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GASTROADHESIVE SUITABILITY STUDIES FOR BACLOFEN SUSTAINED RELEASE FORMULATION

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Abstract:

The present study is to investigate gastromucoadhesive suitability of natural polysaccharides for development of baclofen sustained release tablet formulations by increase gastric residence. Baclofen formulations were prepared by wet granulation technique and evaluated blend by FTIR, DSC for compatibility, hardness, friability, in-vitro drug release, gastric residence and mucoadhesive strength. The formulated tablets were found to have good mechanical properties and official compliance. Based on in-vitro drug release pattern and ex-vivo mucoadhesive study; the formulation B4 with drug-polymer ratio 1:2 and mucoadhesive-release retardant ratio 3:1 containing 13% hibiscus polysaccharide (HEC) and 7 % xanthan gum (XNG) was found to be promising for mucoadhesion and sustained release characteristics. Formulation B4 exhibited the highest efficiency of mucoadhesion strength (26 gm) and mucoadhesion retention in 0.1 N HCL medium even at the end of 5.6 hours when compared with other formulations. The accelerated stability studies revealed that the tablets retain their characteristics even after stressed storage conditions. The study reveals that hibiscus esculentus polysaccharide could be used as an effective natural pharmaceutical mucoadhesive along with xanthan gum in the development of stable, gastromucoadhesive sustained release matrix tablets of baclofen.

Key words: *Baclofen (BCLF), Hibiscus Esculentus polysaccharide (HEC), Xanthan gum (XNG), Gastromucoadhesive matrix tablet*

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INTRODUCTION:

Recent approaches to increase the gastric residence time of drug delivery systems include bioadhesive devices. Mucoadhesive drug delivery system utilize the property of bioadhesion where certain polymers become adhesive after hydration that can be used for targeting drug to a particular region of the body for extended period of time [1]. The hypothesis for this research study is that if drug can be delivered in a controlled manner to the duodenum at a rate that does not exceed the maximum rate of its absorption, then the oral bioavailability of drug could be improved. Based on this hypothesis, the bioadhesive tablets were designed in such a way that it should be retained in the stomach for a prolonged period of time, thus maximizing the exposure of this drug to its absorption site [2]. Baclofen is a centrally acting skeletal muscle relaxant used in the long-term treatment of spasticity resulting from multiple sclerosis and spinal cord injuries. Baclofen is rapidly, extensively absorbed and eliminated from gastrointestinal tract as a result short half-life 2.5 to 4 hours in plasma [3]. In addition, many reports stated that absorption of baclofen is through facilitated-intestinal transport. Therefore, gastric and intestinal transient times have a significant effect on the rate and extent of oral absorption of the drug [2, 4].

The mucoadhesive material of *hibiscus esculentus* polysaccharide (HEC) was extracted from the natural source by aqueous extraction and precipitating the addition of acetone. The isolated biomaterial shows promising inbuilt mucoadhesive properties [5]. Since this natural mucoadhesive agent is edible, easily biodegradable and may provide an alternative to conventional synthetic mucoadhesive agents. Due to bioadhesive property of HEC, mucoadhesive tablets are expected to remain in the upper GIT and release its drug content for a long period of time, thus providing sustained therapeutic effect. Another component, xanthan gum (XNG) has been a dominant hydrophilic material used in controlled release dosage forms due to its non-toxic nature, ease of compression, and capacity to accommodate high levels of drug loading. One of its most important characteristics is high swellability which exerts a significant influence on the release kinetics of an incorporated drug in it. Upon contact with water or biological fluid the latter diffuses into the device, resulting in polymer chain relaxation with volume expansion [6, 7]. In the present investigation, preliminary use of HEC and XNG natural polysaccharides in different proportion were still retained ability of residence in favor of mucoadhesion to increase the residence time, which helps in the controlled and predetermined release of baclofen (BCLF) at or above the absorption window.

MATERIALS AND METHODS:

Baclofen was obtained as a gift sample from Unicure Pharmaceutical Limited, Gujarat, India. *Hibiscus esculentus* polysaccharide was isolated by simple maceration from *hibiscus esculentus* unripe fruits which were purchased from the local market, Amravati district Maharashtra. All excipients and chemicals were used of (analytical) USP grades.

Preparation baclofen mucoadhesive matrix tablets

The tablets were prepared by a wet granulation method using 8 mm biconcave punches in rotary tablet punching machine (10 station rotary tablet compression machine Cadmach, Ahmadabad, India) [7]. The composition of the different formulations of BCLF tablets is listed in the table 1. All excipients except magnesium stearate and talc were accurately weighed and passed through # 80 meshes.

Table 1: Composition of preliminary batches of baclofen

Formulation Code	FH1	FH2	FH3	FH4	FH5	FH6	BF1	BF2	BF3	BF4	BF5	BF6
Drug: polymer ratio	1:1	1:2	1:3	1:1	1:2	1:3	1:1.5	1:1.5	1:1.5	1:2	1:2	1:2
Baclofen	20	20	20	20	20	20	20	20	20	20	20	20
Hibiscus esculentus polysaccharide	20	40	60	20	40	60	30	-	20	30	20	25
Xanthan gum	-	-	-	-	-	-	-	30	10	10	20	15
Microcrystalline Cellulose	104	84	64	-	-	-	-	-	-	-	-	-
Dicalcium Phosphate	-	-	-	104	84	64	93	93	93	83	83	83
Polyvinyl pyrrolidone K30	-	-	-	-	-	-	3	3	3	3	3	3
Magnesium Stearate	4	4	4	4	4	4	2	2	2	2	2	2
Talc	2	2	2	2	2	2	2	2	2	2	2	2
Total Weight (mg)	150	150	150	150	150	150	150	150	150	150	150	150

The drug (BCLF), polymer (HEC, XNG) and filler dicalcium phosphate were mixed thoroughly. The four ratios drug: polymer, 1:1, 1:1.5, 1:2 and 1:3, were established for each of the two polymers used for producing hydrophilic matrices. A sufficient volume of granulating agent of polyvinyl pyrrolidone solution was added slowly to achieve the granulation endpoint. After the enough cohesiveness obtained, passed through # 10 mesh, granules were dried at room temperature to evaporate the isopropyl alcohol and then were dried at 50°C for 30 min. The granules were collected and passed through # 12 mesh, lubricate with magnesium stearate and talc which were further compressed into matrix tablets.

Fourier Transform Infrared (FTIR) spectral analysis

FTIR spectrums were recorded on samples prepared in potassium bromide (KBr) disks using FTIR spectrophotometer (Model-1601 PC, Shimadzu Corporation, Japan). The scanning range was 400 to 4000 cm^{-1}. The FTIR spectrums of pure baclofen, *hibiscus esculentus* polysaccharide, xanthan gum, polyvinyl pyrrolidone, physical mixture of baclofen: *hibiscus esculentus*: xanthan gum: povidone and formulation blend were taken [8].

Differential scanning calorimetry analysis

The DSC curves baclofen, *hibiscus esculentus* polysaccharide, xanthan gum, and povidone, physical mixture of baclofen: *hibiscus esculentus* polysaccharide: xanthan gum: povidone and formulation blend were obtained using differential scanning calorimeter (Shimadzu DSC-60, Shimadzu Limited, and Japan) at increasing heating rate at 10˚C/min and heated over a temperature range of 50˚C to 300˚C in an atmosphere of nitrogen (20ml/min). Accurately twelve mg of sample was taken in a hermetically sealed, flat bottom aluminium sealed pan and placed at sample stage and thermograms were recorded [8].

Pre-compression parameters

Before final compression of tablets, properties of the gastro retentive mucoadhesive granules were evaluated for bulk density, tapped density, angle of repose and compressibility as in-process characterization. All the experiments were done in triplicates and expressed as mean± SD.

Determination of bulk density and tapped density [9]

Weighed the granules (W), was poured into the graduated cylinder and the volume (V_0) was note. Then the graduated cylinder was closed with lid, set into the density determination apparatus. The density apparatus was set for 100 taps and after that, the volume (V_f) was measured. The bulk density, tapped density was found out by using the formulae;

$$\text{Bulk density} = W/V_0$$
$$\text{Tapped density} = W/V_f$$

Angle of repose [9]

Angle of repose was determined using funnel method. The height of the funnel was adjusted in such a way that the tip of funnel just touches the heap of the blends. Accurately weighed blends are allowed to pass through the funnel freely on to the surface. The height and diameter of the powder cone was measured and angle of repose was calculated using the following equation;

$$\tan \theta = h / r$$

Where, θ = Angle of repose, h = height of the pile, r = radius of plane surface occupy by the powder.

Post-compression parameters

Properties of the gastro retentive mucoadhesive tablets, such as appearance, thickness and diameter, surface pH, hardness, friability, weight variation and content uniformity were determined as per procedures described in the Indian Pharmacopoeia.

Appearance, thickness, size and shape

The general appearance and elegance of tablet was identified visually, which include shape, color, presence or absence of an odor, taste, surface texture etc. The thickness and diameter of the tablets were determined by using vernier calipers (Mitutoyo, Japan). Three tablets were used from each batch and results were expressed in millimeter. Mean and SD values were also calculated.

Hardness [9]

Hardness of the tablets was evaluated using Monsanto hardness tester, which is expressed in kg/cm^2. The hardness of the tablets was measured during start and between the compressions.

Friability [9]

Friability of tablets was determined using Roche friabilator. Twenty tablets were weighed and placed in a chamber. According to guideline friabilator was operated at 100 revolutions (25 rpm for four minutes) and the tablets were subjected and the tablets were subjected for combined effect of abrasion and shock because the plastic chamber carrying the tablets drops them at a distance of six inches with every revolution. The tablets were then dusted and reweighed and the percentage of friability was calculated by using the following formula

$$\text{Friability} = \left(\frac{\text{weight loss}}{\text{weight of tablets before operations}}\right) \times 100$$

Weight variation [9]
Weight variation test of tablets was performed according to guidelines of USP 2004, twenty tablets were taken and their weight was determined individually and collectively on a digital weighing balance. The percentage deviation was calculated and checked for weight variation.

Content uniformity [9]
The amount of powder equivalent to 20 mg of the drug was weighed and dissolved in 100 ml of distilled water. After 10 minutes of centrifugation, aliquots of 1ml were taken from this solution and diluted to 100mL with 0.1 N HCl (10µg/ml). The absorbance of resulting solutions was measured in an UV spectrophotometer at 219.8nm. Simultaneously, 10µg/ml of BCLF standard solution was prepared in the same medium and the absorbance was recorded. Drug content was calculated.

***In-vitro* drug dissolution study [7]**
In-vitro dissolution of BCLF from mucoadhesive tablets (n=3) was determined using United State Pharmacopoeia (USP) XXIV dissolution testing apparatus II (paddle method). The dissolution test was carried out in 900 ml of 0.1 N HCl of pH 1.2 at a temperature of 37 ±0.5°C and a speed of 50 rpm. A sample (10 ml) of the solution was withdrawn from the dissolution apparatus at 1 hour interval for 10 hour, and the samples were replaced with fresh dissolution medium. The samples were filtered through a 0.45µ membrane filter and diluted to a suitable concentration with 0.1N HCl. Absorbance of these solutions was measured at 219.8 nm using a UV/Vis spectrophotometer. The dissolution studies of all the batch formulations were performed in six replicates. Cumulative percentage of drug release was calculated using an equation obtained from a standard curve. The drug in 0.1N HCl followed Beer-Lambert's law in the range of 2-20 µg/ml with correlation co-efficient of 0.999. Regression analysis was made for the slope, intercept and correlation coefficient values. The regression equations of calibration curves were y = 0.057x + 0.001 (r^2 = 0.999) at 219.8 nm for baclofen. The desirable drug release profile was optimized by analyzing the similarity with theoretical drug release profile.

***In-vitro* mucoadhesion strength studies [10, 11]**
The mucoadhesive capacity of all formulations was determined by the modified physical balance method. The apparatus consists of a modified double beam physical balance in which the right pan on lower end has been attached by a glass slide with copper wire. A glass vial of 3.8 cm diameter and 2 cm height was kept in a beaker filled with media 0.1N HCl of pH 1.2, which was then placed below right side of the balance. Goat stomach mucosa was used as a model membrane and media 0.1N HCl was used as moistening fluid. The goat stomach mucosa was obtained from local slaughter house. The underlying mucous membrane was separated using surgical blade and wash thoroughly with buffer media 0.1N HCl. The thickness of stomach mucosa employed in experiments ranged from 1.3 to 2.5 mm. It was then tied to a glass slide and this slide was fixed over the protrusion in the glass vial using a thread and two sided adhesives. The glass block was then kept in a glass beaker. The beaker was filled with 0.1N HCl up to the upper surface of the goat stomach mucosa to maintain stomach mucosa viability during the experiments. The one side of the tablet was attached to the glass slide of the right arm of the balance and then the beaker was raised slowly until contact between goat mucosa and mucoadhesive tablet was established and additional weight, to make the right side weight equal with left side pan. A preload of 5 g was placed on the slide for 5 min (preload time) to establish adhesion bonding between mucoadhesive tablet and goat stomach mucosa. The preload and preload time were kept constant for all formulations. Next, water was dropped into the beaker at a speed of 2 ml·min^{-1} until the tablet and membrane were pulled apart by the gravity of water as shown in figure 1. The addition of water was stopped when mucoadhesive tablet was detached from the goat stomach mucosa. The beaker containing water was weighed and the minimum detachment force was calculated accordingly. The detachment force in gram (g) was transformed into Newton (N, force of adhesion) by using a conversion factor (1g=0.009806N). The test was performed at room temperature, and the mean of three measurements was used as the mucoadhesive strength of the tablets.

Fig 1: Modified physical balance for mucoadhesion strength and *in-vitro* wash off test

***In-vitro* gastro retention time**

The *ex-vivo* mucoadhesion time studies were performed after application of tablets on freshly cut goat stomach mucosa. The mucosa was fixed on a glass slide using double sided adhesive and one side of glass slide was fixed to thread whose another end was fixed with the arm of tablet disintegration test apparatus [12]. A side of each tablet was wetted with 50 µl dissolution fluid and was attached to the mucosa by applying a light force with a fingertip for 20 seconds. The beaker was filled with 900 ml of simulated gastric fluid and kept at 37˚C; after 2 minutes the slide was placed in a beaker and the apparatus was started. Care was taken that while up and down motion of the arm tablet should remain in a medium. The adhesion behavior and mucoadhesive retention time of tablets were monitored until a complete detachment or dissolution occurred.

Stability studies

The selected formulations were packed in blisters with PVC with aluminium foil. ICH specifies the length of study and storage conditions for accelerated testing**:** 40˚C ± 2˚C / 75 % RH ± 5 % for 3 months using REMI environmental chamber SGM-6S, Mumbai, India. At specified time intervals, of 0, 1, 2 and 3 months for accelerated testing condition, the samples were taken and evaluated for their drug content, hardness, friability, mucoadhesive strength and drug release characteristics and compared with the initial values before storage [13].

RESULTS AND DISCUSSION:

Extended-release dosage forms with prolonged residence times in the stomach are highly desirable for drugs with narrow absorption windows, stability problems in the intestinal or colonic environments, locally acting in the stomach, and poor solubility in the intestine [12]. In alleged cases of incompatibility, IR spectrum of pure drug is compared with that of the drug-excipient mixture and pure excipient. Excipients are believed to be as inert substance but they can have considerable impact on ultimate pharmacological availability of drug substances when added to a formulation. The magnitude of this effect depends on the physiochemical characteristics of the drug and quantity and properties of the excipients [14]. Studies of drug-excipient compatibility represent an important phase in the preformulation stage of the development of solid dosage forms. The occurring interactions between drug(s) and excipients are discovered and proved by IR spectroscopy with the following important characteristics: appearance of new IR absorption band(s), broadening of band(s), and alteration in intensity [15]. The IR spectra for pure baclofen and its formulations with various polymers and other excipients are taken to establish the physical characterization of drug and its formulations (figure 2).

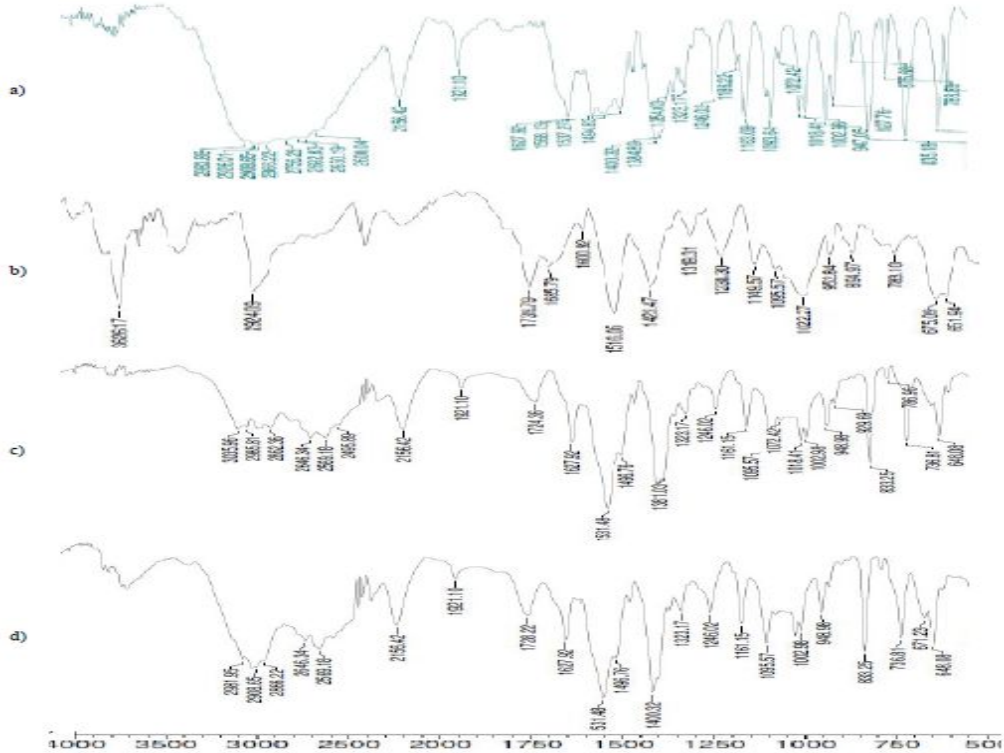

Fig 2: FT-IR spectrum of a) BCLF, b) BCLF-HEC-XNG, c) BCLF-HEC-XNG-PEG-DCP physical mixture and d) BCLF blend of formulation

Chemically, baclofen is β-(Amino methyl)-4-chlorobenzenepropanoic acid. The prominent peaks of the baclofen pure drug were shown at 1093.64cm^{-1} (due to -C-Cl), 1537.27cm^{-1} (due to -COOH), and 1627.92 cm^{-1} (due to –NH_2). These prominent peaks of drug were also present in the IR spectrum of physical mixture and its formulation blend. From this, it clearly indicates that the drug was not interacted with the polymers used in the formulations. It means that the drug remains in the same normal form in its pure state and after its formulations.

DSC thermo gram provides both qualitative and quantitative information about the physicochemical state of the drug present in formulation. The DSC thermograph of the pure drug, HEC, physical mixture (1:1) and combination formulation were obtained (figure 3). The thermograph of pure baclofen showed a melting endothermic peak at 216.27°C. The thermograph of the drug-loaded formulation showed two different peaks related to baclofen (211.42°C) and HEC (80.58°C). The endothermic peak of physical mixture of the drug and polymers is slightly decreased to 210.85°C. It was found that the endothermic peaks of physical mixtures of the drug with excipients reflected the characteristic features of baclofen alone. Thus, it was thought to indicate that there was no evidence of interactions between baclofen and the used excipients. The DSC analysis of the drug alone elicited an endothermic peak very close to the reported value of baclofen's melting point [16].

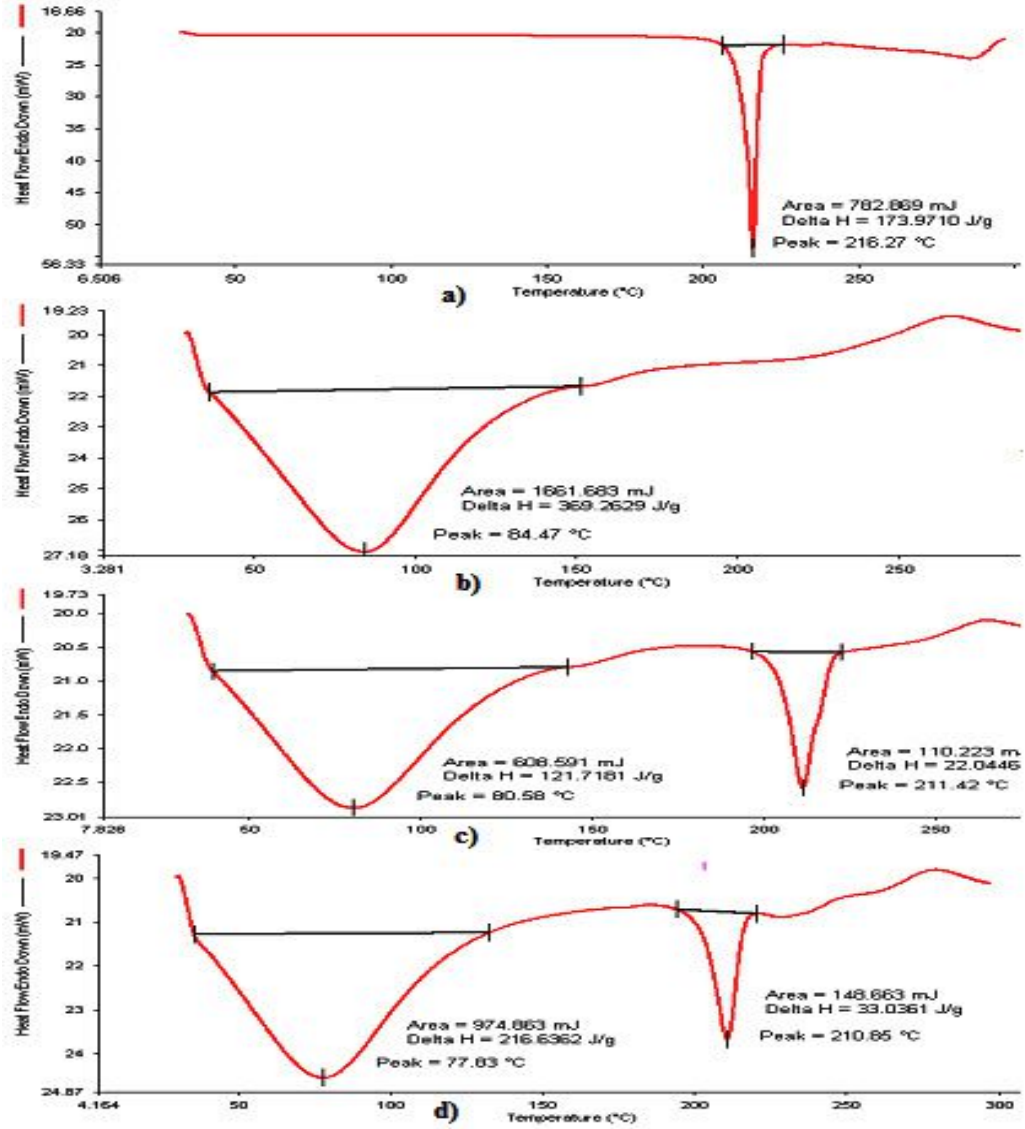

Fig 3: DSC thermogram of a) pure drug, b) HEC, c) physical mixture and d) formulation blend

Preliminary batches of BCLF mucoadhesive tablets were prepared by a wet granulation method using mucoadhesive polysaccharide and rate controlling polymer xanthan gum, microcrystalline cellulose, dicalcium phosphate as filler, talc and magnesium stearate as glidant, lubricant and water as granulating fluid. The batch size was laboratory scale (100 tablets). The granules evaluation is an investigation of physical properties of a drug along with excipients. It is the first step in the rational development of dosage forms. The results of precompression parameters and in-process quality control (IPQC) of batches are shown in table 2. The overall objective of the evaluation of granules was to generate useful information to the formulation in developing stable and bioavailable dosage form. The bulk and tapped density give an insight on the packaging and arrangement of the particles and the compaction profiles of the material. The bulk and tapped density of prepared granules were found to be in the range of 0.42 – 0.49 and 0.47 – 0.52 respectively. Carr's compressibility index and hausner ratio are determined to be less than 14.28% and <1.17 for all formulations which indicates that the prepared granules of all the formulations have good free flow property. The tablets were observed visually for their physical appearance such as color and texture. All the formulations were found good appearance, having white color and smooth surface texture. Thickness of all tablet formulations was found in between 2.13-2.83 mm and diameter of the tablets was found to be about 7.09 to 8.03 mm. The results of all these were in compliance with the specification of I.P are indicated in table 3.

Table 2: Pre-compression studies of BCLF preliminary batches

Preliminary Batch	Bulk density (gm/cc)	Tapped density (gm/cc)	Carr's index	Hausner's ratio	Angle of Repose (°) (mean ± SD)
FH1	0.48± 0.14	0.51± 0.02	4.0± 0.11	1.04± 0.01	22±0.12
FH2	0.46± 0.01	0.49± 0.01	6.12± 0.12	1.07± 0.03	25±0.09
FH3	0.49± 0.12	0.52± 0.12	5.76± 0.09	1.06± 0.04	26±0.14
FH4	0.44± 0.05	0.48± 0.07	8.33± 0.05	1.09± 0.07	27±0.12
FH5	0.42± 0.08	0.48± 0.08	12.5± 0.06	1.14± 0.02	26±0.18
FH6	0.43± 0.03	0.47± 0.02	8.51± 0.08	1.09± 0.04	24±0.14
B1	0.42 ± 0.01	0.49 ±0.03	14.28± 0.22	1.17± 0.02	27±0.15
B2	0.44 ± 0.08	0.48 ± 0.04	8.33± 0.50	1.09± 0.02	28±0.45
B3	0.42 ± 0.04	0.49 ± 0.11	14.28±0.78	1.17±0.09	30±0.11
B4	0.47 ± 0.11	0.49 ± 0.02	4.08± 0.20	1.04± 0.04	26±0.05
B5	0.42 ± 0.12	0.48 ± 0.12	12.5± 0.02	1.14± 0.08	26±0.18
B6	0.43 ± 0.05	0.49 ± 0.02	12.24± 0.22	1.14± 0.12	28±0.09

(Average ± Standard deviation, n=3)

Table 3: In process quality control (IPQC) test for preliminary batches of BCLF

Batches	Diameter (mm) ± S.D	Thickness (mm) ± S.D	Hardness (Kg/cm2) ± S.D	Friability (%)± S.D	Weight variation ± S.D	Content uniformity (%) ± S.D
FH1	7.09± 0.06	2.13±0.1	2.87± 0.12	0.87± 0.1	148.25± 0.18	97.5± 0.35
FH2	8.01± 0.03	2.43± 0.09	4.2± 0.11	0.78± 0.13	149.15± 0.12	99.31± 2.10
FH3	8.02± 0.06	2.43± 0.1	3.2±0.06	0.78± 0.04	151.5± 0.65	100.42± 1.03
FH4	8.03± 0.02	2.72±0.02	2.97± 0.1	0.52± 0.03	148.25±0.42	98.5± 1.15
FH5	8.02± 0.02	2.6± 0.04	3.67± 0.12	0.65± 0.12	150.0± 0.6	99.12± 0.20
FH6	8.03± 0.04	2.72± 0.1	2.86± 0.04	0.52± 0.07	151± 0.2	100.3± 1.2
B1	8.01± 0.06	2.33± 0.01	3.87± 0.14	0.77± 0.10	150.25± 0.78	96.31± 2.35
B2	8.01± 0.03	2.83± 0.11	4.1± 0.15	0.75± 0.12	150.35± 0.50	100.31± 3.30
B3	8.02± 0.06	2.53± 0.01	4.02± 0.06	0.68± 0.02	150.5± 0.73	101.42± 1.73
B4	8.03± 0.02	2.62± 0.02	3.97± 0.12	0.5± 0.02	150.35± 0.58	98.03± 1.65
B5	8.02± 0.02	2.6± 0.01	4.67± 0.10	0.75± 0.16	150.45±0.62	97.42± 2.20
B6	8.03± 0.04	2.82±0.03	3.86± 0.02	0.5± 0.08	150± 0.18	98.03± 1.25

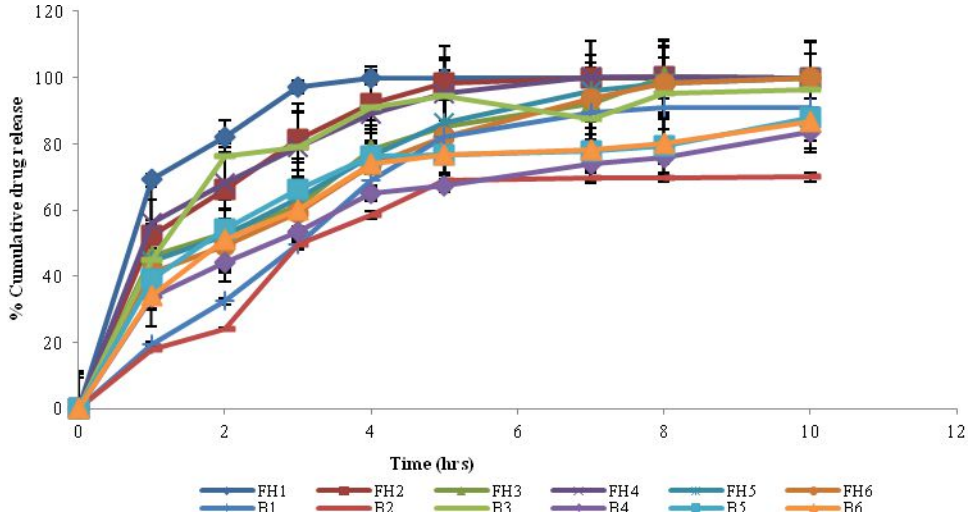

Figure 4: *In-vitro* drug dissolution of baclofen formulations

The formulations of BCLF showed hardness value in the range of 2.8 to 4.67 kg/cm^2. The pharmacopoeial limits of deviation for tablets of 150 mg are ± 7.5 % i.e. % i.e. ± 11.25 mg for BCLF. The average percentage deviation for all tablets formulations was found to be within the specified limits and hence all formulation complied with the test for uniformity of weight. Uniformity of the drug content was found the ranged from 96.03 % to 101.42 %. All the post compression parameters were found according to official limit.

Formulations containing HEC in combination with XNG were compared to explore the effect of polymers and the amount of the drug release. The baclofen was released about 100% within 8 hrs from batches FH1 to FH6. Percent of drug release at the end of 10 hrs for B1, B2, B4, B5 and B6 were 91.04±0.3%, 69.88±0.3%, 96.33±0.3%, 83.53±0.3%, 87.80±0.3 and 100.0% respectively. It was evident from the dissolution profiles that while the drug release rate was controlled, more than 82% of BCLF was released with B1, B3 and B6 while B2, B4 and B5 by the end of 5 and 10 h, respectively. In the matrices formulation, HEC was used as bioadhesive agents and XNG as prolonged release polymer. These polymers produce gel-forming matrices and in contact with gastric fluid, possess sufficient structure to form a gel layer and achieve a mucoadhesion on gastric mucous membrane. The values indicated a xanthan gum (B2) significantly retard the drug release from matrices as compare to *hibiscus esculentus* polysaccharide (B1). To deliver the drugs in a controlled manner to the stomach region, in addition to mucoadhesive requirement of release retardant in combination of different proportion to achieve maximum gastric retention time, maximum mucoadhesion strength and release retardation. *In-vitro* drug dissolution of formulation containing drug-polymer in ratio of 1:1.5, 1:2 and mucoadhesive-release retardant at 1:1, 1.5:1 and 3:1is depicted in figure 4.

B6 batch showed a sharp increase in drug release, almost 100% at 4 hours. B3 batch also showed a steep increase in drug release after 4hours which approached 96% in 10 hours. B4 batch showed a linear drug release, whereas B5 batch showed a slight increase in drug release. The results of drug release studies revealed that mucilage-gum retards the drug release for longer time periods as compared with the individual polysaccharide. This part of the study correlated with the earlier research findings. A formulation with an appropriate controlled release profile and 90% drug release over a 6–12 hours period was desired for the purpose of this study. Therefore, for this study, formulation with drug-polymer ratio 1:2 and mucoadhesive-release retardant ratio 3:1 containing 13% HEC or 7 % XNG (B4) in combination was considered most suitable for the extended mucoadhesive system. The mucoadhesive effect was studied by varying the ratio of HEC to XNG. The extended retardation of drug release observed with XNG may be attributed to the three dimensional gel network structure developed by polymer following penetration of dissolution medium into the tablet matrix. An incorporation of XNG decreased the release rate of drug because the polymer absorbs water and forms a gelatinous barrier layer at the surface of the tablet matrix. Usually, water diffusivity depends on the total concentration of viscosity-inducing agents in a system and this governs diffusion of water into matrix systems. The *in-vitro* mucoadhesive study was performed on modified physical balance

and measures the mucoadhesive strength (g) requires to detachment the tablets. The results were shown in figure 5. The acidic environment favours the presence of excess uncharged COOH groups which form stronger hydrogen bonds with water and strengthen the mucoadhesive bond. Formulation B2 was having the lowest mucoadhesive force because the XNG having a lower viscosity while formulation (B4) containing HECM and XNG shows the higher mucoadhesion force due to higher viscosity. An increase in concentration of gum increases mucoadhesive strength of the formulation. In order to increase the mucoadhesive strength of low viscosity polymer containing XNG was combined with HECM having good mucoadhesive property. From the above results it was found that polymers having high molecular weight and high viscosity exhibited higher adhesion. HECM and XNG were found to be having good mucoadhesive strength. HECM and XNG possess hydroxy and carboxy groups, respectively required for bioadhesion. Batch B4 with 13% polysaccharide and 7 % gum shows greater mucoadhesive strength. Adhesion was reported to be affected by hydration. Hydration of the mucoadhesive polymer is essential to initiate the mucoadhesive bonding process. In case of tablets applied in the dehydrated state, which is most convenient, it is essential that sufficient water is available so that rapid hydration takes place, and a flexible rubbery state occurs. The capillary force arises when water from the space between the mucosa and the polymer was taken up by a dry system. Once the bond is formed, reduction in the rate of swelling due to water uptake from the tissue surface may only prolong the association of the tablet with the mucosa. Removal of water from the underlying mucosa layer by the hydrating polymer may increase the cohesive forces of mucus; this plays a vital role in the establishment of an effective mucoadhesive bond [17]. Undoubtedly, this might be a new approach to prolong the release of such drugs. It is evident from result that in comparison with matrices formulated with xanthan gum alone, those formulated with admixtures of polysaccharides showed higher mucoadhesion.

In-vitro gastro retention time was performed for all the matrix tablet formulations (B1-B6) of baclofen. The detachment time of the formulations (B1-B6) is shown figure 5. The detachment time was found to be in the range of 113 to 363 min and B4 to B6 have range 4.63-5.63 hours, suggesting that these formulations have the sufficient mucoadhesive strength to remain intact with gastric mucosa for a long time to release the drug in a controlled manner. Formulation B4 exhibited the highest efficiency of mucoadhesion retention in 0.1 N HCL medium even at the end of 5.6 when compared with other formulations. The significantly greater mucoadhesive property of mucilage-gum matrices may be due to the presence of a certain amount of unionized carboxyl groups within polysaccharide which forms a strong gel network with the mucus glycoprotein network of the intestinal mucosa. The use of HEC to XNG was set as optimal formulation as it recorded the highest mucoadhesive bond strength. Such behaviour may be attributed to the synergistic mucoadhesive effect of HEC and XNG. The preliminary trails showed that the bioadhesion of the BCLF increases significantly with increase in HEC concentration. Higher concentrations of HEC upon exposure to the moist surfaces lowered the pH of the microenvironment which caused an increase in bioadhesion. Higher amount of HECM leads to system with good bioadhesive properties, but inefficient drug release control. On the other hand, low amount of HECM together with high amount of XNG leads to insufficient bioadhesion and the ability of formulation to release drug completely.

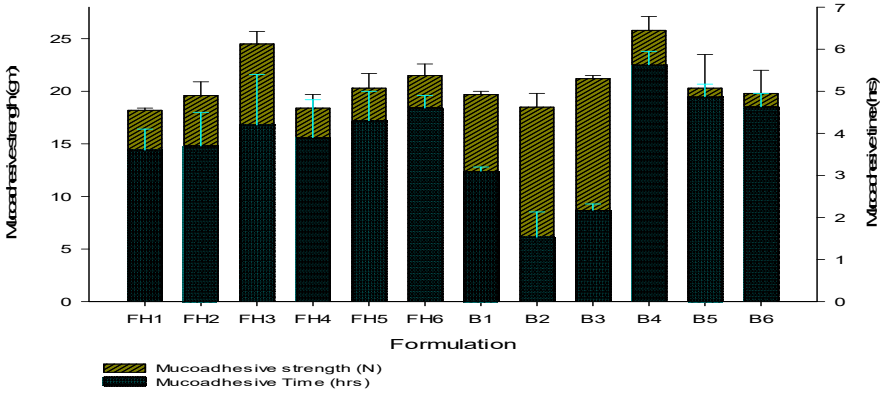

Figure 5: *Ex-vivo* mucoadhesive strength and mucoadhesive retention time of baclofen preliminary formulation

Table 4: Results of short term physical stability study

Parameter	Study Period		
	0	1 month	3 month
Hardness	3.96±0.01	3.92±0.02	4.4±0.01
Thickness	2.6±0.04	2.6±0.04	2.6±0.03
Friability	0.48±0.03	0.48±0.01	0.48±0.02
Drug Content	98.08±0.6	97.54±1	97.5±.5
Dissolution Profile	96.51±1.2	94.66±1	96.04±1.5

All the values are represented in mean±SD (n=3)

The periodic data of stability study is presented in table 4. Statistical analysis of the results, before and after conducting the stability studies for 3 months, was carried out using paired Students t-test [18]. No significant difference ($p > 0.05$) was observed in the tablet appearance, hardness or thickness. The drug dissolution profile was compared of before and after stability studies.

The optimized formulation (B4) values were found more than 50 (94.66 and 96.04 respectively after one and three months) that indicate a good similarity between both the dissolution profiles. Similarly, no significant difference was observed in the post formulation parameter. The results of stability studies indicate that the developed formulation has good stability.

CONCLUSION:

The gastroadhesive tablet of baclofen (B4) with *hibiscus esculentus* polysaccharide and xanthan gum showed good controlled release for longer time periods, mucoadhesive strength and *ex-vivo* mucoadhesion time than the other formulations and therefore, it was considered as the optimized formulation. The results of stability studies for formulations B4 revealed no change in physical appearance, hardness and drug indicating the formulation was stable. The study reveals that *hibiscus esculentus* polysaccharide could be used as an effective natural pharmaceutical mucoadhesive along with xanthan gum in the development of stable, gastroadhesive sustained release matrix tablets of baclofen.

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