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Formulation and Evaluation of Mucoadhesive Drug Delivery System of Baclofen

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ABSTRACT

The aim of the present investigation was to improve the bioavailability of baclofen by increasing the residence time of the drug by preparing gastro-retentive mucoadhesive sustained release matrix tablet. Tablets were prepared by direct compression method and evaluated for hardness, weight variation, thickness, swelling index, mucoadhesive force, mucoadhesive retention period and *in-vitro* drug release. Formulation of an optimized batch containing sodium alginate, HPMC K100M, Carbopol 974P, and ethyl cellulose was found to control the release of Baclofen for more than 12 hrs with the higher cumulative percentage of drug release. The mucoadhesive studies revealed that batch B8 and B1 found to be good mucoadhesive strength and mucoadhesive retention period. Mucoadhesive system found to be a promising approach for gastro-retentive controlled delivery of Baclofen which is capable of sustained release for 12 hours. The swelling and bioadhesion ability was found to be dependent on the composition of the polymer in the tablet.

INTRODUCTION

Baclofen, a centrally acting skeletal muscle relaxant, is found to be rapid absorption and elimination pattern and having absorption window in the upper gastrointestinal tract which may lead to low bioavailability. Baclofen on arrival to colon its absorption is found to be low, hence is difficult to formulate into a sustained release system. (1) In the present investigation, efforts have been made to increase the residence of baclofen at or above the absorption window by preparing a gastro-retentive tablet as it is stable at the gastric condition. Oral controlled release dosage systems have been developed for many years due to their significant therapeutic and commercial advantages. Many drugs, having a narrow absorption window in the upper part of the gastrointestinal tract are not considered to be the ideal candidate for such type of system. (2) Gastro retentive dosage forms are fabricated to sustained and prolong the release of drug to the stomach. Fast GI transit results in an incomplete release of drug in the absorption zone and diminishes the efficacy of the dose. From the last three decades, many approaches are used to retain the dosage form in the stomach, such as bioadhesive systems, swelling and expanding systems, and floating systems and by delayed gastric emptying approach. (3) Floating System helps to achieve increased residence time for the dosage form in the stomach and sustained the release of the drug. Dosage forms designed for mucoadhesive drug delivery should be small and flexible, high drug loading capacity, good mucoadhesive properties, smooth surface, and convenient application. The present investigation aimed to improve the bioavailability of baclofen by increasing the residence time of the drug by formulating gastro-retentive mucoadhesive sustained release matrix tablet. Different formulations of mucoadhesive Baclofen tablets were prepared using a different concentration of HPMC K100M, sodium alginate, carbopol 974P, and ethyl cellulose. (4)

MATERIALS AND METHODS:

Baclofen was obtained from Wellona pharma, Surat. Sodium alginate, HPMC K 100M, and ethyl cellulose were purchased from Loba Chem Ltd, Mumbai. Carbopol 974 P was obtained by Colourcon pharma, Goa. All other excipients were of analytical grades.

Standard Calibration curve

10 mg of Baclofen was weighed and dissolved in 10 ml of 0.1N HCl to give a solution of 1000 µg/ml concentration. From this solution, 1 ml was taken and diluted to 10 ml using

0.1N HCl to produce a stock solution of 100 µg/ml. From this stock solution, different concentrations were prepared. The absorbance of these solutions was measured at 220 nm by UV spectrophotometer. The standard curve for Baclofen is shown in the figure-1.

Table 1: Standard graph of Baclofen

S. No	Concentration (ug/ml)	Absorbance
0	0	0
1	2	0.196
2	4	0.831
3	6	1.151
4	8	1.463
5	10	1.826

Preparation of Baclofen Mucoadhesive Tablets

Baclofen mucoadhesive tablets were prepared by direct compression method as per the formula is shown in the Table-2. Baclofen was blended with the required amount of polymer and other excipients. (5) Accurately weighed quantities of the drug and polymers were taken and mixed by trituration in a glass mortar-pestle. Magnesium stearate was added to it and was properly mixed. Compression was carried out using 8 mm standard flat punches in rotary compression press.

Table 2: Formulation of mucoadhesive tablets

S. No	Ingredients	B1	B2	B3	B4	B5	B6	B7	B8	B9
1	Baclofen	25	25	25	25	25	25	25	25	25
2	HPMC K100M	90	80	70	-	-	-	60	40	20
3	Sodium alginate	-	-	-	100	80	60	20	40	60
4	Carbopol 974 P	30	30	30	30	30	30	30	30	30
5	Ethyl cellulose	10	10	10	10	10	10	10	10	10
6	Magnesium stearate	2	2	2	2	2	2	2	2	2
7	Talc	2	2	2	2	2	2	2	2	2
8	Avicel	41	51	61	31	51	71	51	51	51

Pre-Compression Parameters

1. Angle of Repose

The angle of repose of granules was determined by the funnel method. The blend was poured through a funnel until a maximum cone height (h) was obtained. The angle of repose was calculated by using the following formula.(6)

$$\mathbf{Tan\ \theta = h/r}$$

Where 'h' is the height of pile and 'r' is the radius of pile

2. Bulk Density

Bulk density (P_b) was determined by pouring the blend into a graduated cylinder. The bulk volume (V_b) and the weight of the powder (M) were determined. The bulk density was calculated by using the following formula.(7)

$$\mathbf{P_b = M/V_b}$$

Where 'M' is the Weight of powder and 'V_b' is the volume of the powder.

3. Tapped Density

The volume was measured by pouring the blend into a graduated cylinder and tapping the powder blend for around 500 times. The Tapped density was calculated by using the following formula.(8)

$$\mathbf{Pt = M/Vt}$$

Where 'M' is the Weight of powder and 'V_t' is the volume of the powder.

4. Carr's index

Carr's Index is measured using the values of bulk density and tapped density. The following equation is used to find the Compressibility Index. (9)

$$\text{Carrs index} = \frac{P_b - Pt}{Pt} \times 100$$

Where 'P_b' is the bulk density of powder and 'Pt' is the tapped density of the powder.

5. Hausner's Ratio

Hausner's ratio is an indirect index of ease of powder flow. It was calculated by the following formula. (10)

Hausner ratio = Tapped density/Bulk density

Table 3: Specifications for flow properties.

Flow Character	Carr's index (%)	Hausner's ratio	Angle of repose
Excellent	<10	1.00-1.11	25-30
Good	11-15	1.12-1.18	31-35
Fair (aid not needed)	16-20	1.19-1.25	36-40
Passable (may hang up)	21-25	1.26-1.34	41-45
Poor (must agitate/vibrate)	26-31	1.35-1.45	46-55
Very poor	32-37	1.46-1.59	56-65
Very, very poor	>38	>1.60	>66

Post-Compression Parameters

1. Weight Variation

To study weight variation, 20 tablets of each formulation were weighed using an electronic balance. The weight value of each tablet was reported in mg and the average weight of each tablet in the different formulation was calculated. (11)

2. Hardness Test

The hardness of six tablets was determined in each formulation by using a Monsanto hardness tester in kilogram (kg/cm^2) and the average hardness of each tablet was calculated. (12)

3. Friability Test

Six tablets were placed in a friabilator and subjected to100 rpm for 4 min. The initial weight and final weight of the tablets are noted. The friability was calculated by using the following formula. (13)

$$\% \text{ friability} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

4. Determination of drug content

About 40 mg of Baclofen powder was taken in 50 ml of volumetric flask diluted with 1.2 pH buffer and was shaken to dissolve the drug in the buffer. The solution was filtered through filter paper and absorbance was measured at 220 nm by UV visible spectrophotometer. (14)

5. *In-vitro* Dissolution Studies

In-vitro release of mucoadhesive buccal tablets of Baclofen was carried out using the USP II (paddle apparatus). The speed of paddle was adjusted to 50 rpm and the pH of the release medium was maintained at 1.2 pH. Samples of 10 ml were withdrawn at specific time intervals and sink condition was maintained. Then the amount of baclofen released was determined spectrophotometrically at 220 nm. (15)

6. *In-vitro* Mucoadhesive Studies

Modified Balance Method

Mucoadhesive strength of the tablet was measured on the modified physical balance, which consists of modified double beam physical balance in which the right pan was loaded with additional weight to make the right side weight equal with left side pan. Two Teflon blocks were fabricated. First Teflon block was kept in a beaker containing pH 1.2 buffers, which was then placed below the right side of the balance. The goat stomach mucosa tissue, which was procured from a local slaughterhouse, was placed in the buffer. The separation of the mucous membrane was done using a surgical blade and washed with buffer media. It was then tied over the protrusion in the Teflon block using the

thread and kept in a glass beaker. The beaker was filled with buffer media 0.1 N HCl of pH 1.2 up to the upper surface of the goat stomach mucosa to maintain stomach mucosa viability during the experiment. The one side of the prepared tablet was attached to the small Teflon block of the right arm of the balance and then the beaker was raised slowly until the contact between goat mucosa and a mucoadhesive tablet was established. (16) A preload of 10 g was placed on the small Teflon block for five minutes to establish adhesion bonding between mucoadhesive tablet and goat stomach mucosa. (17) After five minutes preload was removed from the block and counterweights were added on left side pan. The weight required to detach the tablet from the mucosa was noted as mucoadhesive strength in grams.

Force of adhesion (N) = Mucoadhesive strength X 9.81/100

Bond strength (N/m^2) = force of adhesion (N) / surface area of tablet (m^2)

Table 4: Pre compression parameters of Baclofen powder blend

S. No.	Batch	The angle of repose (θ)	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index	Hausner's ratio
1	B1	29.7	0.36	0.41	16.3	1.20
2	B2	28.6	0.36	0.42	15.2	1.18
3	B3	31.4	0.37	0.41	12.6	1.09
4	B4	32.8	0.54	0.62	13.8	1.16
5	B5	26.7	0.54	0.63	12.1	1.11
6	B6	28.7	0.52	0.62	12.6	1.19
7	B7	31.2	0.35	0.41	14.7	1.17
8	B8	31.6	0.36	0.41	13.9	1.21
9	B9	29.9	0.36	0.42	13.5	1.14

7. Tablet Adhesion Retention Period Study

The adhesion retention period of tablets was evaluated by *in-vitro* method by using the modified USP disintegration test apparatus. (18) An agar plate (1%w/w) was prepared in 0.1N HCl (pH 1.2). Aside of tablet was wetted with 50µL of 0.1N HCl and attached to the center of agar plate by applying light pressure with a fingertip for 20 sec. After 5 min the agar plate was attached to USP disintegration test apparatus and move up and down in

0.1N HCl pH 1.2.

8. Swelling Studies

The swelling index of tablets was determined in pH 1.2 buffer at room temperature by using the following equation. (19)

$$\text{Swelling index (SI)} = (Wt - W0)/W0 \times 100$$

Where Wt is the weight of the swollen tablet, W0 is the initial weight of the tablet.

RESULTS AND DISCUSSION:

All the pre-compression parameters were found to be within prescribed limits which showed good free flowing property shown in table-4. The hardness of all tablets prepared was maintained within the 6.19 to 7.23 kg/cm^2. The weight variation was found to be acceptable and within the limits. Friability results were found in the range of 0.23 to 0.47 % that is less than 1%. The drug content was found to be more than 97 % shown in Table – 5. The prepared mucoadhesive tablets of all the formulations studied, exhibited a controlled pattern of drug release up to 12 hrs.

Drug release from the formulation B2 and B3 containing a different concentration of HPMC K100M was found to be sustained as compared to B1. In the tablets of HPMC K100M, a hydrophilic swellable polymer, a retarded drug release was shown. Increased concentrations of HPMC K100M caused a larger amount of gel formation. Gel layer thus formed increases the diffusion path length of the drug, consequently controlling drug release by diffusion through the gel as well as erosion of the gel barrier. Its viscous nature also influences the diffusion coefficient of the drug. As a result, drug release was found to be decreased as the amount of HPMC K100M was increased.

In-vitro drug release from the formulation containing sodium alginate, ethyl cellulose and carbopol 974P containing a different concentration of sodium alginates as a polymer is given in Fig-2. It was observed that as the concentration of polymer increases the drug release was found to be more sustained. Formulation B6 showed sustained drug release as compared to B5 & B4. This result was in agreement with earlier reported studies which have demonstrated that higher water soluble drugs are released significantly faster in the simulated gastric fluid than in simulated intestinal fluid, however, due to hydration of

alginate, a hydro colloidal layer of high viscosity is produced. This makes up a diffusion barrier decreasing the migration of drug across it.

Formulation B8 exhibited sustained drug release as compared to B7 & B9. Mucoadhesive strength was observed to be increased with an increase in the concentration of polymer i.e. HPMC K100M and sodium alginate. The polymer swells readily when they come in contact with a hydrated mucous membrane. The water sorption lowers the glass transition temperature below ambient conditions, and polymers become increasingly rubbery due to, increased mobility of the polymer chains.

Increase in the amount of polymer can provide more adhesion sites and polymer chains for interpenetration into the mucin, resulting in the increasing the mucoadhesive strength. All the formulated mucoadhesive tablets were found to be stable throughout the period of swelling, without any disintegration.

It was observed that the percent swelling indices of all the formulated mucoadhesive tablets were found to be good, but when compared, batch B1 was found to exhibit highest percent swelling index which may be due to the high concentration of HPMC K100M. HPMC K100M swells to a large extent upon contact with water and leads to greater gel formation and thus forms a gelatinous barrier which sustained the drug release.

Table 5: Post compression parameters of Baclofen tablets

S. No.	Batch	Weight variation (mg)	Hardness (Kg /cm)	Friability (%)	Drug content (%)	The swelling index after 12 hrs time (%)
1	B1	202.4	6.70	0.47	97.11	180
2	B2	203.1	6.48	0.33	98.33	160
3	B3	204.3	6.82	0.41	98.54	140
4	B4	204.2	7.22	0.31	98.32	135
5	B5	204.5	7.23	0.23	99.52	120
6	B6	205.2	7.04	0.35	99.71	110
7	B7	204.3	6.59	0.23	96.53	140
8	B8	205.3	5.98	0.37	99.21	120
9	B9	204.1	6.19	0.34	99.34	100

Table 6: *In-vitro* drug release of Baclofen tablets

S. No.	Time (hrs)	B1	B2	B3	B4	B5	B6	B7	B8	B9
1	0	0	0	0	0	0	0	0	0	0
2	1	12.43	13.47	14.57	13.64	15.67	14.42	14.55	15.43	14.58
3	2	28.54	26.45	27.51	28.57	29.31	30.21	30.24	30.62	31.24
4	4	33.21	32.64	33.54	34.29	36.27	37.25	35.64	40.12	40.12
5	6	48.21	46.12	48.12	49.28	51.61	52.45	51.48	51.34	50.29
6	8	58.34	57.31	59.44	61.27	60.28	61.28	60.28	62.54	61.08
7	10	68.14	66.54	67.12	68.57	69.47	70.65	70.69	70.12	71.25
8	12	74.21	72.19	76.24	77.29	78.22	79.58	79.32	81.63	79.25

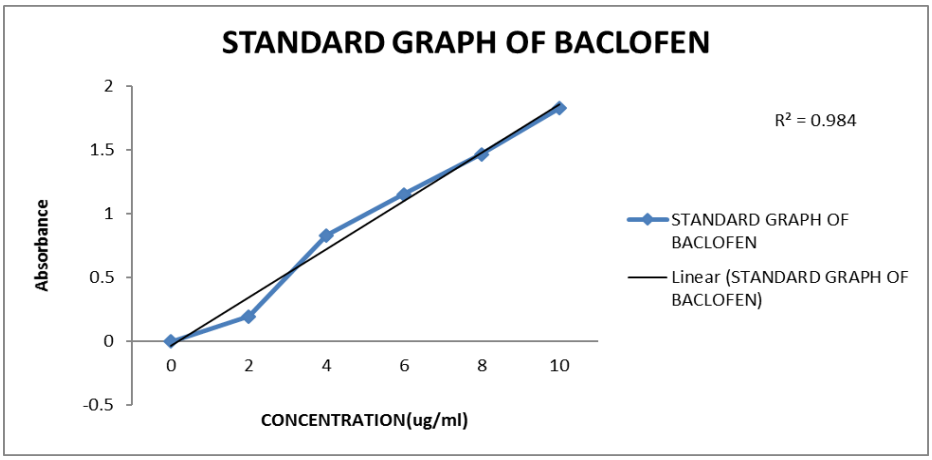

Fig-1: Standard graph of Baclofen

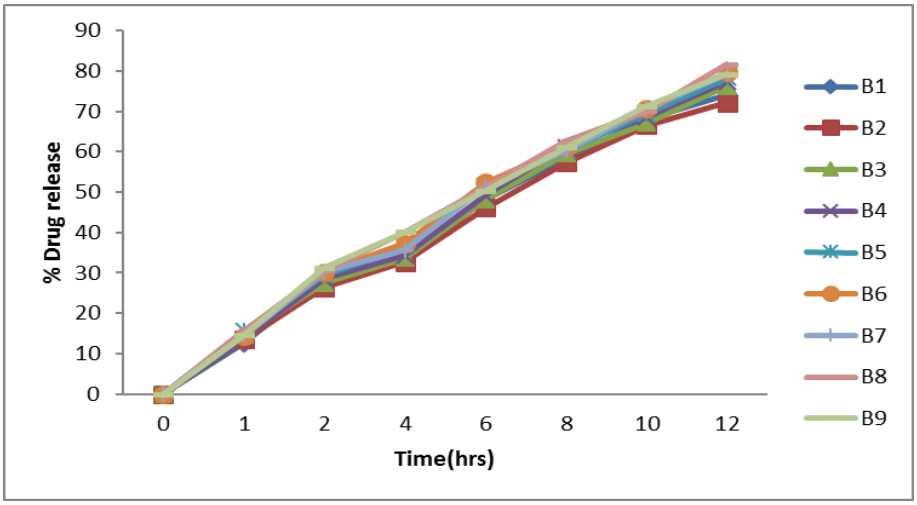

Fig-2: *In-vitro* drug release of Baclofen

CONCLUSION:

Mucoadhesive tablets were capable of sustained release of Baclofen up to 12 hours. The swelling and bio- adhesion ability was dependent on the composition of the polymer in the tablet. Among the entire formulation, batch B8 containing HPMC K100M, sodium alginate, carbapol-974P & ethyl cellulose showed good swelling, mucoadhesion property along with best drug release profile. Thus the residence time of baclofen can be increased by preparing gastro-retentive tablet for effective treatment.

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CONFLICT OF INTEREST:

No conflict of interest was associated with this work.

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