International Standard Serial Number : 0976-1403

Deccan J. Pharmaceutics & Cosmetology 2(3): July-September 2011

DECCAN PHARMA JOURNAL SERIES

ARMS Online Publications

www.deccanpharmajournals.com

(Research Article)

Received; accepted

FORMULATION AND EVALUATION OF BACLOFEN BILAYER FLOATING TABLETS USING HPMC K4M AS RELEASE RATARDANT POLYMER

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Keywords:

Baclofen, Bilayer floating tablet, HPMC, SSG, TFT

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ABSTRACT

The present investigation concerns the development of a bilayer floating tablet, which has immediate release layer which produces required effective drug concentration and sustained release layer which prolong the gastric residence time and increases bioavailability of drugs, which are predominantly absorbed from gastric region .With this aim, bilayer floating dosage form containing baclofen as drug, SSG as superdisintegrant and HPMC as release retarding polymer was prepared. Sodium bicarbonate and citric acid were used as gas generating agents. Some factors were investigated concerning the effect of release retarding polymer on drug release behaviors like TFT and t_{24}%. A 3^2 factorial design was applied to optimize the drug release profile. The result of full factorial design indicates that moderate amount of the release retardant polymer and gas generating agent controlled the release behavior. All tablets are evaluated for in vitro dissolution and other evaluation parameters as per I.P.guidelines. It can be concluded from Release kinetic models that the release followed Korsmeyer's Peppas, as the correlation coefficient (R^2 value) was high in all the evaluated models. The release mechanism followed non-Fickian diffusion as the release exponent (n-value) was >0.5 in all the optimized formulations.

INTRODUCTION:

Baclofen is an oral medication that relaxes the skeletal muscle, chemically related to gamma-amino butyric acid (GABA), a naturally-occurring neurotransmitter in the brain. It is believed that baclofen, acting like GABA, blocks the activity of nerves within the part of the brain that controls the contraction and relaxation of skeletal muscle. The evidences suggest that baclofen is transported from the gastrointestinal tract and the bioavailability of baclofen administered as tablet relative to baclofen intravenous infusion is about 40%. It is stable and well absorbed within pH range 1-4.

Currently, the most commonly used dose form of baclofen is the immediate release (IR) tablet 10-20 mg to be administered three times a day. Also, the frequent administration of conventional baclofen immediate release tablets leading to fluctuations in plasma concentration, producing side effects such as dizziness and muscle weakness. These side effects are considered as major deterrents to the prescribers for up-titration of the dosage for optimization of therapy. In addition, as baclofen immediate release has to be taken three times a day, there is noncompliance by the patients. The noncompliance's can be overcome by medication which requires a minimal number of doses suggesting a once a day sustained release formulation. The short half life of baclofen (2-4 h) the high solubility, chemical and enzymatic stability and absorption profile of baclofen in acidic pH values (of stomach) points to the potential of gastroretentive dosage form.

Gastroretentive bilayer tablets of baclofen were prepared to provide an immediate release layer designed to release one-third of the baclofen content to achieve an effective plasma concentration and the sustained release layer which releases the drug over several hours using a gastro retentive drug delivery system. Immediate release layer was prepared by using the superdisintegrant sodium starch glycolate while sustained release layer was prepared using gas generating agents like sodium bicarbonate, citric acid and release retardant polymer, hydroxypropyl methylcellulose by direct compression method. HPLC and UV

spectrophotometric analytical methods were used for estimation of baclofen from formulations.

OBJECTIVE:

The objective of the present research work is to provide a gastroretentive system for sustained release as well as immediate release of therapeutically active agent, baclofen in upper part of gastro-intestinal tract in the form of bilayer floating matrix tablet. One of the layers is an immediate release layer designed to release one-third of the baclofen content to achieve an effective plasma concentration. The other layer is a sustained release layer which releases the drug over several hours using a gastro retentive drug delivery system.

MATERIALS:

Baclofen was gift sample from Alkem Labs. Mumbai; Hydroxypropyl methylcellulose K4M was collected from Colorcon Pvt. Ltd. Mumbai; Sodium Starch Glycolate, Sodium Bicarbonate and Citric Acid from S.D. chemicals Mumbai. All other chemical and excipients were of analytical grade.

METHODS:

Factorial Design:

A 3^2 randomized full factorial design was used in development of the dosage form. In this design, 2 factors were evaluated each at 3 levels and experimental trials were performed using all possible 9 combinations. In the present study, the amount of HPMC K4M (X_1) and content of sodium bicarbonate (X_2) were selected as independent variables. The total floating time (TFT) and percentage drug release at 24 hours (t_{24}) were selected as dependent variables. The formulations were given.

Preparation of Baclofen Bilayer Floating Tablet:

For the optimized formulation calculated by factorial design, we take baclofen: 30 mg, HPMC K4M:100 mg, sodium starch glycolate: 15 mg, sodium bicarbonate: 30 mg, lactose: 25 mg, magnesium stearate: 2.5 mg. The bilayer tablet was compressed on a Six-Station Rotary Tableting compression machine on 9 mm concave shaped punch. The hardness was maintained at 7-8 kg/cm^2. The bottom layer was first compressed

with lower pressure, which was then followed by filling of the die cavity by the upper layer powder. The final compression was done only after both the powders occupied the die cavity one on top of the other. Both the layers were identified on the basis of color since the immediate release layer had red color and the sustain release layer has white color.

EVALUATION OF TABLETS:

Physical Evaluation:

Tablets were evaluated for different parameters such as Strength (Monsanto hardness tester), Friability (Roche type friabilator), Uniformity of content(UV Spectrophotometer) Weight variation, Matrix Integrity. Buoyancy Lag Time and Buoyancy Time This test was performed in beaker containing 200 ml 0.1 N HCl as a testing medium maintained at 37°C. The time required for the tablet to rise to the surface and float was determined as buoyancy lag time. Buoyancy time is the total time for which the tablets float in dissolution medium (including buoyancy lag time) before getting disintegrated or settling down.

Differential Scanning Calorimetry (DSC) Studies:

Thermal analysis was performed using a Mettler Toledo DSC-823'e system with a differential scanning calorimeter equipped with a computerized data station. All samples were weighed and heated at a scanning rate of 10°C/min between 30 and 300°C and 40 ml/min of nitrogen flow.

***In vitro* Dissolution Studies**

The release rate of baclofen from matrix tablets was determined using USP dissolution testing apparatus II (Paddle type). The dissolution test was performed using 900 ml of 0.1 N HCl, at 37 ± 0.5°C and 100 rpm. A 10 ml sample solution was withdrawn from the dissolution apparatus for 30 min, 1 hr and there after every hour for 24 hrs. Samples were replaced by its equivalent volume of dissolution medium. The samples were filtered through Whatman filter paper and solutions were analyzed at 266 nm by UV Spectrophotometer (SHIMADZU, V-1800, Japan). Cumulative percentage drug release was calculated.

Swelling Behavior

Tablets were placed in the dissolution medium and their respective weight was checked at 0 h, 2 h, 4 h, 6 h, 8 h and 12 h. The tablet was taken out from the dissolution medium and the excess water was allowed to drain out and the tablet was weighed. The swelling index was calculated by using following formula.

$$\text{Swelling index} = \frac{W_1 - W_0}{W_1}$$

RESULTS:

Formulation Development by Factorial Design:

These formulations were obtained by using 3^2 factorial design which are evaluated for various parameters.

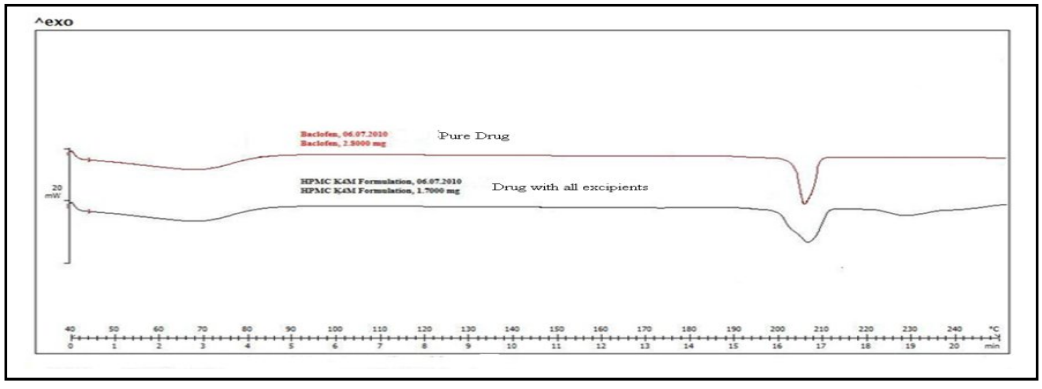
Formulation Code	F1	F2	F3	F4	F5	F6	F7	F8	F9
Formulation of immediate release layer									
Baclofen	10	10	10	10	10	10	10	10	10
SSG	15	15	15	15	15	15	15	15	15
Lactose	27	27	27	27	27	27	27	27	27
Mg.Stearate	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Colour	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Subtotal (mg)	**55**	**55**	**55**	**55**	**55**	**55**	**55**	**55**	**55**
Formulation of sustained release layer									
Baclofen	20	20	20	20	20	20	20	20	20
HPMC K4M	80	80	80	100	100	100	120	120	120
$NaHCO_3$	20	30	40	20	30	40	20	30	40
Lactose	45	35	25	25	15	5	25	15	5
Citric Acid	15	15	15	15	15	15	15	15	15
Subtotal (mg)	**180**	**180**	**180**	**180**	**180**	**180**	**200**	**200**	**200**
Total (mg)	**235**	**235**	**235**	**235**	**235**	**235**	**255**	**255**	**255**

Evaluation of Tablets:

All the evaluation parameters of tablets were found to be in the I.P. limits.

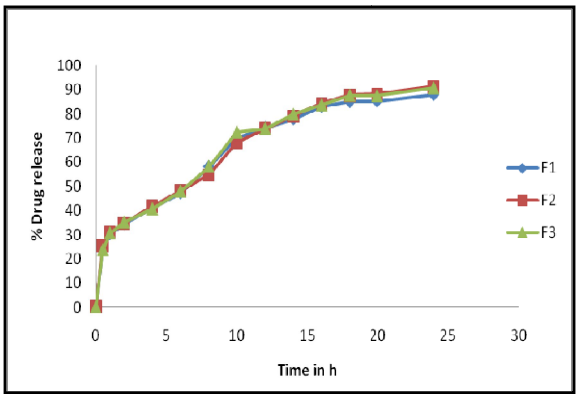
Parameter	F1	F2	F3	F4	F5	F6	F7	F8	F9
% Drug Content	99.31 ±0.64	99.59 ±0.43	99.67 ±0.02	99.45 ±0.78	99.78 ±0.04	99.12 ±0.64	99.18 ±0.24	99.63 ±0.43	99.45 ±0.05
Hardness (Kg/cm^2)	7-8	7-8	7-8	7-8	7-8	7-8	7-8	7-8	7-8
Thickness (mm)	5 ±0.33	5 ±0.08	5 ±0.05	5 ±0.01	5 ±0.32	5 ±0.02	5 ±0.03	5 ±0.03	5 ±0.05
%Friability	0.6 ±0.24	0.62 ±0.64	0.6 ±0.05	0.64 ±0.64	0.9 ±0.64	0.66 ±0.43	0.61 ±0.78	0.66 ±0.64	0.92 ±0.02
Wt. variation (mg)	0.235 ±0.07	0.235 ±0.16	0.235 ±0.19	0.235 ±0.07	0.235 ±0.2	0.235 ±0.19	0.255 ±0.07	0.255 ±0.21	0.255 ±0.14
TFT(hrs)	8	85	97	10	12	12	24	≥24	≥24

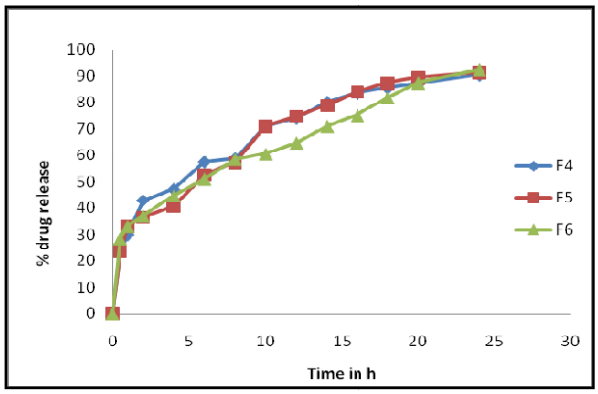
DSC Study: The DSC study of the given formulation shown that there is no interaction between drug and excipients.

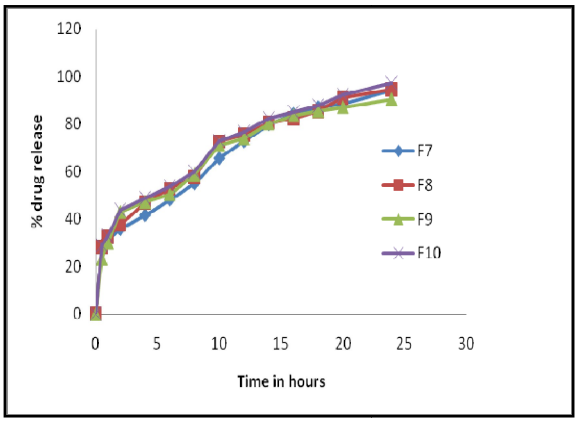


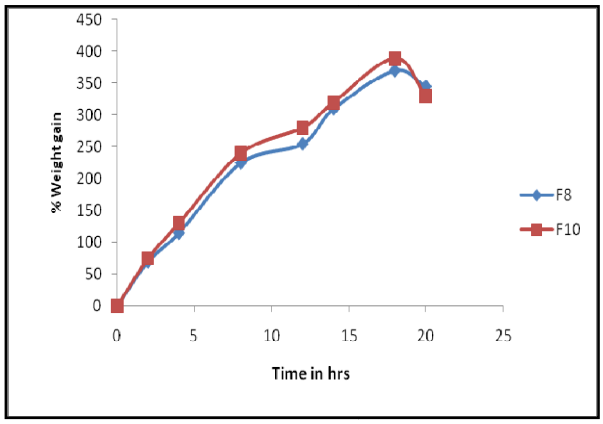
In vitro Dissolution Study and Swelling behavior:

The comparative dissolution study of F1 –F10 was done and results obtained were given in the form of the graphs. The swelling behavior of F8 and F10 was also shown in the following graph.









Kinetic Treatment:

To analyze the mechanism of drug release from the matrix tablets, data obtained from the drug release studies was subjected to different kinetic treatments. The best fit model for prepared formulation follows Korsmeyer -Peppas model (r^2= 0.9923) and n value was found to be 0.694 which signified that release pattern of optimized batch follows the non Fickian diffusion.

Conclusion:

The current study attained the successful design, preparation and

evaluation of floating bilayer sustained release formulation of a slightly soluble drug baclofen by gastroretentive drug delivery system which also had an immediate release layer (one third of drug content) as well as sustained the release profile and achieved gastric retention for the desired period of time by the other layer.

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