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RESEARCH ARTICLE

PREPARATION, IN VITRO AND IN VIVO EVALUATION OF FLOATING-BIOADHESIVE TABLETS OF BACLOFEN USING NATURAL GUMS

Narendar Dudhipala, Greeshma Ellaboina, Mahipal Donthi and *Nagaraj Banala

Department of Pharmaceutics, University College Pharmaceutical Sciences (Kakatiya University, Warangal, Telangana 506 009, India

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ABSTRACT

The content of the investigation was to prepare and evaluate the floating-bioadhesive tablets of baclofen (BC) to sustain the drug release. BC is a skeletal muscle relaxant and is used to treat muscle symptoms and also acts as antispastic agent. BC have biological half-life of 1.5 to 4 h and also shows pH dependent solubility. Hence, it is considered as a potential candidate for development of floating-bioadhesive drug delivery system. The BC tablets were prepared by wet granulation method using guar gum and xanthan gum as gel forming agents and sodium bicarbonate as gas generating agent. The prepared tablets were evaluated for physical parameters, in vitro buoyancy and *in vitro* dissolution studies. Further, *in vivo* radio graphic studies of optimized formulation were performed in healthy human volunteers in fasting condition. *In vitro* release studies revealed that guar gum and xanthan gum containing (F9) tablets of baclofen showed 97.89±1.04% of drug release at 8 h time period. DSC studies revealed that no interaction between drug and other excipients. *In vivo* radio graphic studies revealed that the tablets showed mean gastric residence time of 4 ± 0.8 h in the stomach. Therefore, the results conclusively demonstrate the sustained effect of baclofen was achieved by the combination of floating and bioadhesive mechanism.

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INTRODUCTION

Sustained release (SR) formulations offer several pharmacokinetic and pharmacodynamic advantages over conventional dosage forms such as maintenance of constant therapeutic levels for prolonged period of time and minimize the fluctuations in plasma drug concentration. SR formulations might lower the risk of treatment failure (Shweta *et al*., 2005), improve patient compliance by reducing dosing frequency and administration of total dose. However, SR dosage forms were not only developed to control the drug release for a specific period of time but also to prolong the residence time of the dosage form in the stomach or proximal part of small intestine. The presence of a dosage form in the upper part of gastrointestinal tract was important especially for drugs that are degraded or metabolised in the intestine or drugs had local action in the stomach (Deshpande *et al*., 1997; Hwang *et al*., 1998).

Corresponding author: **Nagaraj Banala,**
Department of Pharmaceutics, University College Pharmaceutical Sciences (Kakatiya University, Warangal, Telangana 506 009, India.

Further, for drugs with poor solubility in the intestine and those with site-specific absorption limitations, gastric retention approach might increase the overall gastrointestinal absorption (Rouge *et al*., 1996). Approaches to increase the gastric residence time of drug delivery systems include bioadhesive systems (Ponchel and Irache, 1998), swelling systems that increase their size (Matharu *et al*., 2011; Whitehead *et al*., 1998), low density systems (Streubel *et al*., 2008), floating systems (Doodipala *et al*., 2011), high density systems (Klaussner *et al*., 2003), unfoldable and expandable systems, magnetic systems, and super porous, biodegradable hydrogel systems (Chordiya *et al*., 2013). When the bulk density less than that of gastric fluids, floating drug delivery system (FDDS) remains buoyant in the stomach for a longer period of time without reducing the gastric emptying rate (Narendar *et al*., 2016). While the system floats on the gastric contents, the drug is released slowly at the desired rate from the system, resulting in an increased gastric retention time (GRT) and better control of fluctuations in plasma drug levels (Bechgaard and Neilson, 1978). The main drawback of FDDS is that it is effective only when the fluid level in the stomach is sufficiently high. As the stomach empties and the tablet moves into the pylorus, which results the buoyancy of the dosage form may be retard (Ramesh and Kishan, 2014).

This limitation can be overcome by using bioadhesive polymers to enable it to adhere to the mucous lining of the stomach wall (Chitnis *et al*., 2001). Floating- bioadhesive drug delivery systems offer the advantages of i) increased contact time with stomach mucosa, ii) more effective absorption and bioavailability of drugs with absorption window in the stomach and proximal intestine, and iii) reduced dosing frequencies (Ramesh and Kishan, 2014). Baclofen (BC), is a skeletal muscle relaxant and an antispastic agent. It is used to treat muscle symptoms caused by multiple sclerosis, including spasm, pain, and stiffness (*Mezler et al., 2001*). It exhibits pH dependent solubility, more solubility in acidic environment (stomach pH) and decreased in solubility with increased pH (intestinal pH). BC has biological half-life of 1.5 – 4 h with variable absorption. Hence, BC is considered as a good candidate for the development of sustained release systems. Previously, Suresh and Rao, 2011, developed the floating matrix tablets of Baclofen using hydrophilic polymers for improved gastric residence time. Thakar *et al*., 2013 reported the enhanced oral bioavailability of BC, using statistical design. But, no gastro retentive floating-bioadhesive delivery system is reported for this drug till now. Due to these characters it is considered as a potential candidate for development of floating-bioadhesive drug delivery system.

The aim of this investigation was to prepare and evaluate the floating-bioadhesive tablets of BC, using natural gums such as guar gum and xanthan gum alone and/or combination as adhesive polymers. Further, the gastric residence time of optimized formulation was evaluated in healthy human volunteers under fasting conditions.

MATERIALS

Baclofen was a kind gifted sample from Dr. Reddy's laboratory, Hyderabad, India. Avicel pH 102, xanthan gum and guar gum were purchased from Sigma Aldrich chemicals Ltd., Mumbai, India. Sodium bicarbonate purchased from SD fine chemicals, Mumbai, India. Talc and magnesium stearate were purchased from Merck Pvt. Ltd., Mumbai, India. All other chemicals used were of analytical grade.

METHODS

Preparation of floating-bioadhesive tablets of Baclofen (BCFB)

Floating-bioadhesive tablets containing baclofen were prepared by wet granulation method, using guar gum and xanthan gum as adhesive polymers. The required quantities of the drug, polymer and excipients were accurately weighed and all the ingredients were screened through sieve no.40 except lubricant. Then all the ingredients were transferred into a mortar, thoroughly blended in a glass mortar with pestle for 15 min. This blend is granulated with PVP k30 solution. To this dried granules, the lubricant was added and mixed thoroughly for 2-3 mins. The lubricated mixtures were compressed with 8 mm flat faced punches using rotary tablet compression machine (RDD3, Riddhi, Ahmadabad, India). Each tablet contained 20 mg of Baclofen.

Evaluation of Final Blend: The flow properties of granules (before compression) were characterized in terms of angle of repose, tapped density, bulk density, Carr's index and Hausner ratio (Narendar Reddy *et al*., 2012).

Drug and excipients compatibility study by Differential Scanning Calorimetry

DSC analysis of pure drug, pure polymers, physical mixtures (1:1 ratio of drug: polymer) and optimized formulation were performed using DSC instrument ((DSC4000, Perkin Elmer, USA). Approximately 8-10mg of sample were heated in aluminum crucible within a heating range of 40–300^{o}C and at a rate of 10^{o}C/min using dry nitrogen as the effluent gas, empty aluminium crucible is used as reference.

Evaluation of physicochemical properties

The formulated tablets were evaluated for weight variation, thickness, crushing strength, friability, content uniformity, in-vitro buoyancy and in vitro release studies. The prepared floating-bioadhesive tablets were evaluated for uniformity of weight using 20 tablets (IP, 1996), hardness (Monsanto tester) using 6 tablets, thickness (Vernier calipers) using 6 tablets, friability (Roche friabilator) using 10 tablets, drug content using 10 tablets, in vitro buoyancy using 6 tablets and in vitro dissolution studies using 6 tablets. The results were expressed as mean ± SD.

Drug content uniformity

Randomly collected 20 tablets were triturated in a mortar and equivalent weight of the powder was taken in a volumetric flask containing 100 mL 0.1N HCl, followed by stirring for 30 min. The solution was filtered through the 0.45µm size filter and absorbance was measured at 286 nm by UV-visible spectrophometer (Systonics-117, Hyderabad, India).

Determination of *in vitro* buoyancy

The *in vitro* buoyancy of BCFB tablet was determined in six replicates using United States Pharmacopoeia (USP) dissolution apparatus II (Electrolab, TDT-06T, Mumbai, India) in 900 ml of 0.1 N HCl maintained at 37 ± 0.5 °C with paddle rotation of 50 rpm (Rosa *et al*., 1994). The FLT as well as TFT were determined visually. The time taken by the tablet to emerge onto surface of dissolution medium and the total time, the tablet remained buoyant on fluid surface were noted as FLT and TFT, respectively for all the formulations.

In vitro drug release studies

The *in vitro* dissolution of prepared BCFB tablets was studied in three replicates using USP dissolution apparatus II (Electrolab, TDT-06T, Mumbai, India). The dissolution medium was 900 mL of 0.1 N HCl (pH 1.2), temperature was maintained at 37 ± 0.5^{o}C with a paddle rotation at 50 rpm. Five mL of aliquots were withdrawn at predetermined time intervals by means of a syringe and immediately replaced with 5ml of fresh dissolution medium each time. Samples were filtered using membrane filter (0.45 µm) and suitably diluted with dissolution medium wherever necessary and absorbance of the samples was measured at λ_{max} 286 nm by using double beam UV-Visible spectrophotometer (Elico, SL 210, India).

Drug release analysis and kinetics

The *in vitro* drug release profiles were subjected to different kinetic models to explain the release kinetics for RSFBT. In this study, the *in vitro* drug release profiles were subjected to zero-order, first-order (Wagner, 1969), Higuchi (Higuchi,

1963) and Korsmeyer-Peppas kinetic models (Korsmeyer *et al*., 1983). The goodness of fit was evaluated using the correlation coefficient values (R^2). Zero-order: $F = K_0t$; where F is the fraction of drug released at time t, and K_0 is the zero-order release constant. First-order: $\ln (1 - F) = -K_1t$; where F represents the fraction of drug released at time t, and K_1 is the first-order release constant. Higuchi model: $F = K_Ht^{1/2}$; where F represents the fraction of drug released at time t, and K_H is the Higuchi constant. Korsmeyer–Peppas model: $F = K_Pt^n$; where F represents the fraction of drug released at time t, K_P is the rate constant and n is the release exponent, indicative of the drug release mechanism. Further, the Korsmeyer–Peppas model was employed in the analysis of *in vitro* drug release behavior of these formulations to distinguish between competing release mechanisms. If a value of $n \leq 0.5$, indicates the Fickian release mechanism. The value of n between 0.5 and 1 is an indication of non-Fickian release mechanism (both diffusion controlled and swelling controlled). When, $n \geq 1$, it is case-II transport and this involves polymer dissolution and polymeric chain enlargement or relaxation.

Ex vivo residence time

The *ex vivo* residence study was determined with porcine stomach mucosa. The mucosa was isolated from the porcine stomach and that was tied to the glass slide 2.2 x 7 cm in size. The tablet was kept in to the middle of the slide and pressed for 1min time with a drop of 0.1N HCl for providing wetting property to the tablet. Then the tablet was introduced into the beaker containing 500 mL of 0.1N HCl (pH 1.2) in the presence of little agitation by a magnetic stirrer at 25 rpm. The study was carried out for the 12 h time period.

In vivo radio graphic study

The *in vivo* gastric residence time of Baclofen floating-bioadhesive tablets can be determined by x-ray technique. All the ingredients used in this were transparent to X-ray, and therefore, to make the tablet formulation X-ray opaque, 20 mg of the dicalcium phosphate was replaced with barium sulphate ($BaSO_4$) and weight of all other ingredients were kept constant so that the final tablet weight remained same. The protocol of radiological study was approved by the Institutional Ethics Committee, University College of Pharmaceutical Sciences, Kakatiya University, India. Three healthy male volunteers participated after giving an informed written consent. The subjects weighed in between 65–68 kg (66.3 ± 1.5 kg), in height from 165-167 cm (166 ± 1.0 cm) and in the age group of 25-34 years (29 ± 4.5 years). The study was conducted under the guidance of an expert radiologist. About 30 min before starting the study, the volunteers were fed with low calorie food having 100 g bread and 200 ml water. The optimized, $BaSO_4$-loaded tablet was administered orally to every volunteer with 200 ml of water. At different time intervals like, 1, 1.5, 3 and 5 h, the volunteers were exposed to abdominal X-ray imaging in a standing position and tablet movements could be noticed [19].

Results and discussion

The Baclofen floating-bioadhesive tablets were prepared by effervescent technique, using wet granulation method as per the composition in Table 1. Formulation F1 to F3, F4 to F6 and F7 to F9 are prepared with guar gum, xanthan gum and combination of both guar gum and xanthan gum, respectively.

Flow properties of pre-compressed powder

The prepared granules are subjected to flow properties and the results are showed in Table 2. From the results, the angle of repose of the granules were varied in the range of 26.4° to 34.7°, Carr's index was found to be in the range of 13.2 to 17.8 and Hausner's ratio ranged from 1.18 to 1.25. These values are in pharmacopoeial limits and also signify that the prepared granules exhibits good flow properties.

Post compression evaluation parameters

All the prepared formulations were tested for physical parameters like weight variation, hardness, thickness, friability and represented in Table 3. The thickness of the tablets was ranged from 2.95±0.27 to 3.35±0.27 mm, hardness of the tablets was fixed to above 6 kg/cm^2. The weight of the tablets 197.3±3.05 to 201±3.6 mg and friability of the tablets was below 1%. The results of the all the parameters were found to be within the Pharmacopoeial limits. The drug content of all the formulations was determined and was found to be within the range of 98.77 - 100.14% and as per permissible limit.

In vitro buoyancy studies

The floating lag time and floating time of BCFB tablets was determined by using dissolution apparatus and results are shown in Table 3. Formulations F1-F3, prepared with guar gum floated with a lag time of 92 to 109 sec. Formulations F4-F6, prepared with xanthan gum showed a floating lag time of 98 to 110 sec. The tablets prepared with combination of both the gums (F6-F9) floated with a lag time of 90 to 102 sec. This is mainly due to evolution of carbon dioxide entrapped inside the hydrated polymeric matrices, resulting from the interaction between gas generating agent and dissolution medium (0.1N HCl), and this leads to lowering of density of matrices below 1 gm/ml enabling the matrices to float. The floating time of all formulations was found to be more than 8h. Among all the formulations, F9 formulation exhibits less (statistically insignificant) floating lag time (90 sec) with floating time more than 8 h.

Ex-vivo residence time

Ex-vivo residence time of the BCFB tablets was determined by using porcine stomach tissue. From the results, residence time of the formulations were in between 6 to 7 h. Formulation F2, F5 and F9 having the greater bio adhesion property due to the formation of high viscous nature of the natural polymer, and also easily cross linked with mucus layer. Therefore, the ratio of polymer increased, residence time will also be increased (Table 4).

In vitro release studies

The *in vitro* drug release studies revealed that formulations F1 and F3 (60 and 100 mg of guar gum) showed a release of 99.45% and 91.43%, respectively, in 6 and 8 h (Fig.1). Formulation F3 (80 mg) showed maximum drug release of 98.99% % in 8 h. The variation in drug release was due to different polymer concentrations in all the three formulations. Formulation F1 wase unable to sustain the drug release for desired period of time but in case of formulation F2 and F3 drug was released in 8 h period.

Table 1. Composition of floating-bioadhesive tablets of Baclofen

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Baclofen	20	20	20	20	20	20	20	20	20
Guar Gum	60	80	100	-	-	-	60	50	40
Xanthan Gum	-	-	-	60	80	100	20	30	40
$NaHCO_3$	40	40	40	40	40	40	40	40	40
Dicalcium phosphate	50	30	10	50	30	10	30	30	30
Crospovidone	20	20	20	20	20	20	20	20	20
Magnesium Stearate	5	5	5	5	5	5	5	5	5
PVP K 30	5	5	5	5	5	5	5	5	5
Total tablet weight	200	200	200	200	200	200	200	200	200

Table 2. Pre compression parameters of granules

Formulations	Angle of Repose	Compressibility Index (%)	Hausner's Ratio
F1	31.8	15.5	1.18
F2	34.1	17.2	1.25
F3	34.7	17.8	1.24
F4	32.2	16.4	1.25
F5	31.3	16.8	1.19
F6	34.8	17.3	1.22
F7	34.7	18.3	1.25
F8	26.9	13.2	1.22
F9	26.4	13.8	1.19

Table 3. Physical parameters of Baclofen floating-bioadhesive tablets

Formulation Code	Weight Variation (mg)	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)	Assay (%)	FLT	FT (h)
F1	198.6±2.30	6.2±0.2	3.25±0.27	0.25	98.96	109	>8
F2	201±3.6	6.0±0.2	3.08±0.20	0.26	99.94	92	>8
F3	198±2.51	6.1±0.3	2.95±0.27	0.33	99.04	105	>8
F4	199.3±3.05	6.1±0.2	2.97±0.19	0.14	99.32	98	>8
F5	200.6±1.15	6.2±0.05	3.18±0.27	0.19	100.14	110	>8
F6	198.3±2.88	6.2±0.2	3.23±0.27	0.28	98.27	105	>8
F7	198.3±2.88	6.2±0.1	3.35±0.27	0.26	99.17	108	>8
F8	197.3±3.05	6±0.2	3.18±0.19	0.26	99.83	90	>8
F9	198±3.46	6.2±0.2	3±0.23	0.14	98.77	104	>8

FLT - Floating Lag Time (sec); FT – Floating time (h)

Table 4. *Ex-vivo* residence time of baclofen floating-bioadhesive tablets in porcine stomach mucosa

Formulation code	*Ex-vivo* retention time (h)
F1	6
F2	6.5
F3	6.5
F4	6
F5	7
F6	6.5
F7	6
F8	6.5
F9	7

Table 5. Regression coefficient (R^2) values of Baclofen floating-bioadhesive tablets for different kinetic models

Formulations	R^2 Values				n value
	Zero Order	First Order	Higuchi	Peppas	
F1	0.9501	0.1956	0.9321	0.9321	0.5
F2	0.9802	0.9271	0.9803	0.9803	0.5
F3	0.9927	0.958	0.9566	0.9993	0.75
F4	0.896	0.1867	0.9127	0.9127	0.5
F5	0.9817	0.849	0.9771	0.9954	0.75
F6	0.9848	0.9579	0.9779	0.9983	0.75
F7	0.9756	0.9689	0.9871	0.9977	0.75
F8	0.9695	0.9733	0.9886	0.995	0.75
F9	0.9383	0.938	0.9977	0.9972	0.5

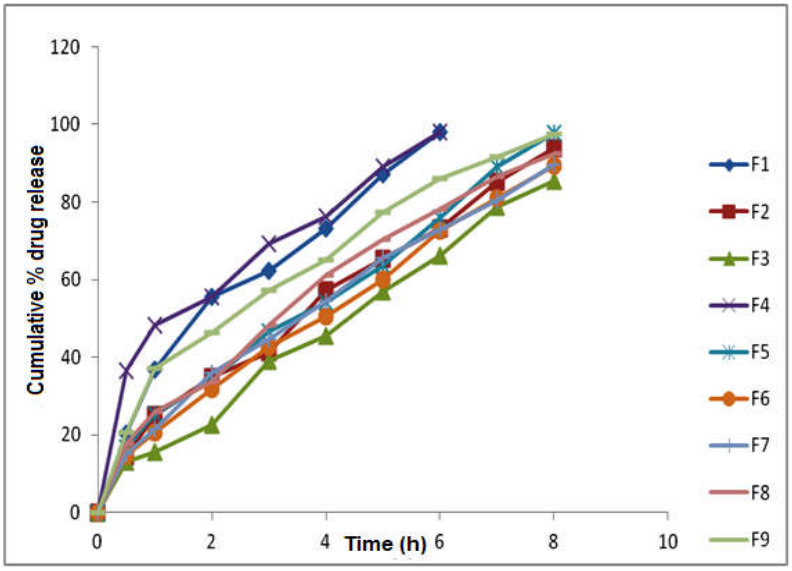

Figure 1. *In vitro* release profiles of baclofen floating-bioadhesive tablets (mean±SD, n=3)

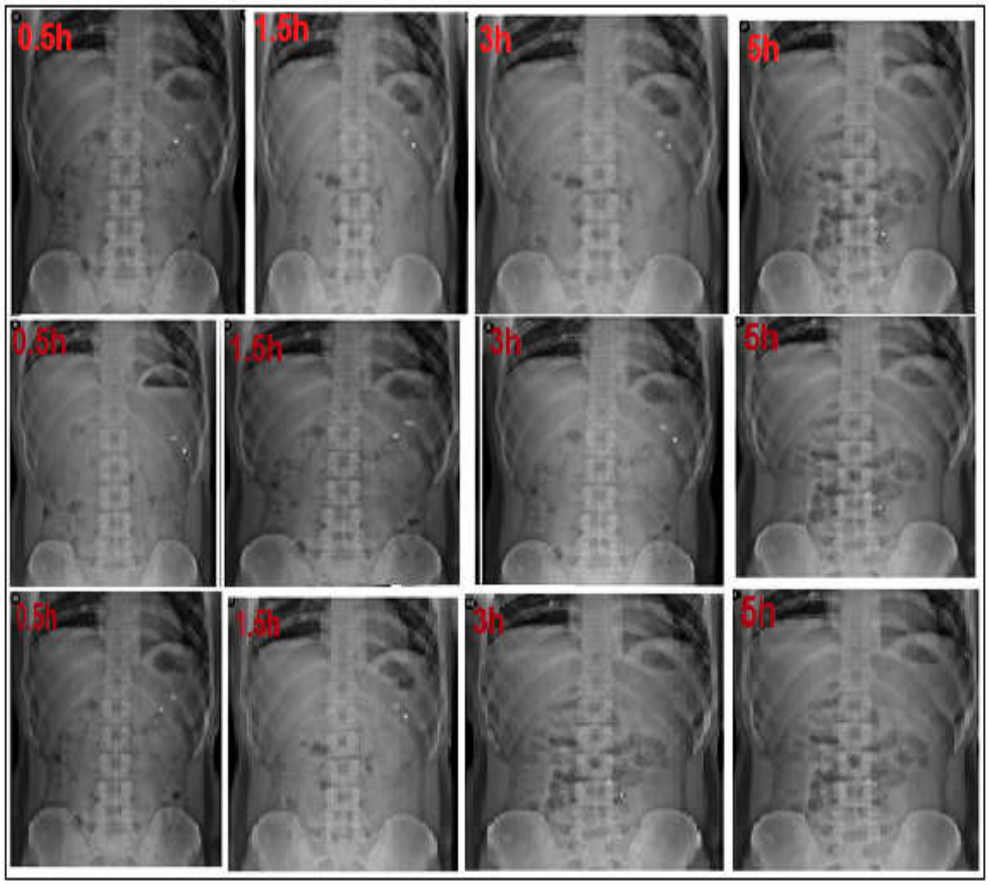

Figure 2. Radiographic images of $BaSO_4$-loaded baclofen floating-bioadhesive tablets in the stomach at different time intervals of 0.5 h, 1.5 h, 3 h and 5 h (mean±SD, n=3)

Formulation F2 showed the desired drug release profile and floated with a lag time of 92 seconds, for these reasons, it was considered as best formulation among all the three formulations. The difference in drug release might be due to the amount of gel layer formed around the tablets. At higher concentrations of polymer, it resulted in a greater amount of gel being formed. This gel increased diffusion length so that drug release was decreased. As the concentration of polymers was increased, the tablets could retain their physical integrity and the drug release was significantly extended.

Formulations F4-F6, composed of Xanthan gum (60-100 mg) showed a release of 98.75, 95.83 and 90.8% in 6 and 8 h, respectively. These variations in drug release were due to changes in polymer concentrations of the tablets. The main reason for retarded drug release is due to the presence of xanthan gum, which readily absorbs water and swells. In addition to its hydrophilic nature, cross-linked structure and insolubility in water makes the xanthan gum as a potential candidate for use in controlled release drug delivery systems.

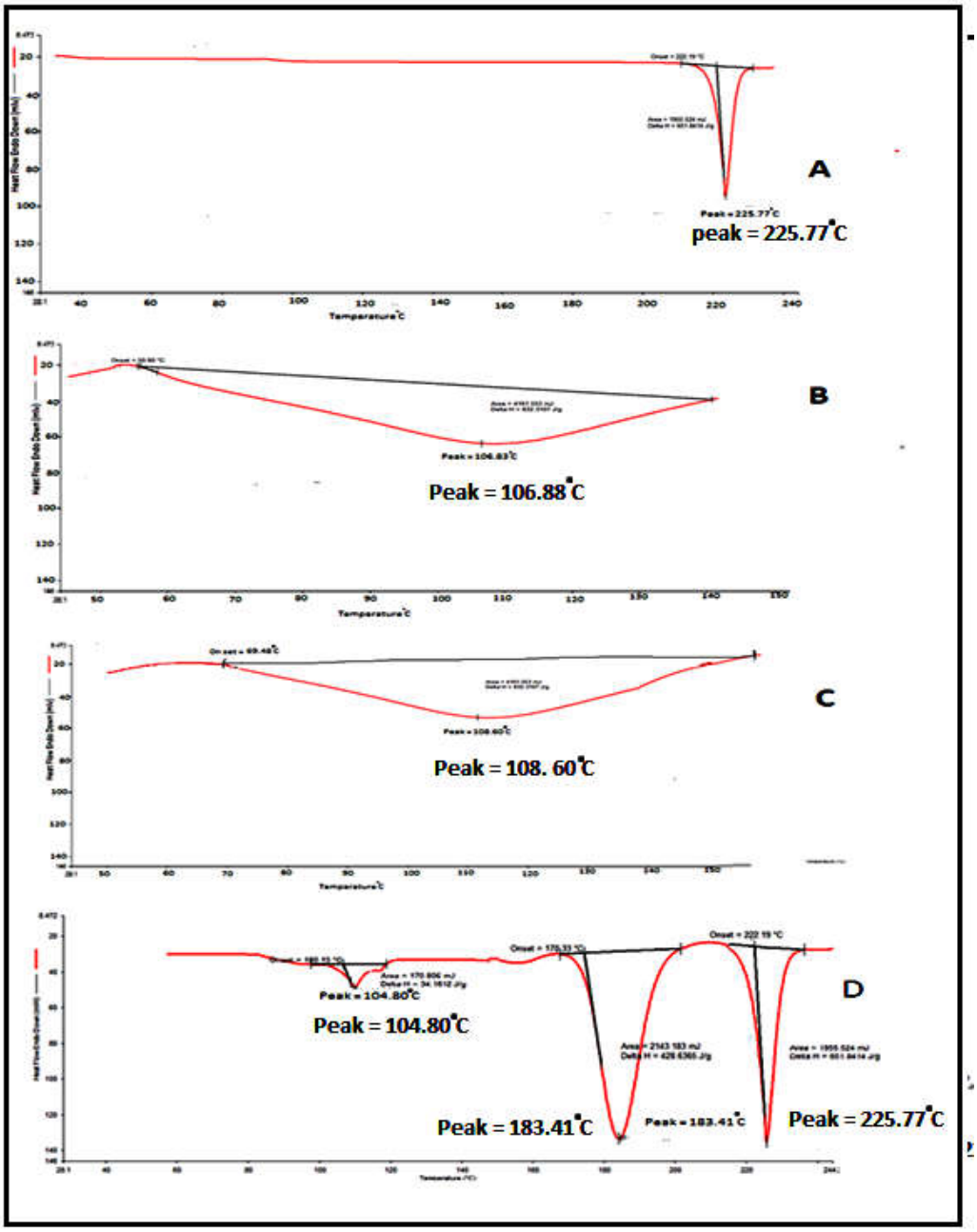

Figure 3. DSC thermograms of A) pure Baclofen, B) pure guar gum, C) pure xanthan gum and D) Optimized formulation

Formulations F7, F8 and F9 prepared with combination of guar gum and xanthan gum, resulted in the floating lag time of 90 to 110 sec. From the dissolution studies the drug release was found to be 93.87, 99.79 and 89.95% in 8 h. In all the formulations, formulation F9 (40 mg of guar gum and 40 mg of xanthan gum) met the desired drug release profile in 8 h and floated with a lag time of 90 seconds. It was, therefore, considered the best formulation among all the prepared formulations.

Release kinetics

The data obtained from in vitro dissolution studies were fitted into different kinetic models viz., zero order, first order, Higuchi and Peppas model (Table 5). The Higuchi plots were found to be linear as indicated by their high regression values (R^2 = 0.997). To confirm the exact mechanism of drug release from these tablets, the data were fitted to Peppas model. Regression analysis was performed and R^2 values were found in between 0.912 to 0.997 for different formulations.

The values of the release exponent were in the range of 0.5 to 0.75; this suggested that the release of baclofen from FBT tablets followed Fickian transport mechanism. This means that water diffusion and also the polymer rearrangement played important role in the drug release.

***In vivo* radiographic studies (X-Ray Studies)**

The corner stone of this investigation was to examine whether the BCFBT could be buoyant and retained in the stomach. The *in vivo* buoyancy of tablet was confirmed by X-ray imaging at different time intervals post-administration of the $BaSO_4$-loaded BCFB tablets.

The radiographic studies were performed in healthy human volunteers in fasting conditions and results were showed in Figure 2. From the results, the mean gastric residence time of floating tablet was found to be to be 4 ± 0.8 h.

Differential Scanning Calorimetry (DSC)

The thermal properties of the drug, natural polymers, mixture of drug and other excipients are of important interest, since DSC can help to determine the interaction among different components of the formulations. The DSC curve of pure Baclofen showed a single sharp exothermic peak at 225.77°C and it was corresponding to its melting point (Figure 3). The DSC thermograms of pure polymers exhibited decomposition temperature at 105.8°C for guar gum and at 108.60 C for xanthan gum. The optimized formulation (F9) exhibited sharp melting endothermic peak of drug at 225.77°C, decomposition temperature of gums mixture (merged) at 104.80°C and sodium bicarbonate endothermic peak at 183.41°C. From the DSC analysis, it was confirmed that there was no interaction between drug and other excipients of the developed formulation.

Conclusion

Baclofen floating-bioadhesive tablets were successfully prepared with natural polymers like guar gum and xanthan gum in alone, and combination of gums. All formulations were tested for physicochemical parameters and were found to be within the limits. The optimized formulation (F9) showed sustain drug release with Higuchi mechanism. The mean gastric residence time of th F9 formulation was found to be 4 ± 0.8h in healthy human volunteers.

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Conflict of interest

The authors declare that there is no conflict of interest.

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