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Studies on fabrication of baclofen sr matrix tablets; *In-vitro* release pattern overview

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ABSTRACT

To develop the sustained release matrix tablets of baclofen, for treatment of spastically resulting from multiple sclerosis, flexor spasm and muscular rigidity. The matrix tablets were prepared by wet granulation method using hydroxypropyl methylcellulose K4M, K100M and Xanthan gum in various concentrations. The granules showed satisfactory flow properties and compressibility. All the nine formulations showed acceptable pharmacopoeial standards. The result of formulation B7 (25% hydroxypropyl methylcellulose K4M and K100M) extented the release of baclofen up to 12hrs.Model fitting analysis for formulation B7 fitted in the zero order model and korsemeyer- peppas model. The 'n' values obtained from the peppas-korsemeyer equation suggested that, drug release was non-Fickian difussion mechanism. Successful formulation was found stable after evaluation for physicochemical parameters when kept for 30 days at room temperature, 40ºC and 2-8ºC. It concluded that sustained release matrix tablets of baclofen containing 25% of HPMC K4M and HPMC K100M provide a better option for extended release of drug.

Key words: Baclofen, SR Matrix tablets, and Xanthan gum.

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INTRODUCTION

The basic rational for controlled drug delivery is to alter the pharmacokinetic and pharmacodynamics of pharmacological active moieties by using novel drug delivery system or by modifying the molecular structure and physiological parameters inherent in the selected route of administration. The release of drug from swellable matrix tablets is based on glassy-rubbery transition of polymer as a result of water penetration into the matrix. The interaction between water, polymer and drug are the primary factors for drug release. However, various formulation variables such as polymer grade, drug – polymer ratio, drug solubility and drug and polymer particle size, can influence drug release rate to greater or lesser degree. The central element of the mechanism of drug release in the gel layer (rubbery polymer), which is formed around the matrix. The gel layer is capable of preventing matrix disintegration and further rapid water penetration.Water penetration, polymer swelling, drug dissolution and diffusion and matrix erosion are phenomenon determining gel layer thickness. Finally drug release is controlled by drug diffusion through the gel layer and/or by erosion of the gel layer. It is desirable that the duration of drug action becomes more a design property of a rate controlled dosage form and less or not at all a property of the drug molecules inherent kinetics properties. Thus optional design of controlled release systems necessitates a thorough understanding of the pharmacokinetics and pharmacodynamics of the drugs [1-3].

The present study was an aim to formulate and evaluate the sustained release oral matrix tablets[4] by using Baclofen as a model drug to prolong the release of drug for extended period of time in order to;

- Improve patient compliance
- Reduce dosing frequency.
- Increase bioavailability of the drug.

Objectives of study

Baclofen is a skeletal muscle relaxant and antispastic agent, with half life of 3-4 hours and requires multiple daily doses to maintain adequate plasma concentrations. Hence it is a suitable candidate for sustained release tablets.

MATERIALS AND METHODS

Materials

Baclofen were obtained as gift sample from Tablets India Limited, Chennai HPMC K4M and HPMC K100M from Colorcon Asia Pvt. Ltd, (India), Xanthan gum, Lactose, and Polyvinylpyrollidine-k-30 from Sigma Chemicals Company were purchased. Talc, Magnesium Stearate from Qualigens (India) and Hydrochloric acid LR from E-Merck (India). All the chemicals used were of Laboratory grade.

Preparation of matrix tablets by wet granulation method [5]

Different tablet formulations were prepared by wet granulation method. Tables No.5 shows composition of each tablet formulation. The formulations are composed of polymers HPMC K_4M, HPMC $K_{100}M$, Xanthan gum in the ratio 1:1 and 1:2 in various percentages. All powders were passed through 100-mesh sieve.

The lactose and the polymer were mixed uniformly. Drug was added to the lactose and blended for 20min. Solution of PVP K30 and isopropyl alcohol was added to the above mixture for making dump mass. Dump mass was passed through sieve no.40 and dried the granules for 2 hrs at 50^{o}C. The resulting granules were mixed with magnesium Stearate and talc in polyethylene bag for 10 min. The lubricated granules were compressed using 9mm punch (single punch tablet machine) in to tablets. Compression pressure was adjusted during tableting of each formula to get the tablet hardness in the range of 5 to 7 Kg/$cm^{3.}$ The total weight of tablet was kept at 200 mg.

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Evaluation of tablet [6-8]

All the prepared Sustained release tablets were evaluated for following official and unofficial parameters.

Weight Variation
Thickness
Hardness Test
Friability Test
Drug content
In-Vitro Release Study
Swelling study

Weight variation

Twenty tablets were randomly selected form each batch and individually weighed. The average weight and standard deviation of 20 tablets was calculated. The batch passes the test for weight variation test if not more then two of the individual tablet weight deviate from the average weight by more than the percentage shown in Table No 1 and none deviate by more than twice the percentage shown.

Table No.1. Percentage deviation allowed under weight variation

Percentage deviation allowed under weight variation test.	
Average weight of tablet (X mg)	PERCENTAGE DEVIATION
130 mg or less	10
130mg to 324 mg	7.5
more than 324 mg	5

Thickness

Twenty tablets were randomly selected form each batch and there thickness was measured by using vernier caliper. Thickness of three tablets from each batch was measured and mean was calculated and shown in Table No:-1.

Hardness

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 kg/cm^2. Three tablets were randomly picked and hardness of the tablets was determined values are shown in Table No:-1

Friability [9,10]

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 sown in Table No:-1 The percentage friability was measured using the formula,

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

Where,

% F - Friability in percentage, Wo - Initial weight of tablet, W - Weight of tablets after revolution

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Content Uniformity

Twenty tablets from each batch were powdered and weighed accurately equivalent to 100 mg Baclofen. Dissolve the weighed quantity of powder into 100 ml of 0.1 N NaOH solution by stirring it for 15 min. 01 ml of solution was pipette out into 10 ml volumetric flask, to it 01 ml of 05% Ninhydrin solution was added and boil this solution for 03 min, cool it and make up the volume with distilled water. Immediately analyze the drug by taking absorbance at 403 nm using reagent blank. The % drug content of all Batches are shown in Table No.1

In-vitro release study

In-Vitro drug release studies were carried out using Tablet dissolution test apparatus USPXXIII at 50 rpm. The dissolution medium consisted of 900ml of Standard buffer pH 1.2 for the first 2 hrs, followed by pH 6.8 for remaining period of time. Temperature maintained at 37°±1.The sample of 5ml was withdrawn at predetermined time intervals and an equivalent amount of fresh dissolution fluid equilibrated at the same temperature was replaced. From that 5ml sample, 1ml sample was withdrawn and placed in a 10ml volumetric flask, to it add 1ml of 5% Ninhydrin solution and 01ml of 0.1 N NaOH solution, boil for 3 min at water bath, cool it at room temperature and make the volume with distilled water [11-15]. The diluted samples were assayed at 403 nm against reagent blank and results are shown in Table No:-2.

Swelling study

Swelling of tablet involves the absorption of a liquid resulting in an increase in weight and volume. Liquid uptake by the particle may be due to saturation of capillary spaces within the particles or hydration of macromolecule. The liquid enters the particles through pores and bind to large molecule; breaking the hydrogen bond and resulting in the swelling of particle. The extent of swelling can be measured in terms of % weight gain by the tablet [10]. Results are shown in Table No:-3

For each formulation batch, one tablet was weighed and placed in a Petri plate containing 25 ml of 6.8 pH buffer solution. After each interval the tablets was removed from beaker, remove excess of buffer by using filter paper and weighed again up to 12 hours. The swelling index was calculated using following formula.

$$\text{Swelling Index (S.I.)} = \{(Wt-Wo)/Wo\} \times 100$$

Where,

S.I. - Swelling index, Wt - Weight of tablet at time t, Wo - Weight of tablet before placing in the Petri plate.

Stability studies

The success of an effective formulation can be evaluated only through stability studies. The purpose of stability testing is to obtain a stable product which assures its safety and efficacy up to the end of shelf life at defined storage conditions and peak profile.

The prepared Matrix tablets (B7) of Baclofen were placed on plastic tubes containing desiccant and stored at ambient conditions, such as at room temperature, 40±2°c and refrigerator 2-8°C for a period of 30 days and results are shown in Table No: 4

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RESULTS

Table:-1.Physical parameters of tablets of each batch

B. NO.	WEIGHT VARIATION (MG)*	THICKNESS (MM)*	HARDNESS (KG/CM^2)*	FRIABILITY (%)	DRUG CONTENT (%)
B1	203 ±2.75	2.46 ±0.05	6.83 ±0.28	0.56	96.89
B2	201 ±2.33	2.43 ±0.05	6.66 ±0.28	0.54	98.42
B3	202 ±2.24	2.46 ±0.05	6.93 ±0.11	0.61	96.80
B4	202 ±1.78	2.53 ±0.06	6.76 ±0.25	0.59	97.22
B5	201 ±1.59	2.56 ±0.05	6.6 ±0.17	0.62	98.77
B6	202 ±1.93	2.5 ±0.05	6.66 ±0.28	0.64	96.83
B7	201 ±1.67	2.53 ±0.08	6.83 ±0.28	0.53	98.92
B8	202 ±1.71	2.5±0.01	6.6 ±0.17	0.58	97.65
B9	203 ±1.84	2.43±0.05	6.83 ±0.25	0.60	96.72

*Each value represents the mean ± standard deviation (n = 3)

Table:-2. Dissolution profile of batch no-b1 to b9

B. NO.	Time in hours (cumulative % drug release)											
	1	2	3	4	5	6	7	8	9	10	11	12
B1	12.99	29.56	43.64	58.68	66.25	79.66	87.51	96.68	-	-	-	-
B2	17.55	31.71	40.16	52.18	64.21	72.87	82.71	95.79	-	-	-	-
B3	17.73	31.53	40.81	53.72	65.61	72.70	83.70	92.31	-	-	-	-
B4	12.09	25.71	31.48	42.40	49.14	56.84	62.55	68.55	75.16	80.34	84.62	88.71
B5	33.04	52.14	66.63	74.19	85.94	94.06	-	-	-	-	-	-
B6	14.78	24.64	33.98	49.02	63.31	76.79	85.40	93.26	-	-	-	-
B7	10.03	22.76	30.24	39.44	48.24	61.64	67.16	74.80	83.20	89.07	93.37	97.46
B8	15.76	33.41	39.87	47.02	58.63	64.55	70.95	81.75	91.11	98.83	-	-
B9	14.87	31.14	36.82	44.72	52.89	60.24	69.33	78.41	89.49	95.81	-	-

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Table:-3.swelling index of tablets of batch b1 to b9

B. NO.	TIME (HRS)							
	0	1	2	4	6	8	10	12
B1	0	33.33	61.90	71.42	80.95	85.71	104.76	--
B2	0	38.09	47.61	61.90	76.19	85.71	110.30	119.04
B3	0	71.42	76.19	90.47	114.28	119.04	128.57	142.85
B4	0	38.09	66.66	85.71	114.76	128.57	157.14	171.42
B5	0	77.27	86.36	104.54	122.72	136.36	145.59	--
B6	0	80.95	95.23	109.52	128.57	138.09	145.85	161.90
B7	0	66.66	71.42	109.52	133.33	157.14	176.19	185.74
B8	0	57.14	85.71	104.76	114.28	138.09	152.38	161.90
B9	0	71.42	76.19	95.23	119.04	138.09	157.14	176.19

Stability studies of formulations

TABLE:-4.Stability studies of formulations B7 stored at room temperature

Formulation	Tested after time (days)	Hardness $(kg\backslash cm)^2$	Friability (%)	Drug content (%)	Cum % Drug Released
B7	15 30	6.8 6.6	0.58 0.56	98.92 97.22	96.65 96.84

Stability studies of formulations B7 stored at temperature (40ºC)

Formulation	Tested after time (days)	Hardness $(kg\backslash cm)^2$	Friability (%)	Drug content (%)	Cum % Drug Released
B7	15 30	6.6 6.6	0.54 0.58	97.42 97.62	96.75 97.84

Stability studies of formulations B7 stored at temperature (2-8^{o}C)

Formulation	Tested after time (days)	Hardness $(kg\backslash cm)^2$	Friability (%)	Drug content (%)	Cum % Drug Released
B7	15 30	6.8 7.0	0.61 0.64	96.92 98.22	95.65 95.24

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Fig.1: Comparative dissolution profile of batches b1 to b9

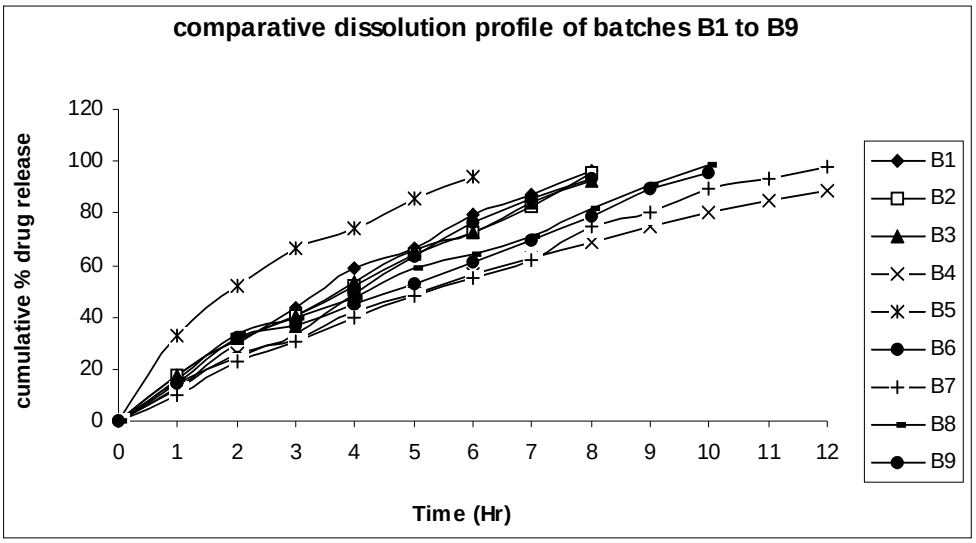
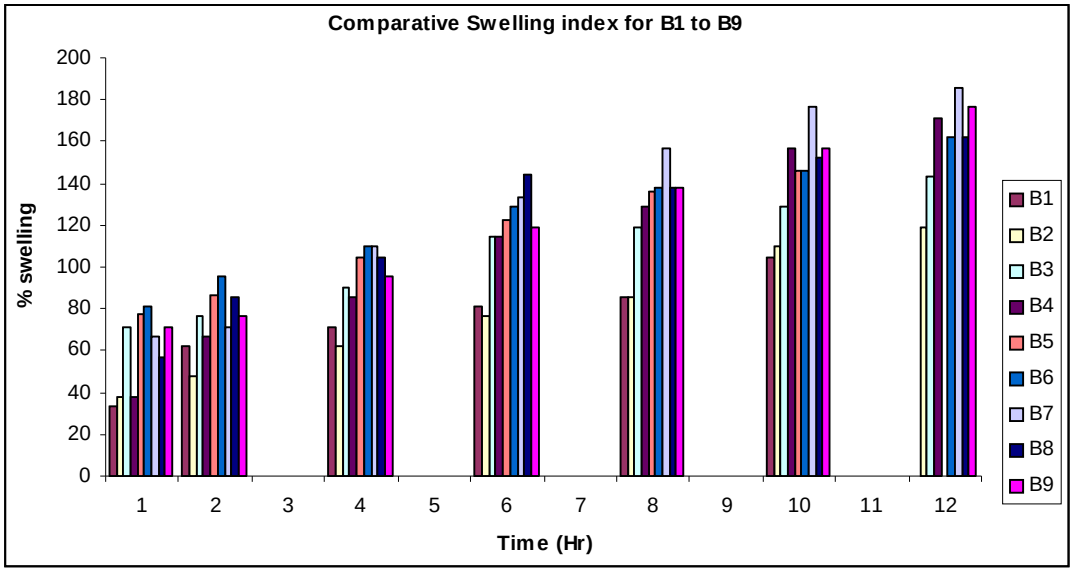


Fig.2. Comparative swelling index for batch b1 to b9



DISCUSSION

Thus, it may be concluded that the drug release from sustained release matrix tablet of Baclofen is best formulation which will shows the good sustainability profile and all evaluation tests are as per prescribed standards.

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