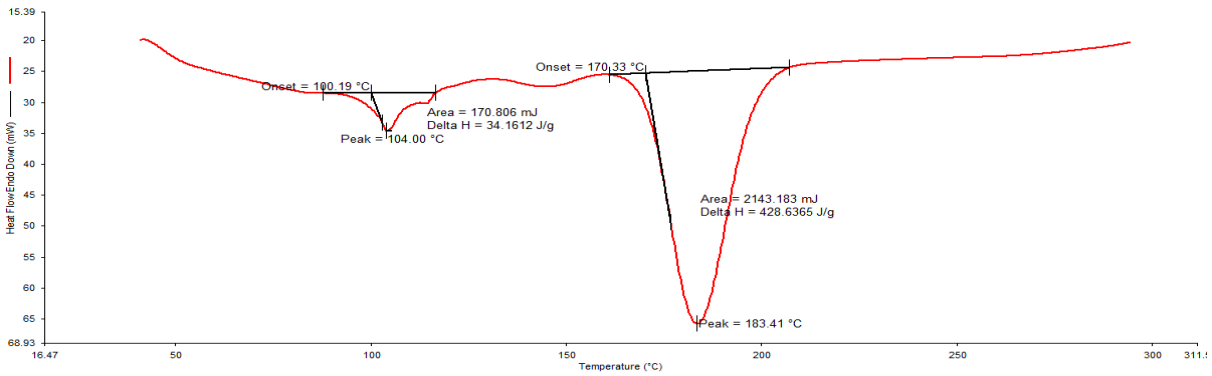

Fig 2: DSC thermogram of Pure Drug Baclofen + Physical mixture

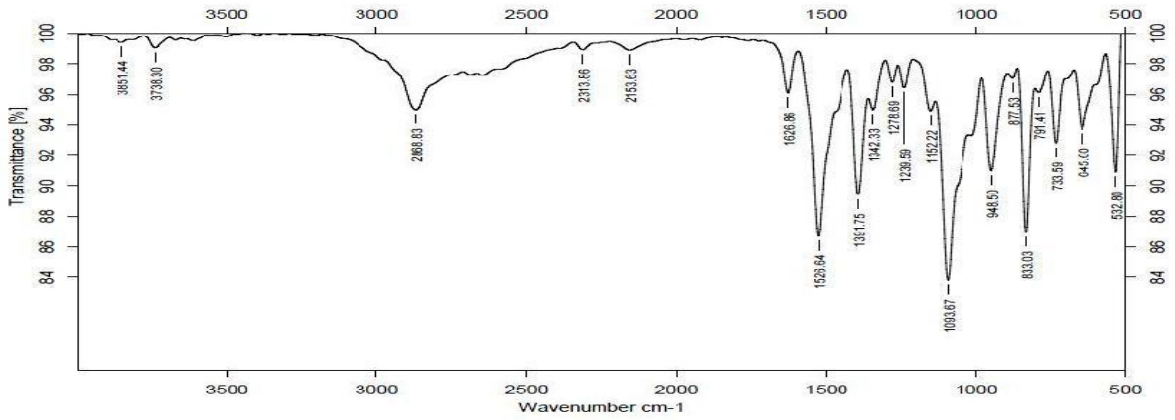

Fig 3: FTIR spectra of Pure drug Baclofen

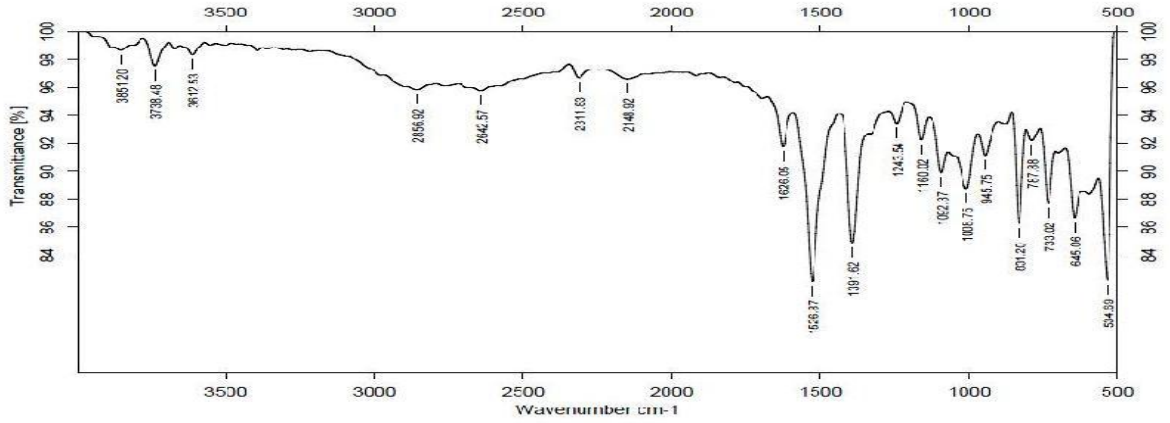

Fig 4: FTIR spectra of Pure drug Baclofen +Physical mixture

Fig 5: *In vitro* buoyancy study of baclofen floating tablets

A ,B,C,D floating lag time of baclofen tablet at 0sec, 5sec, 15sec and 12th hour

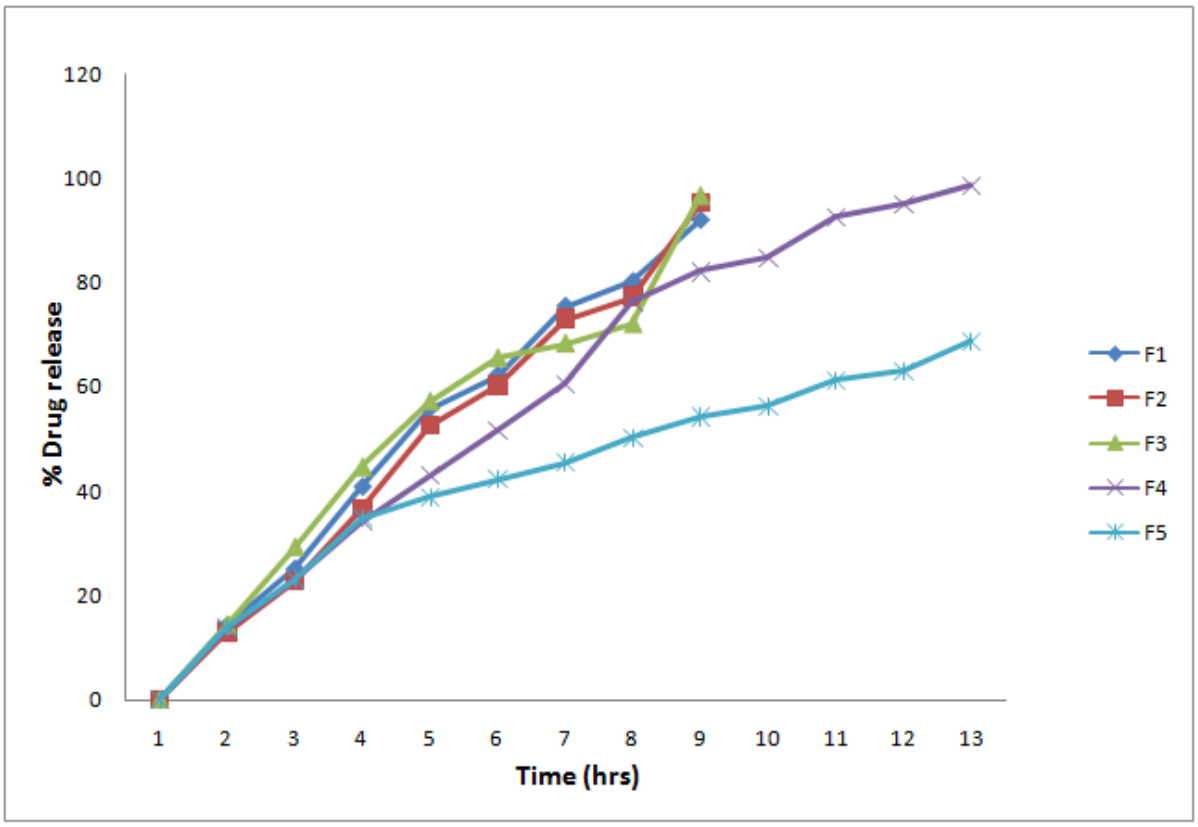

Fig 6: Drug release profiles of baclofen floating tablets composed of guar gum

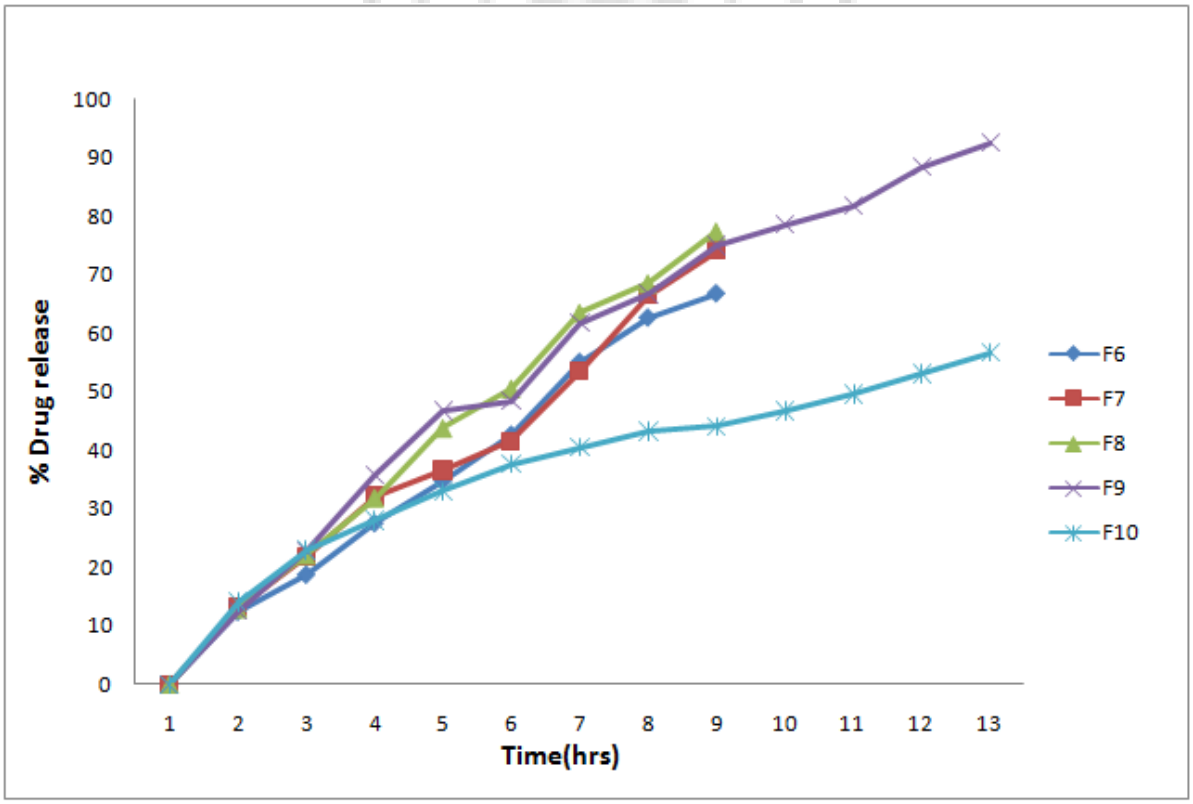

Fig 7: Drug release profiles of baclofen floating tablets composed of xanthan gum

CONCLUSION

Baclofen floating tablets were successfully formulated by floating technique. The optimized formulation (F4) was selected on the basis of *in-vitro* buoyancy and *in vitro* drug release. The addition of gel forming agent and gas generating agent was essential to achieve *in vitro* buoyancy. The results of the *in-vitro* drug release and *in-vitro* buoyancy study showed that the optimized formulation (F4) sustained the drug release (98.47±0.71%) up to 12 h and remained buoyant for >12 h. Optimized formulation (F4) showed no significant change in physical appearance, drug content, floating properties and drug release after storage at 40°C/75% RH and stable for three months.

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REFERENCES

1. Ahuja S. Analytical Profiles of Drug Substances and Excipients. London, UK: Academic Press, 1985; 527-548.
2. Devis SS. Formulation strategies for absorption windows. Drug Discov Today, 2005; 10: 249–257.
3. Rishad R. Jivania, Chhagan N. Patel, Dashrath M. Patel, Nurudin P. Jivani. Development of a Novel Floating In-situ Gelling System for Stomach Specific Drug Delivery of the Narrow Absorption Window Drug Baclofen. IJPR. 2010; 9: 359-368.
4. Brahma NS, Know HK. Floating drug delivery systems: an approach to oral controlled drug delivery via gastric retention. J. Control. Release 2000; 63(1-2): 235-259.
5. Park H., Kinan park. Gastroretentive drug delivery systems., Crit. Reviews in Ther. Drug carrier systems. 1998; 15(3):243-284.
6. Baumgartner S., Kristl J., Vrecer F., Vodopivec P., Zorko B. Optimization floating matrix tablets and evaluation of their gastric residence time. Int J Pharm. 2000; 195:125-135.
7. Lingam M., Bhasker K., Naidu KVS., Chandra Mohan E., Suresh B., Venkateswarlu V., Madhussudan Rao Y. Design and evaluation of polymeric coated minitablets as multiple unit gastroretentive floating drug delivery systems for furosemide. J Pharm Sci. 2009; 98(6): 2122- 2132.
8. Ramesh B., Naidu., Madhusudan Rao Y., Kishan V. Development and evaluation of gastroretentive norfloxacin floating tablets. Acta Pharm. 2009; 59: 211–221.
9. Suresh B., Chandra Mohan E., Ashok T., Madhusudan Rao Y. Formulation of multiple tablets as a biphasic gastroretentive floating drug delivery system for fenoverine. Acta Pharm. 2010; 60:89-97.
10. Mathews BR. Regulatory aspects of stability testing in Europe. Drug Dev. Ind. Pharm. 1999; 25: 831-856.
11. Banker GS, Anderson NR. Tablets. In: Lachmann L, Liberman HA, Kaing JL, editors. The theory and practice of industrial pharmacy, 3rd ed. Varghese publishing house, Mumbai, 1987; p. 297-299.