



Development and characterization of stomach specific 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 gastroretentive mucoadhesive sustained release matrix tablet. Tablets were prepared by direct compression technique and evaluated for hardness, weight variation, thickness, content uniformity, swelling index, mucoadhesive force, mucoadhesive retention period and in vitro drug release. Formulation B8, containing sodium alginate, HPMC K100M, Carbopol 974P and ethyl cellulose was found to control the release of Baclofen for more than 12 hrs with cumulative percentage of drug release 70.79 %. The mucoadhesive studies revealed that batch B8 and B1 found to be good mucoadhesive strength and mucoadhesive retention period. For all formulations, kinetics of drug release from tablet followed by Matrix and Korsmeyer Peppas model, which states that the release of might follow Non-Fickian diffusion as predominant mechanism of drug release. Mucoadhesive system found to be promising approach for gastro retentive controlled delivery of Baclofen which is capable of sustaining release for 12 hours. The swelling and bioadhesion ability were found to be dependent on the composition of the polymer in the tablet.

Keywords: Baclofen; Mucoadhesive tablets; HPMCK 100M; Sodium alginate; ethyl cellulose.

1. INTRODUCTION

Baclofen, a centrally acting skeletal muscle relaxant, is found to be rapid absorption and elimination pattern and having absorption window in upper gastrointestinal tract which may lead to low bioavailability (Ahuja 1985, Devis 2005). Baclofen on arrival to colon its absorption is found to be low, hence is difficult to formulate in to sustained release system. In the present investigation efforts have been made to increase the residence of baclofen at or above the absorption window by preparing gastroretentive tablet as it is stable at gastric condition (Jivani 2009).

Oral controlled release dosage systems have been developed from many years due to their significant therapeutic and commercial advantages (Pawar et al., 2007). 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 (Rajput et al., 2010). Gastro retentive dosage forms are fabricated to sustain and prolong the release of drug to the stomach (Mohamed et al., 2009). Fast GI transit results in incomplete release of drug in the absorption

zone and diminishes the efficacy of the dose (Iannuccelli et al., 1998). From last three decades, many approaches are used to retain the dosage form in stomach, such as, bioadhesive systems (Santus 1997), swelling and expanding systems (Deshpande et al., 1996, Deshpande et al., 1997) floating systems (Menon et al 1994, Whitehead et al., 1998), and by delayed gastric emptying approach (Singh et al., 2000).

Floating System helps to achieve increased residence time for the dosage form in stomach and sustained the release of 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 (Boddupalli et al., 2010).

The present investigation aimed to improve the bioavailability of baclofen by increasing the residence time of the drug by formulating gastroretentive mucoadhesive sustained release matrix tablet. Different formulations of mucoadhesive Baclofen tablets were prepared using different concentration of HPMCK 100M, sodium alginate, carbopol 974P, ethyl cellulose

2. MATERIALS AND METHODS

Baclofen was obtained as gift sample from unicare remedies, Baroda. Sodium alginate, HPMC K 100M and ethyl cellulose were purchased from LobaChemie Ltd, Mumbai. Carbopol 974 P was obtained by Colourcon, Goa. All other excipients were of analytical grades.

2.1 Drug Excipient Compatibility Study

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Table 1: Formulation of Baclofen Mucoadhesive Tablet

S.No.	Batch Ingredients	B1	B2	B3	B4	B5	B6	B7	B8	B9
1	Baclofen	25	25	25	25	25	25	25	25	25
2	HPMCK 100M	90	80	70	-	-	-	60	40	20
3	Sodium alginate	-	-	-	100	80	60	20	40	60
4	carbopol 974P	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 (MCC)	41	51	61	31	51	71	51	51	51

Fourier transform infrared Studies (FTIR)

To investigate possible interaction between drug and polymers, the FTIR spectra of pure baclofen and its physical mixtures (1:1) with sodium alginate, HPMC K100M, Ethyl cellulose and carbopol 974P, were studied. The samples were prepared as KBr discs, compressed under pressure of 10 tons/ nm². The selected wave number range was from 400-4000 cm⁻¹ and spectra were recorded (JASCO-5300) (Patel et al., 2014).

2.2 Preparation of Baclofen Mucoadhesive Tablets

Baclofen mucoadhesive tablets were prepared by direct compression method as shown in the Table 1. Baclofen was blend with required amount of polymer and other excipients. Accurately quantities of the drug and polymers were weighed 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 press and weight of the tablet was adjusted to 200 mg (Buddhadev et al., 2013)

2.3 Evaluation of Baclofen Mucoadhesive Tablets

2.3.1 Pre-Compression Studies

2.3.1.1 Angle of Repose

The angle of repose of granules was determined by the funnel method (Sankar et al., 2013). The blend was poured through a funnel until a maximum cone height (h) was obtained. The angle of repose was calculated using the following formula:

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

2.3.1.2 Bulk Density

Bulk density (P_b) was determined by pouring blend into a graduated cylinder. The bulk volume (V_b) and weight of the powder (M) was determined. The bulk density was calculated as:

$$P_b = M/V_b$$

2.3.1.3 Tapped Density

The volume was measured by tapping the powder for around 500 times. (Roy et al., 2013). The Tapped density was calculated as:

$$Pt = M/Vt$$

2.3.1.4 Carr's compressibility index

Carr's Index is measured using the values of bulk density and tapped density (Abdelkader 2008). The following equation is used to find the Compressibility Index,

$$I = V_0 - Vt/V_0 \times 100$$

2.3.1.5 Hausner's Ratio

Hausner ratio is an indirect index of ease of powder flow (Abdelkader 2008). It was calculated by the following formula:

$$\text{Hausner ratio} = \text{Tapped density/Bulk density}$$

2.3.2 Post-Compression Studies

2.3.2.1 Weight Variation

To study weight variation, 20 tablets of each formulation were weight using an electronic balance. Weight values were reported in mg. mean and SD were calculated (Abdelkader 2008).

2.3.2.2 Hardness Test

The hardness of six tablets was determined using a Monsanto hardness tester in kilogram (kg/cm²) and reported in Mean and SD were calculated (Roy et al., 2013).

2.3.2.3 Friability Test

Six tablets were placed in a friabilator (Electrolab friabilator-USP, Model No. EF-1W) and subjected to 100 rotations in 4 min, dedusted and reweighed. The friability was calculated as the percent weight loss.

2.3.2.4 Thickness

The thickness of the Five tablets were determined using a digital caliper (ASAHI, India). (Roy et al., 2013).

2.3.2.5 Determination of drug content

About 40 mg of Baclofen powder was taken in 50 mL volumetric flask, diluted with 1.2 pH buffer and was shaken to dissolve the drug in buffer. The solution was filtered through 0.45µ membrane filter paper and absorbance was measured at 220 nm (Patel et al., 2014).

2.3.2.6 In Vitro Dissolution Studies

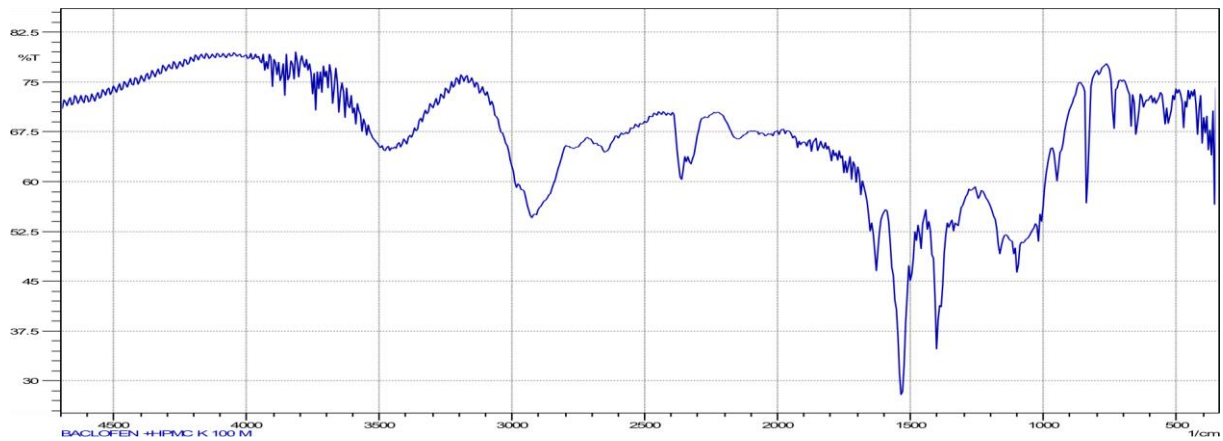


Figure 1: FTIR of HPMC K100M + Baclofen

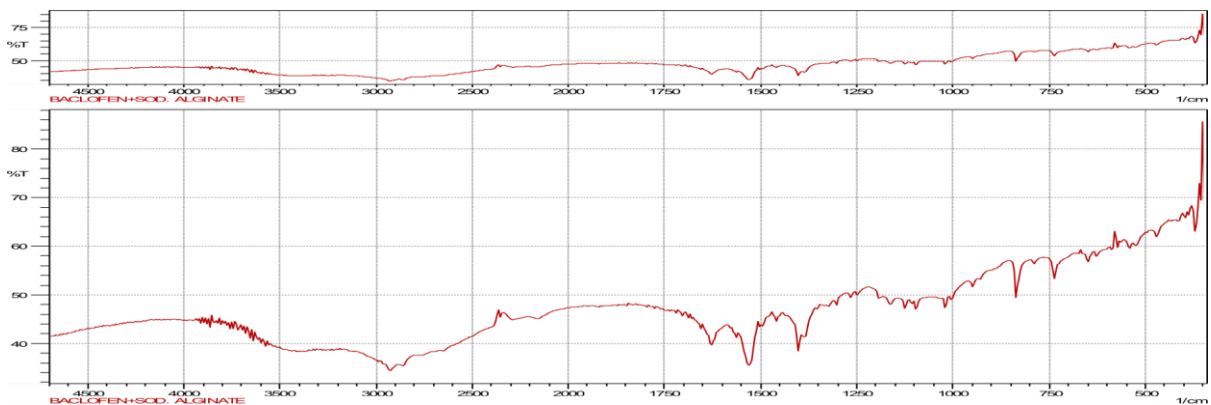


Figure 2: FTIR of Sodium Alginate+ Baclofen

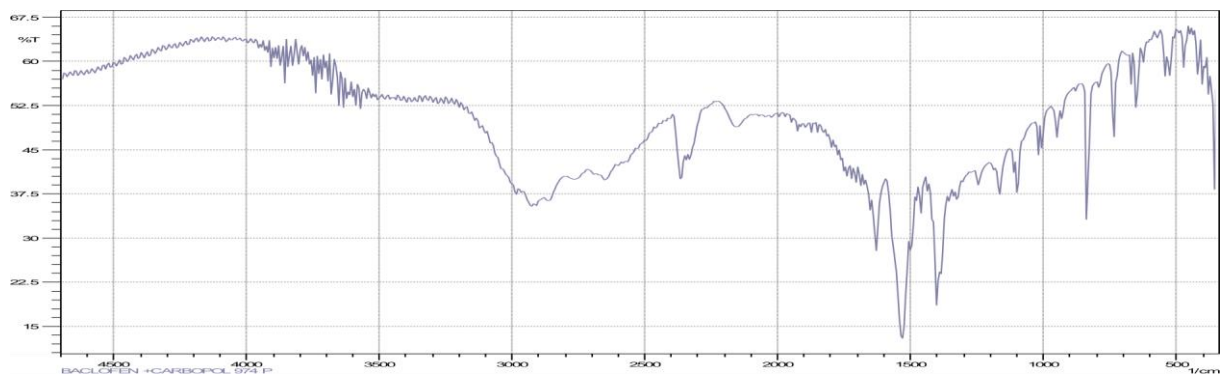


Figure 3: FTIR of Carbopol974P+Baclofen

In vitro release of mucoadhesive buccal tablets of Baclofen was carried out using the USP II (paddle apparatus). The rotation speed was 50 rpm and the pH of the release medium was maintained at pH 1.2. Samples (10 ml) were withdrawn at specific time intervals and sink condition was maintained. Then amount of baclofen released was determined spectrophotometrically at 220 nm (Paul et al., 2012).

2.3.3 *In Vitro* Mucoadhesive Studies

2.3.3.1 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 beaker containing pH 1.2 buffer, which was then placed below right side of the balance. The goat stomach mucosa tissue, which was procured from local slaughter house, was placed in buffer. The separation of mucous membrane was done using surgical blade and washed with buffer media. It was then tied over the protrusion in the teflon block using the thread and kept in glass beaker. The beaker was filled with buffer media 0.1 N HCl of pH 1.2 up to upper surface of goat stomach mucosa to maintain stomach mucosa viability during the experiment (Rajput et al., 2010, Nayak et al., 2010)

The one side of the prepared tablet was attached to the small Teflon block of the right arm of the balance and

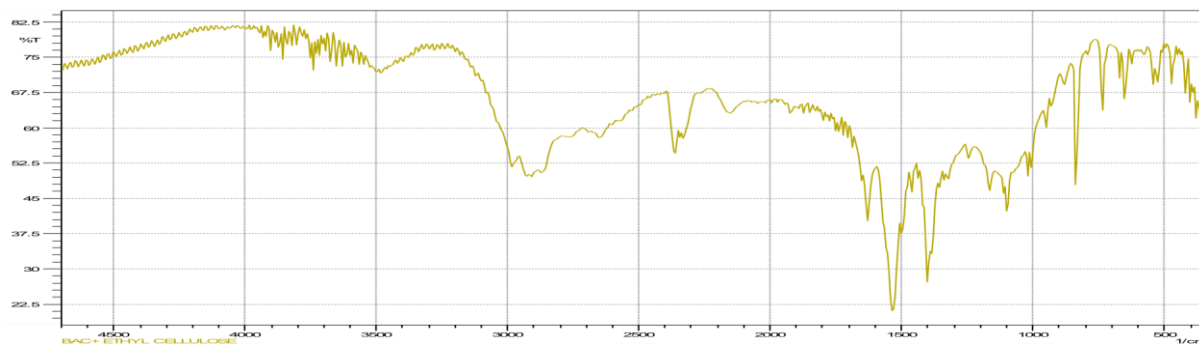


Figure 4: FTIR of Ethyl Cellulose+ Baclofen

Table 2: Pre-compression Parameters

Batch	Bulk density (g/cm ³)	Tapped density (g/cm ³)	Carr's index	Hausners ratio	Angle of repose (θ)
B1	0.360±0.5	0.402±0.18	16.034 ± 0.191	1.203 ± 0.008	29 ± 0.75
B2	0.368±0.20	0.413±0.15	15.234±0.123	1.187 ± 0.019	28 ± 0.65
B3	0.375±0.25	0.418±0.20	12.67±0.142	1.091 ± 0.021	31 ± 0.91
B4	0.543±0.25	0.627±0.28	13.891±0.111	1.182 ± 0.009	32 ± 0.86
B5	0.548±0.25	0.631±0.26	12.141±0.321	1.115 ± 0.027	26 ± 0.72
B6	0.520±0.30	0.632±0.30	12.678±0.110	1.185 ± 0.013	28 ± 0.71
B7	0.358±0.22	0.419±0.16	14.176±0.234	1.172 ± 0.014	31 ± 0.65
B8	0.361±0.24	0.420±0.14	13.974±0.248	1.211 ± 0.017	31 ± 0.25
B9	0.362±0.21	0.422±0.12	13.764±0.222	1.141 ± 0.021	29 ± 0.95

then the beaker was raised slowly until the contact between goat mucosa and mucoadhesive tablet was established. A preload of 10 g was placed on the small Teflon block for five mins to establish adhesion bonding between mucoadhesive tablet and goat stomach mucosa. After 5mins preload was removed from the block and counter weights were added on left side pan. The weight required to detach the tablet from the mucosa was noted as mucoadhesive strength in grams.

$$\text{Force of adhesion(N)} = \text{Mucoadhesive strength} \times 9.81/100$$

$$\text{Bond strength (N/m}^2\text{)} = \text{force of adhesion(N)}/\text{surface area of tablet(m}^2\text{)}$$

2.3.3.2 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. An agar plate (1%w/w) was prepared in 0.1N HCL (pH 1.2). A side of tableted was wetted with 50µL of 0.1N HCL and attached to the center of agar plate by applying light pressure with finger tip 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. The retention period of tablet on the plate was visually noted (Tadros 2010, Nakamura et al., 1996).

2.3.3.3 Swelling Studies

The swelling index of tablets was determined in pH 1.2 buffer at Room temperature The by the following equation (Rajput et al., 2010, Nayak et al., 2010).

$$\text{Swelling index (SI)} = (\text{Wt} - \text{W}_0)/\text{W}_0 \times 100$$

3. RESULTS AND DISCUSSION

3.1 Drug- Excipient Interaction

FTIR spectrum observed exhibited no significant difference thus it was suggested that there was no interaction between the Baclofen & HPMC K100M, Sodium Alginate, Ethyl Cellulose & Carbapol-974P (Fig.1-9).

3.2 Pre-compression parameter

All the pre compression parameters were found to be within prescribed limits which showed good free flowing property (Table no 2)

3.3 Post-compression parameter

The mean thickness was (n=3) ranged from 3.65±0.471mm to 3.98±0.027mm. Diameter of the tablet was found to be in the range of 7.96±0.064mm to 8.02±0.064mm. The hardness of all tablets prepared was maintained within the 6.11±0.473 kg/cm² to 7.23±0.188 kg/cm². The weight variation was found to be acceptable and within the limits. (Table no 3). Friability results were found in the range of 0.235±0.060 to 0.470±0.117% that is less than 1%. The drug content was found to be more than 97.11±1.231%. (Table no. 4).

3.4 In-Vitro Drug Release Study

The prepared mucoadhesive tablets of all the formulations studied, exhibited a controlled pattern of drug release up to 12 h.

Drug release from the formulation B2 and B3 containing different concentration of HPMC K100M was found to be sustained as compared to B1 (Fig. 5). In the tablets of

Table 3: Physical properties of mucoadhesive tablet

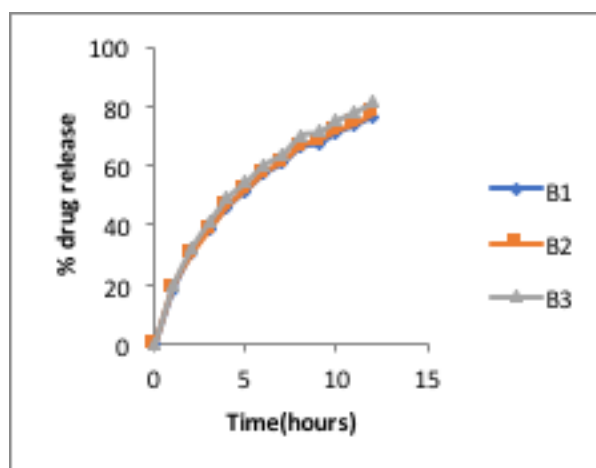
S.No.	Formulation Code	Diameter* (mm)	Thickness* (mm)	Hardness* (Kg/cm ²)	Weight Variation (g) [#]
1	B1	8.02 ± 0.01	3.95 ± 0.015	6.70 ± 0.626	0.202 ± 0.004
2	B2	8 ± 0.02	3.80 ± 0.125	6.48 ± 0.342	0.203 ± 0.0039
3	B3	8 ± 0.026	3.98 ± 0.027	6.82 ± 0.208	0.204 ± 0.0037
4	B4	7.99 ± 0.066	3.95 ± 0.057	7.22 ± 0.176	0.204 ± 0.0058
5	B5	8 ± 0.06	3.92 ± 0.04	7.23 ± 0.188	0.204 ± 0.0046
6	B6	8 ± 0.060	3.9 ± 0.036	7.04 ± 0.381	0.205 ± 0.0029
7	B7	7.96 ± 0.064	3.92 ± 0.05	6.58 ± 0.337	0.204 ± 0.0036
8	B8	8.0 ± 0.0702	3.93 ± 0.03	5.92 ± 0.0723	0.205 ± 0.0031
9	B9	8.02 ± 0.064	3.65 ± 0.471	6.11 ± 0.473	0.204 ± 0.0028

Table 4: Physical properties of Mucoadhesive tablet

S.No.	Formulation Code	% Friability	% Drug Content
1	B1	0.470±0.117	97.11±1.231
2	B2	0.337±0.117	98.33±1.391
3	B3	0.405±0.202	98.54±0.986
4	B4	0.302±0.173	98.65±1.245
5	B5	0.235±0.060	99.34±1.298
6	B6	0.336±0.153	99.71±0.568
7	B7	0.236±0.118	96.98±1.375
8	B8	0.371±0.058	99.23±1.318
9	B9	0.337±0.153	99.34±0.271

HPMC K100M, a hydrophilic swellable polymer, a retarded drug release was shown. Increased concentrations of HPMC K100M caused larger amount of gel formation (Chavanpatil et al., 2006). 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 diffusion coefficient of the drug (Chavanpatil et al., 2006, Singh et al 2006, Nafee et al., 2004). As a result, drug release was found to be decreased as the amount of HPMC K100M was increased. Drug release from the formulation containing sodium alginate, ethyl cellulose and carbopol974P, containing different concentration of sodium alginates as a polymer are given in Fig 6. 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 compare to B5 & B4. This results were in agreement with earlier reported studies which have demonstrated that higher water soluble drugs are released significantly faster in simulated gastric fluid than in simulated intestinal fluid, however due to hydration of alginate, hydrocolloidal layer of high viscosity is produced. This makes up a diffusion barrier decreasing the migration of drug across it (Hodson et al., 1995). Drug release data of formulation containing different concentration of combination of HPMC K100M and sodium alginate as a polymer is shown in fig 7. Formulation B8 exhibited sustained drug release as compare to B7 & B9. Release Kintetic studies showed that the release of maximum batches follows Matrix equation. Which state that the release of drug might follow the mixed kinetics.

It was found that all batches follow Non-Fickian diffusion ($n > 0.5$). The result in Table no. 8 shows that the release of six batches follows Matrix equation and remaining three batches follows Korsmeyer-Peppas equation which states that the release of drug might follow the mixed kinetics. However, all batches follow Non-Fickian diffusion ($n > 0.5$) as projected by Korsmeyer-Peppas equation.

**Figure 5: Cumulative % drug release of mucoadhesive tablets of Formulations (B1-B3) of Baclofen containing HPMC K100M, Carbopol-974P and Ethyl Cellulose**

The results for mucoadhesive adhesion retention periods and mucoadhesive strength are presented in fig.8. From the study of mucoadhesive properties, it was observed that the mucoadhesive strength ranges from 13.13 ± 0.4726 to 21.47 ± 0.5508 g. The Mucoadhesive adhesion tranges from 41 ± 1.414 to 172 ± 2.828 min.

Thus, tablet of batches B1 and B8 show good mucoadhesion property.

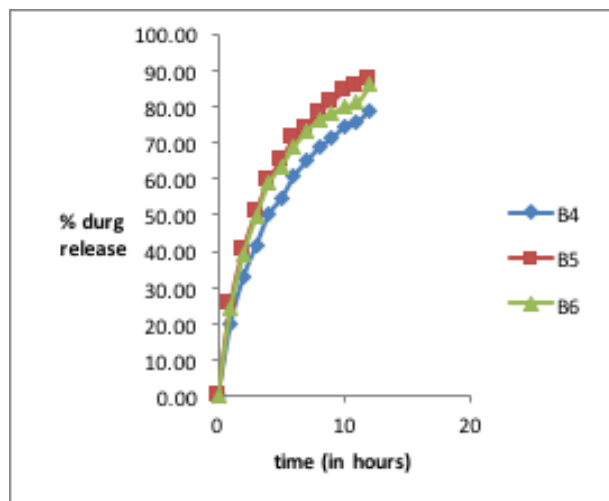


Figure 6: Cumulative % drug release from mucoadhesive tablets of Formulations (B4-B6) of Baclofen containing Sodium Alginate, Ethyl Cellulose and carbopol-974P

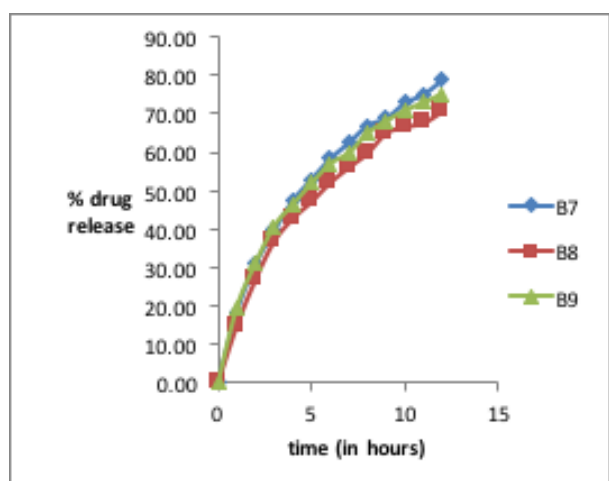


Figure 7: Cumulative % drug release of mucoadhesive tablets of Formulations (B7-B9) of Baclofen containing combination of polymer HPMC K100M, Sodium Alginate, Ethyl Cellulose and Carbopol-974P

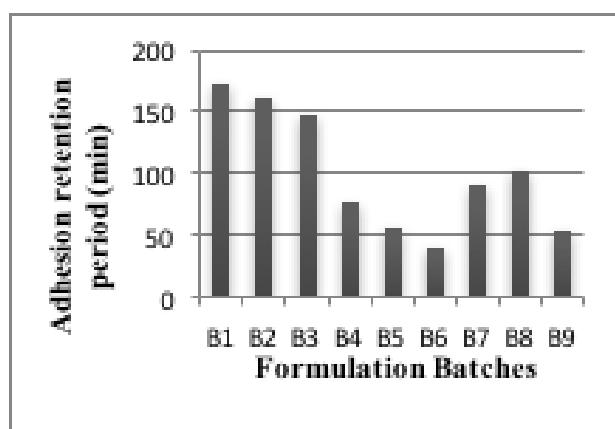


Figure 8: Adhesion Retention Periods of Formulations (B1-B9)

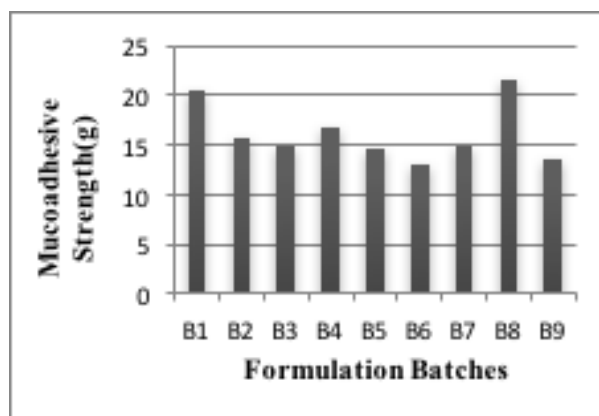


Figure 9: Mucoadhesive Strength of Formulations (B1-B9)

Mucoadhesive strength was observed to be increased with an increase in the concentration of polymer i.e. HPMC K100M and sodium alginate. The polymer swell readily when they come in contact with a hydrated mucus 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 (Varma et al., 2004).

3.6 Swelling Index

All the formulated mucoadhesive tablets were found to be stable throughout the period of swelling, without any disintegration.

As shown in fig 9, 10 and 11, 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 high concentration of HPMC K100M. HPMC K100M swells to large extent upon contact with water and leads to greater gel formation and thus forms a gelatinous barrier which sustained the drug release (Llabot et al., 2004, Varma et al., 2004).

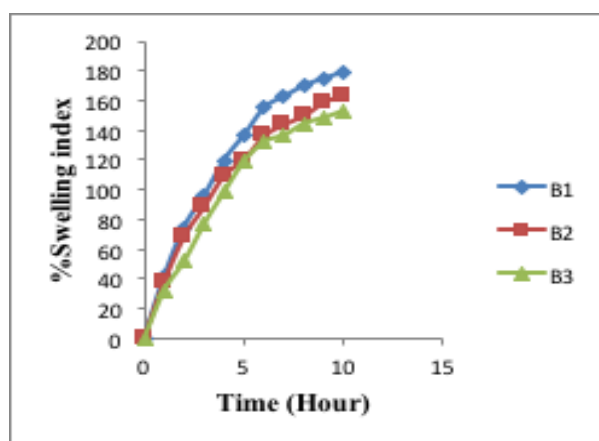


Figure 10: Percent swelling index of Batch B1, B2 and B3

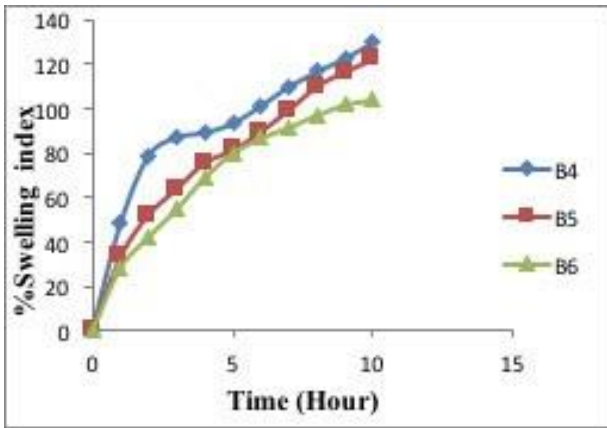


Figure 11: Percent swelling index of Batch B4, B5 and B6

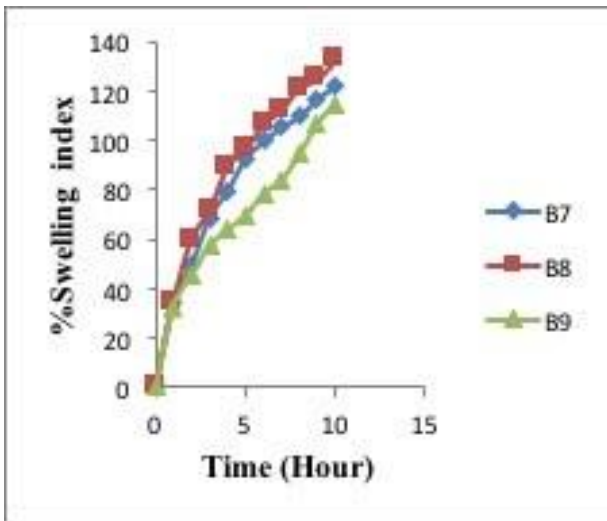


Figure 12: Percent swelling index of Batch B7, B8, and B9

4. CONCLUSION

Mucoadhesive tablets were capable of sustaining release of Baclofen up to 12 hours. The swelling and bioadhesion ability were 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 and mucoadhesion property. Thus the residence time of baclofen can be increased by preparing gastroretentive tablet for effective treatment.

5. REFERENCES

Abdelkader, H., Abdalla, O.Y. and Salem, H., 2008. Formulation of controlled-release baclofen matrix tablets II: Influence of some hydrophobic excipients on the release rate and in vitro evaluation. *Aaps Pharmscitech*, 9(2), pp.675-683.

Ahuja S., 1985 "Analytical Profiles of Drug Substances and Excipients", London, UK: Academic Press, ; 527-548.

Boddupalli, B.M., Mohammed, Z.N., Nath, R.A. and Banji, D., 2010. Mucoadhesive drug delivery system:

An overview. *Journal of advanced pharmaceutical technology & research*, 1(4), p.381.

Buddhadev, S., Odedara, B., Mahajan, T. and Buddhadev, S., 2013. Formulation and Development of Mucoadhesive Tablets of Valsartan. *International Journal of Drug Development and Research*, 5(4) pp145-155.

Chavanpatil, M.D., Jain, P., Chaudhari, S., Shear, R. and Vavia, P.R., 2006. Novel sustained release, swellable and bioadhesive gastroretentive drug delivery system for ofloxacin. *International journal of pharmaceutics*, 316(1), pp.86-92.

Chawla, G. and Bansal, A., 2003. A means to address regional variability in intestinal drug absorption. *Pharm Technol*, 27(6), pp.50-68.

Davis, S.S., 2005. Formulation strategies for absorption windows. *Drug discovery today*, 10(4), pp.249-257.

Dehghan, M. and Kha, F., 2009. Gastroretentive drug delivery systems: A patent perspective. *International Journal of Health Research*, 2(1).

Deshpande, A.A., Rhodes, C.T., Shah, N.H. and Malick, A.W., 1996. Controlled-release drug delivery systems for prolonged gastric residence: an overview. *Drug Development and Industrial Pharmacy*, 22(6), pp.531-539.

Deshpande, A.A., Shah, N.H., Rhodes, C.T. and Malick, W., 1997. Development of a novel controlled-release system for gastric retention. *Pharmaceutical research*, 14(6), pp.815-819.

Hodsdon, A.C., Mitchell, J.R., Davies, M.C. and Melia, C.D., 1995. Structure and behaviour in hydrophilic matrix sustained release dosage forms: 3. The influence of pH on the sustained-release performance and internal gel structure of sodium alginate matrices. *Journal of Controlled Release*, 33(1), pp.143-152.

Iannuccelli, V., Coppi, G., Bernabei, M.T. and Camerini, R., 1998. Air compartment multiple-unit system for prolonged gastric residence. Part I. Formulation study. *International journal of pharmaceutics*, 174(1), pp.47-54.

Jivani, R.R., Patel, C.N. and Jivani, N.P., 2009. Design and development of a self correcting monolithic gastroretentive tablet of baclofen. *Scientia Pharmaceutica*, 77(3), pp.651-668.

Llabot, J.M., Manzo, R.H. and Allemandi, D.A., 2004. Drug release from carbomer: carbomer sodium salt matrices with potential use as mucoadhesive drug delivery system. *International journal of pharmaceutics*, 276(1), pp.59-66.

Menon, A., Ritschel, W.A. and Sakr, A., 1994. Development and evaluation of a monolithic floating dosage form for furosemide. *Journal of pharmaceutical sciences*, 83(2), pp.239-245.

- Nafee, N.A., Ismail, F.A., Boraie, N.A. and Mortada, L.M., 2004. Mucoadhesive Delivery Systems. II. Formulation and In-Vitro/In-Vivo Evaluation of Buccal Mucoadhesive Tablets Containing Water-Soluble Drugs. *Drug development and industrial pharmacy*, 30(9), pp.995-1004.
- Nakamura, F., Ohta, R., Machidab, Y. and Nagaic, T., 1996. In vitro and In vivo nasal mucoadhesion Of Some water-SOLuble. *International Journal of Pharmaceutics*, 1(34), pp.1-73.
- Nayak, A.K., Malakar, J. and Sen, K.K., 2010. Gastroretentive drug delivery technologies: Current approaches and future potential. *Journal of Pharmaceutical Education and Research*, 1(2), p.1.
- Patel, M.C. and Patil, C.C., 2012. Formulation and Evaluation of Mucoadhesive Buccal Tablets of Repaglinide. *Asian Journal of Pharmaceutics*, 4, pp.171-179.
- Paul, Y., Kumar, S. and Sherawat, R., 2012. Design, Development and Characterization Ofmucoadhesive Tablets Of Atenolol.
- Pawar, V.K., Kansal, S., Garg, G., Awasthi, R., Singodia, D. and Kulkarni, G.T., 2011. Gastroretentive dosage forms: a review with special emphasis on floating drug delivery systems. *Drug delivery*, 18(2), pp.97-110.
- Rajput, G., Majmudar, F., Patel, J., Thakor, R. and Rajgor, N., 2010. Stomach-specific mucoadhesive microsphere as a controlled drug delivery system. *Systematic Reviews in Pharmacy*, 1(1), p.70.
- Sankar, R. and Jain, S.K., 2013. Development and characterization of gastroretentive sustained-release formulation by combination of swelling and mucoadhesive approach: a mechanistic study. *Drug design, development and therapy*, 7, p.1455.
- Santus, G., Lazzarini, C., Bottoni, G., Sandefer, E.P., Page, R.C., Doll, W.J., Ryo, U.Y. and Digenis, G.A., 1997. An in vitro-in vivo investigation of oral bioadhesive controlled release furosemide formulations. *European journal of pharmaceutics and biopharmaceutics*, 44(1), pp.39-52.
- Singh, B., Chakkal, S.K. and Ahuja, N., 2006. Formulation and optimization of controlled release mucoadhesive tablets of atenolol using response surface methodology. *AAPS PharmSciTech*, 7(1), pp.E19-E28.
- Singh, B.N. and Kim, K.H., 2000. Floating drug delivery systems: an approach to oral controlled drug delivery via gastric retention. *Journal of Controlled release*, 63(3), pp.235-259.
- Tadros, M.I., 2010. Controlled-release effervescent floating matrix tablets of ciprofloxacin hydrochloride: Development, optimization and in vitro–in vivo evaluation in healthy human volunteers. *European journal of pharmaceutics and biopharmaceutics*, 74(2), pp.332-339.
- Varma, M., Singla, A.K. and Dhawan, S., 2004. Release of diltiazem hydrochloride from hydrophilic matrices of polyethylene oxide and carbopol. *Drug development and industrial pharmacy*, 30(5), pp.545-553.
- Whitehead, L., Fell, J.T., Collett, J.H., Sharma, H.L. and Smith, A.M., 1998. Floating dosage forms: an in vivo study demonstrating prolonged gastric retention. *Journal of controlled release*, 55(1), pp.3-12.