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### Design and development of once-daily bi-layer matrix tablet of Baclofen using HPMC K15: For the effective treatment of muscle spasm

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#### ABSTRACT

*In the present study, Baclofen bi-layer tablets were formulated consisting of two layers such as fast releasing layer and sustaining layer. Fast releasing layer was prepared by using super disintegrant like sodium starch glycolate and sustained release layer was prepared by using synthetic polymer like hydroxy propyl methylcellulose K 15 (HPMC K15) by wet granulation method. The tablets were evaluated for physico-chemical properties such as hardness, friability, thickness, weight variation, drug content uniformity. The In vitro release studies were performed in 0.1 N HCl for first two hr and in 7.4-pH phosphate buffer up to 24 h. It was observed that bi-layer matrix tablets having formulation code BH II which contained 65 % HPMC K15 were successfully sustained the release of drug up to 24 h. FT-IR studies revealed that there was no interaction between the drug and polymer used in the study.*

**Key words:** Bi-layer tablets, Baclofen, Sustained release, HPMC K15.

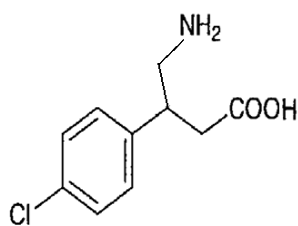
#### INTRODUCTION

Oral route is most preferred route for administration of drugs. Tablets are most popular oral formulations available in the market and preferred by the patient and physician alike. In the long-term therapy for the treatment of chronic disease condition, conventional formulations are required to be administered in multiple dosages and therefore have several disadvantages. Sustained release tablet formulations are much desirable and preferred for such therapy because they offer better patient compliance, maintained uniform drug level, reduce dose and side effects and increase safety margin of high potency drugs[1].

In the matrix tablets the bi-layer concept is used for sustained the release of drug. Drug release from fast releasing layer leads to sudden rise to blood concentration. However blood

concentration is maintained as steady state, as the drug is release from the sustained release layer[2].

Baclofen is structural analog of gamma-amino butyric acid is a centrally acting skeletal muscle relaxant, which is widely used in the treatment of spasticity resulting from multiple sclerosis, muscle spasms, muscular rigidity and spinal cord injuries[3]. Baclofen is rapidly absorbed from gastro-intestinal tract and the peak plasma concentration is achieved within about 2 hr. It is largely excreted in the urine, 80 % as unchanged drug and, the rest as metabolites. The elimination half-life has been reported to be 4 h and thus make it a potent candidate for sustained release dosage form[4].



Structure of Baclofen

Hence in the present research investigation an attempt was made to fabricate Baclofen bi-layered matrix tablets using HPMC K-15 as release retardant at different concentration.

## MATERIALS AND METHODS

Baclofen was obtained as gift sample from Hetro drugs, Hyderabad, sodium starch glycolate was obtained as gift sample from Maple Biotech Pune, HPMC K15, PVP K-30, mannitol, magnesium stearate, talc were procured commercially from S.D. Fine chemicals Mumbai. All other chemicals were of analytical grade.

### Fourier Transform Infrared (FT-IR) spectroscopy

Compatibility studies were carried out to know the possible interactions between Baclofen and excipients used in the formulation. Physical mixtures of drug and excipients were prepared to study the compatibility. Drug polymer compatibility studies were carried out using FT-IR spectroscopy. IR spectrum of pure drug and polymers were seen in between 400-4000  $\text{cm}^{-1}$  is shown in Figure 1 and 2.

### Calculation of theoretical release profile of Baclofen from sustained release layer [5]

The total dose of Baclofen for once daily-sustained release formulation was calculated by the following equation, using available pharmacological data.

$$Dt = \text{Dose} (1 + 0.693x t / t_{1/2})$$

Where,  $Dt$  = Total dose of drug.

Dose = Dose of immediate release part

$t$  = time in hour during which the sustained release is desired (24 hr)

$t_{1/2}$  = half life of the drug (4 h)

Therefore,  $Dt = 5(1 + 0.693x 24/4)$

$Dt \approx 26 \text{ mg}$

Therefore maintenance dose =  $D = 26 - 5 = 21$  mg

Hence, the formulation should release 5 mg drug in 1 hr like conventional tablets and 0.875 mg per hour up to 24 h, thereafter.

### **Preparation of bi-layer tablets**

Baclofen matrix tablets were prepared by wet granulation technique. The drug, polymer and other excipients used were passed through sieve number 80 before their use in the formulation. The layer with sustaining dose was formulated with various amount of HPMC K15. The dose in the formulation for fast release was 5 mg. The maintenance or sustaining dose of Baclofen was 21 mg.

### **Formulation of fast dissolving layer**

The fast release layer was formulated by mixing the drugs uniformly with sodium starch glycolate.

### **Formulation of sustained release layer**

Accurately weighed quantity of Baclofen, HPMC K15 and mannitol were taken mortar and mixed. The powders were mixed with the sufficient quantity of PVP K 30 in distilled water until wet mass formed. The cohesive mass obtained was pass through sieve number 16 and the granules were dried in an oven at  $50^{\circ}$  C for an h. The dried granules were again sieved through sieve # 22. The granules were mixed required quantities of talc and magnesium stearate. The required amount of granules for sustained release layer was compressed into tablets in the single punch tablet machine using 8 mm round and convex punches. Over this compressed layer, required quantity of fast releasing layer powder was placed and compressed lightly to form a bi-layer tablet.

### **Powder characterization [5,6,7]**

#### **Angle of repose**

Angle of repose was determined by using funnel method. The granules were poured from funnel that can be rise vertically until a maximum cone height 'h' was obtained. Then the diameter of the powder cone was measured and the angle of repose was calculated using the following equation.

$$\theta = \tan^{-1} (h/r)$$

#### **Bulk Density:**

Apparent bulk density was determined by placing pre-sieved granules into a graduated cylinder and measuring the volume and weight as it is. The bulk density is calculated by using following formula.

$$\text{Bulk density} = \text{Weight of powder} / \text{volume of packing}$$

#### **Tapped density**

A quantity of 2 gm of powder from each formula was introduced into a 10 ml measuring cylinder. After a initial volume was observed, the cylinder was allow to fall under its own weight on the hard surface from the height of 2.5 cm at two second intervals. The tapping was continued until no further change in the volume was noted. The tapped density was calculated by using following formula.

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Tapped density = weight of powder / tapped volume of packing.

### **Compressibility index**

Compressibility index of granules was determined by Carr's compressibility index.

$$\text{Carr's index: } [(TBD - LBD) \times 100] / TBD$$

### **Evaluation of tablets [8,9]**

#### **Hardness test**

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablets was determined using Monsanto hardness tester. It is expressed in  $\text{kg/cm}^2$ . Three tablets were randomly picked and hardness of the tablets was determined values are reported.

#### **Wight variation**

Twenty tablets were randomly selected from each batch and average weight was calculated. Then individual tablet were weighted and individual weight was compared with an average weight.

#### **Thickness**

Twenty tablets were randomly selected from each batch and their thickness was measured by using vernier caliper. Thickness of three tablets from each batch was measured and mean was calculated.

#### **Friability**

Friability test is performed to assess the effect of friction and shocks, which may often cause tablet to chip, cap or break. Roche friabilator was used for the purpose. This device subjects a number of tablets to the combined effect of abrasion and shock by utilizing a plastic chamber that revolves at 25 rpm dropping the tablets at distance of 6 inches with each revolution. Twenty tablets were weighed and placed in the Roche friabilator, which was then operated for 25 rpm for 4 min. After revolution Tablets were deducted and reweighed. Compressed tablets should not loose more than 1% of their weight. Values are reported. The percentage friability was measured using the formula,

$$\% F = \{1 - (W_o/W)\} \times 100$$

#### **Drug Content**

Ten tablets were weighted and powdered. Powder equivalent to 100 mg of Baclofen was transfer in the 100 ml volumetric flask and 70 ml phosphate buffer having pH 7.4 is added. Then flask was shaken for 10 min. Finally the volume was made up to the mark with phosphate buffer. Then it was analyzed in U. V. spectrophotometer at 266 nm.

#### ***In vitro* drug release study[10]**

*In vitro* drug release study was performed using dissolution apparatus USP type II paddle method with a stirring speed 50 rpm at  $37^{\circ}\text{C} \pm 0.5$  in 900 ml of 0.1 N HCl for first 2 h and 900 ml of 7.4 pH phosphate buffer up to 24 h. The samples were collected at per selected time intervals with

replacement of equal volume of dissolution media. The absorbance of collected samples was measured spectrophotometrically at 266 nm[11].

## RESULTS AND DISCUSSION

The prepared bi-layer tablets were evaluated for various physical properties. The angle of repose ranged between 23.25<sup>0</sup> to 26.54<sup>0</sup>. The bulk density was within the range of 0.58 to 0.61 gm/ml. The tapped density ranged between 0.68 to 0.71 gm/ml. compressibility index was found to be 12.50 % to 12.87 %. These values indicate that the prepared granules shows good flow properties.

The hardness of all the prepared formulations was within the range of 6.53 to 7.0 kg/cm<sup>2</sup>, indicating satisfactory mechanical strength. The particle loss in the friability test was below 1% for all the formulations, which is an indication of good mechanical resistance of tablets. The variation in the weight was within the range of pharmacopoeial specifications. The percentage of baclofen in the all formulations was ranging from 97.92 - 99.46 %, indicating content uniformity was within limits. The thickness and diameter of Baclofen tablets was found to be in the range of 4.293 to 4.435 mm and 7.919 to 7.995 mm respectively, which shows uniform thickness and diameter.

### Drug-Excipients interaction study:

The drug-excipient study was done by Fourier transform infrared (FT-IR) spectroscopy study, the prominent peaks of Baclofen pure drug (Fig. 1) were shown at 1100cm<sup>-1</sup> (due to -C-Cl), 1530 cm<sup>-1</sup> (due to -COOH), and 1610 cm<sup>-1</sup> (due to -NH<sub>2</sub>). These prominent peaks of Drug were also present in the IR spectrum of formulation BH II (Fig. 2). From this it clearly indicates that, the drug was not interacted with the HPMC.

**Table 1: Composition of Baclofen bi-layer matrix tablets**

Ingredients (mg/tab)	Formulations		
	BH I	BH II	BH III
	<b>Immediate Release layer</b>		
Baclofen	5	5	5
SSG	10	10	10
	<b>Sustained release layer</b>		
Baclofen	21	21	21
Manitol	113	67	21
HPMC K15	152	198	244
PVP K-30	15	15	15
Mg. stearate	2	2	2
Talc	2	2	2
Total weight	320	320	320

### *In vitro* drug release study:

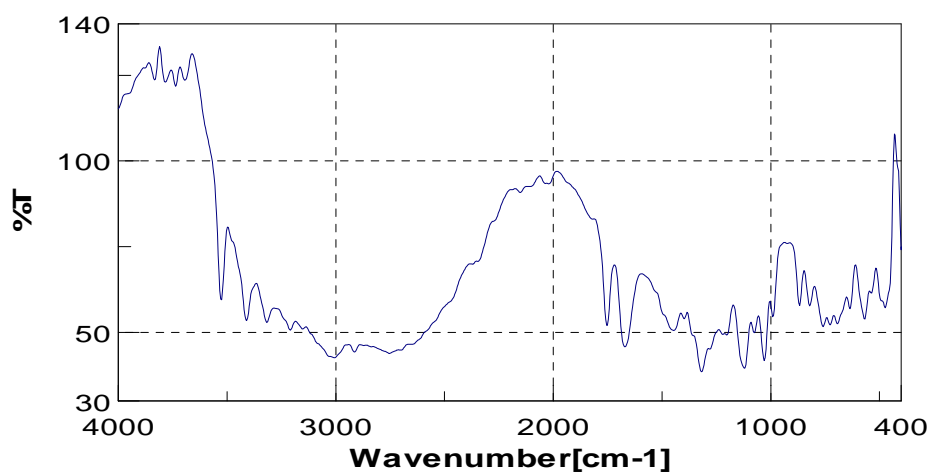
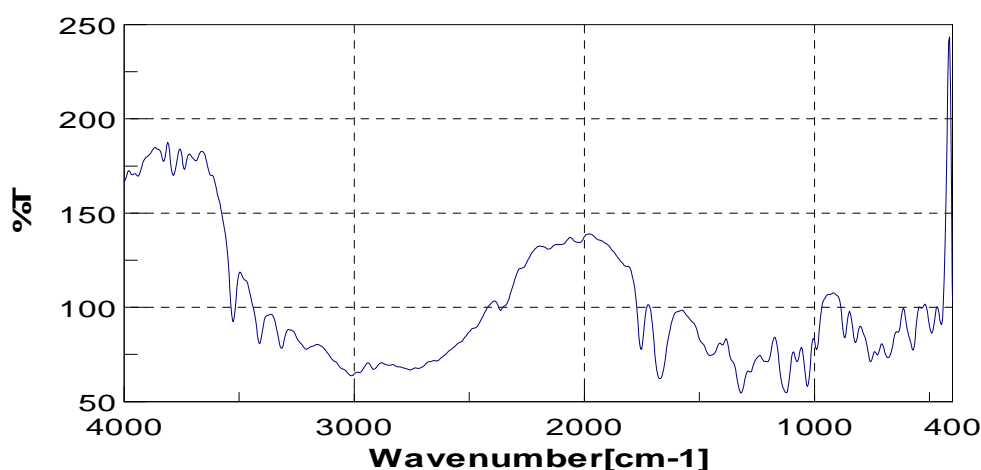
The release of Baclofen from fast releasing layer was analyzed by plotting the percent drug release Vs time. It shows initial burst effect was shown in Fig. 4. From all the formulations over 18 % of Baclofen was released within two h of dissolution study. The formulation BH I, BH II and BH III shows 98.82 % drug release within 12 h, 99.25 % within 24 h and 88.82 % within 24 h respectively.

**Table 2: Properties of Granules**

Formulation Code	Bulk Density (gm/ml) ± SD, n=3	Tapped Density (gm/ml) ± SD, n=3	Angle of Repose(θ) ± SD, n=3	Carr's Index (%) ± SD, n=3	Hausner's Ratio ± SD, n=3
BH I	0.757±0.03	0.865±0.27	27.60±1.2	12.52±1.46	1.14±0.03
BH II	0.730±0.02	0.834±0.51	23.94±1.7	12.47±1.11	1.10±0.05
BH III	0.616±0.04	0.701±0.34	24.41±1.4	12.26±1.09	1.14±0.01

**Table 3: Evaluation of Tablet Parameter**

Formulation Code	Hardness (kg.cm <sup>2</sup> ) ± SD, n=3	Thickness (mm) ± SD, n=3	Weight Variation ± SD, n=3	Friability ± SD, n=3	Drug Content ± SD, n=3
BH I	7.0±0.10	4.34±0.09	319±1.50	0.6±0.001	96.65±1.20
BH II	6.5±0.31	4.29±0.03	318±0.45	0.8±0.002	95.65±1.42
BH III	6.5±0.20	4.43±0.05	321±0.65	0.7±0.004	95.61±0.94

**Fig. 1: IR spectrum of Baclofen****Fig. 2: IR spectrum of formulation BH II**

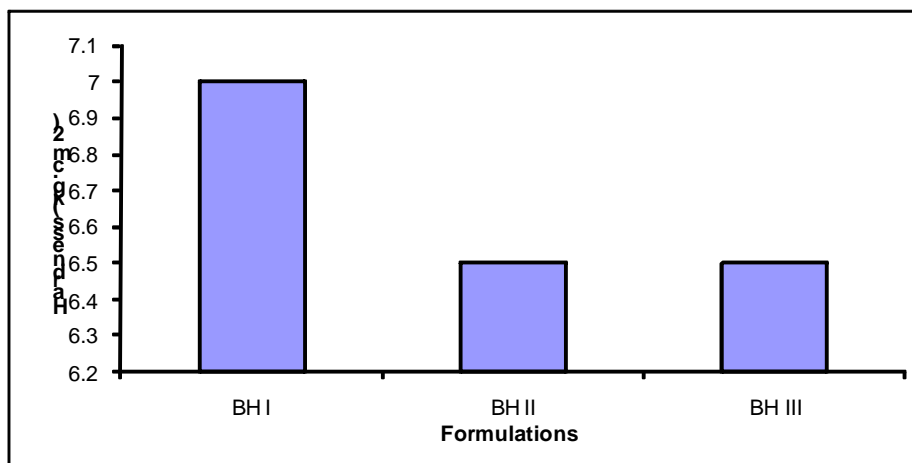


Fig.3: Comparison of hardness of different formulations of Baclofen bi-layer tablets

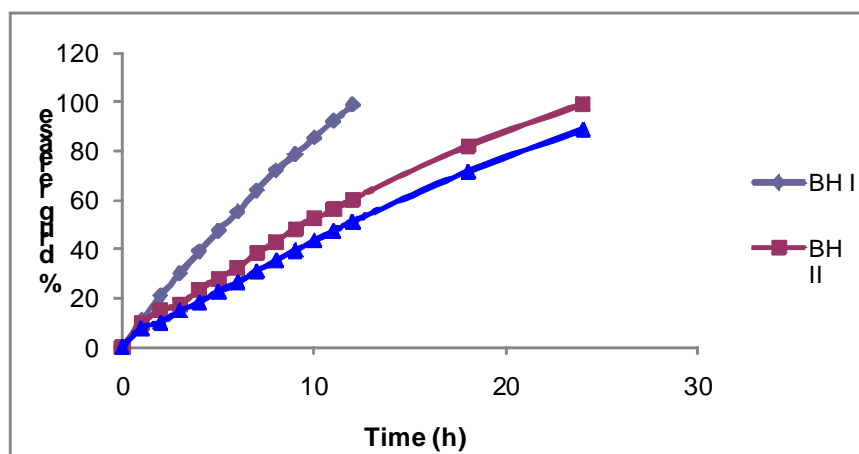


Fig. 4: *In vitro* drug release profile of formulation BH I, BH II and BH III

## CONCLUSION

*In vitro* release studies demonstrated that the release of Baclofen from the prepared bi-layer matrix tablets was dependent on polymeric level. When we increased the polymeric concentration from 65 % to 80 %, due to this increased concentration of HPMC K15 drug release was retarded and only 88.82 % of drug was released at the end of 24<sup>th</sup> h. When we decreased the polymer concentration from 65 % to 50 %, 98.82 % drug released was shown at the end of 12<sup>th</sup> h. In all the formulations an initial burst release was seen to provide the loading dose of the drug, followed by the controlled release for 24 h (Formulation code BH II). From these results it clearly indicates that the prepared formulations are potential of the Baclofen bi-layer matrix tablet as an alternative to the conventional dosage form for the effective treatment of muscle spasm.

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