Sustained-release effervescent floating matrix tablets of baclofen: development, optimization and in vitro-in vivo evaluation in healthy human volunteers

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ABSTRACT

Background and the purpose of the study: Baclofen, a centrally acting skeletal muscle relaxant, is indicated in the long-term treatment of spasticity. It is difficult to formulate baclofen sustained release dosage forms because its absorption on arrival to colon (or even before) is low or nonexistent. In the present investigation efforts were made to improve the bioavailability of baclofen by increasing the residence time of the drug through sustained-release matrix tablet formulation via gastroretentive mechanism.
Methods: Tablets were prepared by wet granulation technique. The influence of gas generating and gel forming agents, amount of baclofen and total weight of tablet on physical properties, in vitro buoyancy, floating lag time, drug release, DSC, X-ray studies were investigated. The release mechanisms were explored and explained by applying zero order, first order, Higuchi and Korsmeyer equations. The selected formulations were subjected to stability study for the period of three months.
Results: For all formulations, kinetics of drug release from tablet followed Higuchi's square root of time kinetic treatment heralding diffusion as predominant mechanism of drug release. Formulations containing 20 mg and 40 mg (F-1 and F-7) showed similar release profiles. There was no significant change in the selected formulations, when subjected to accelerated stability conditions over a period of three months. X-ray imaging in six healthy human volunteers revealed a mean gastric retention period of 5.50±0.7 hrs for the selected formulation.
Conclusion: Stable, sustained release effervescent floating matrix tablets of baclofen could be prepared by wet granulation technique.

Keywords: Floating tablets, Gastroretentive, Hydrophilic polymers, Mean dissolution time, Sustained release.

INTRODUCTION

Baclofen, a centrally acting skeletal muscle relaxant, is indicated in the long-term treatment of spasticity resulting from multiple sclerosis and spinal cord injuries. Baclofen is rapidly and extensively absorbed and eliminated. The half-life of the drug is ~2.5 to 4 hrs in plasma (1). Baclofen has absorption window in upper G.I. tract, and as result display low bioavailability (2).

Baclofen is difficult to formulate in to sustained release dosage forms because on arrival to colon (or even before) its absorption is diminished or nonexistent, In the present investigation efforts were made to increase the residence time of baclofen at or above the absorption window through preparation of gastroretentive tablet considering the fact that it is stable under gastric condition (3).

The principle of buoyancy offers a simple and practical approach to achieve increased residence time in the stomach. The impact of formulation variables on the release rate, mean dissolution time and release mechanism was also evaluated by the use of mathematical models.

MATERIAL AND METHODS

Materials

Lioresal (25 mg tablets, batch number 82001 P, Novartis Pharma, India) was purchased from market, Baclofen was a generous gift from Natco P harmaceuticals,(Hyderabad, India), Hydroxy propyl methyl cellulose (HPMC K15M, 100M, 6cps) were obtained from Colorcon Asia Private Limited (India), PVPK 30 was obtained from BASF (Germany). All excipients were of USP/NF grades and all other chemicals used were of analytical grades.

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Equipment
The HPLC system consisted of 2695 separation module (Waters, USA), equipped with 2996 PDA detector. The data were collected and analyzed via empower software. A 5 μm C_{18} ACE column (250 mm X 4.6 mm I.D) (Advanced chromatography technologies) was used. The flow rate of the mobile phase was 0.6 ml/minute.

Methods
Kinetic modeling of drug release
The dissolution profiles of all the batches were fitted to zero order, first order, Higuchi and Peppas equations (4) (equation 1-4 respectively).

$$M_t = M_0 + k_0t \tag{1}$$

$$\ln M_t = \ln M_0 + k_1t \tag{2}$$

$$M_t = M_0 - k_Ht^{1/2} \tag{3}$$

$$M_t/M_\alpha = K_t^n \tag{4}$$

In these equations, M_t is the cumulative amount of drug released at any specified time (t), M_0 is the dose of the drug incorporated in the delivery system and M_t/M_α is a fraction of drug released at time (t). k_0, k_1, k_H and K are rate constants for zero order, first order, Higuchi and korsmeyer model respectively, n is the release exponent. The n value is used to characterize different release mechanisms as given in table 1 for cylindrical shaped matrices (5).
The dissolution data were also fitted to the well-known exponential Zero Order equation, which is often used to describe drug release behavior from polymeric systems.
The best fit with higher correlation ($r^2 > 98$) was found with Higuchi's equation for all the formulations.
The mean dissolution time was calculated by the following expression:

$$\text{Mean dissolution time (MDT)} = \frac{\int_0^\infty (M\,max - M\,(t)\,dt)}{M\,max}$$

M(t) and M max are the amount of drug released at time t, and the maximal amount of drug released (6), respectively.

Solubility studies
The equilibrium solubility of baclofen was measured in 0.1M hydrochloric acid (pH of 1.2), acetate buffer (pH of 4.5), and phosphate buffer of pH 6.8. Excess amounts of the drug were added to 50 ml-stoppered conical flasks (n=3). The flasks were shaken mechanically at 37°C±0.5 °C for 24 hrs. After 2 days of equilibrium, aliquots were withdrawn and filtered (0.22μm pore syringe filter). Then, the filtered samples were diluted with an appropriate

Table 1. Diffusion exponent and solute release mechanism for cylindrical shape.

Diffusion exponent (n)	Overall solute diffusion mechanism
0.45	Fickian diffusion
0.45<n<0.89	Anomalous (non-Fickian) diffusion
0.89	Case-II transport
n>0.89	Super case-II transport

amount of 0.1 M hydrochloric acid to obtain final solutions of pH 1.2 which were subjected to HPLC analysis.
Drug-excipient interactions
The physicochemical compatibilities of the drug and the used excipients were tested by differential scanning calorimetric (DSC) analysis. DSC thermograms of the drug alone, drug-excipient physical mixture and tablets were derived from a DSC (2-C, Perkin-Elmer, New York, NY) with a thermal analysis data station system, computer, and plotter interface. The instrument was calibrated with an indium standard. The samples (2-4 mg) were heated (20-300 °C) at a constant scanning speed (10 °C/min) in sealed aluminum pans, using nitrogen as purging gas.

Preparation of baclofen sustained release matrix tablets
All the tablet formulations were prepared by using wet granulation technique. The composition of the 20, 25, 30 and 40 mg baclofen tablets are given in table 2. Polyvinyl pyrrolidone was accurately weighed and dissolved in isopropyl alcohol. All excipients except magnesium stearate were accurately weighed and passed through No. 40 mesh ASTM. Calculated amount of the drug, polymer (HPMC K 15M or 100M or 6 cps etc) and filler Microcrystalline cellulose (Avicel pH101) were mixed thoroughly. A sufficient volume of the specified granulating agents were added slowly to achieve the granulation endpoint. After the time that enough cohesiveness was obtained, granules were dried at room temperature to evaporate the IPA and then were dried at 50 °C for 30 minutes. The semi-dried granules were passed through No. 10 mesh ASTM and drying was continued for another 1 hour and 30 minutes. The granules were collected and passed through # 22 mesh ASTM. Magnesium stearate was passed through # 80 mesh ASTM to lubricate the granules. The granules were compressed using 8 mm round standard concave punches. The composition of the different formulations is shown in table 2.

Evaluation of tablets
Thickness
The thickness of the tablets was determined by using vernier calipers (Mitutoyo, Japan). Ten tablets from

each batch were used. Thickness values are reported in millimeters. Mean and SD values were also calculated.

Average weight of the dosage unit
To study weight variation, 10 tablets of each formulation were weighed using an electronic balance (Mettler Toledo, Switzerland). Values are reported in milligrams. Mean and SD value were also calculated.

Drug content
Twenty tablets were first weighed individually and then placed in a mortar and powdered with a pestle. An amount equivalent to 40 mg of the drug was taken into a 50 ml volumetric flask, treated with 10 ml of diluting solution (30 % Methanol : 4% Glacial acetic acid: 66% Water) and sonicated for 15 min. The solution was filtered through a 0.22 μm PVDF syringe filter SLGV Millipore, and then the drug content was measured by HPLC as per USP-NF 29 (7).

Hardness test
For each formulation, the hardness of 6 tablets was determined using a hardness tester (Sotax HT_1, Sotax, Switzerland). Hardness values are reported in Newton's (N). Mean and SD values were also calculated.

Friability test
For each formulation, 6.5 g of dedusted tablets were weighed, placed in a friabilator (Electrolab, Mumbai, India) and subjected to 100 revolutions for 4 min. The tablets were then dedusted and re-weighed. The friability was calculated as the percentage of the weight loss.

In vitro release studies
In vitro release studies of the control, and baclofen matrix tablets were monitored. The release experiments were performed in a 1000-ml dissolution medium containing hydrochloric acid (pH of 1.2), kept at 37 °C ± 0.5 °C and stirred at 50 rpm, using USP dissolution apparatus II. A 5-ml sample was withdrawn through a 0.45 μm filter and replaced with another 5 ml of a suitable fresh dissolution medium at pre-selected intervals up to 12 hrs. The amount of the drug was determined by HPLC as per USP-NF 29 (7).

Stability studies
Formulations F-1 and F-7 were subjected to 25°C± 2°C/60% ± 5 %RH and 40°C ± 2°C /75 ± 5%RH (Newtronic, Mumbai, India) in closed HDPE bottles along with 1 g desiccant for 3 months.

Abdominal X-ray imaging
For the X-ray experiment 40 mg of the drug of the formulation F-7 was replaced with barium sulfate and its other ingredients were kept constant. This amount was determined experimentally to allow X-ray visibility but not to hinder tablet buoyancy.

After overnight fasting, the volunteers were fed with a low calorie food. After ½ hour, a barium sulfate-labeled tablet was given to every subject with 200 ml of water. The volunteers were asked to take 200 ml water after every 1 hour. At different time intervals (0, 0.5, 1.5, 4 and 6 hrs post-administration of tablets), volunteers were exposed to abdominal X-ray imaging (Genesis 50, Josef Betschart AG, Brunnen, Switzerland) in standing position.

A radiograph was made just before administration of the tablet, at zero time, to ensure the absence of radio-opaque material in the stomach. The distance between the source of X-rays and the subject was kept constant for all images. Thus, the observation of the floating tablet movements could be easily observed (8) and the mean gastric retention period could be estimated.

RESULTS AND DISCUSSION
Baclofen solubility in physiological solutions of pH of 1.2, 4.5 and 6.8 and at 37 °C were 25, 5.8 and 5.1mg/ml, respectively.

The DSC analysis of the drug alone elicited an endothermic peak at 210°C (theoretical value is 208°C) (9) and it was found that the endothermic peaks of physical mixtures as well as tablet reflected the characteristic features of baclofen alone. From the results of thermograms of baclofen and its physical mixtures (1:1) which is shown in figure 1, it appears that there was no drug excipient interaction.

Preparation and In vitro evaluation of baclofen gastro retentive floating tablets
Granules were prepared and compressed with the ratio 22 and 25% of the floating agent when the total weight of the tablets were 180 mg and 200 mg respectively to get the floating lag time within 5 min with the same concentration of same polymer. The formulations with 200 mg tablet weight were compressed with 22.2% floating agent and the floating lag time was found to be higher than 10 minutes. The results of physical evaluation are listed in table 3.

Figure 2, shows chromatograms of the standard baclofen (10μg/ml) and sample. Figure 3 and 4, show percent of the drug release of the prepared baclofen tablets and marketed tablets at pH 1.2.

*In vitro buoyancy and Mean dissolution time*
Floating lag time of all formulations and floated for more than 10 hrs in dissolution medium pH 1.2 (Table 4) was less than 4 min. MDT values for all formulations are listed in table 4. A higher value of MDT indicates a higher drug retarding ability of the polymer and vice versa. Lowest MDT was observed with F-6 formulation which contained HPMC K15M polymer.

Table 2. Formulation compositions of baclofen floating tablets.

Formula	F-1	F-2	F-3	F-4	F-5	F-6	F-7	**F-8**
Baclofen (mg)	**20**	**20**	**25**	**25**	**30**	**30**	**40**	**40**
Avicel 101 (mg)	24.2	24.2	30.25	24.1	24	24	24	24
Methocel K 100M (mg)	65	-	-	65	65	-	60	-
Methocel K 15M (mg)	-	65	81.25	-	-	60	-	60
HPMC E6-LV (mg)	20	20	25	20	20	17.2	17	17
Sodium bicarbonate (mg)	40	40	50	45	50	40	50	50
PVPK 30 (mg)	9	9	11.25	9	9	7	7	7
Mg Stearate	1.8	1.8	2.25	1.9	2.0	1.8	2.0	2.0
Total (mg)	180	180	225	190	200	180	200	200
Remarks	*Floated*	*Floated*	*Not floated*	*Floated*	*Floated*	*Floated*	*Floated*	*Floated*

Table 3. Physical evaluation of baclofen floating tablets.

Formula	Compression Force (Tonnage)	Hardness (N)	Friability (%)	Thickness (mm)	Weight (mg)	Drug Content (%)
F-1	3	95±5	0.12	3.12±0.05	180±2.2	101.41±0.64
F-2	3	88±6	0.14	3.13±0.08	180±1.9	101.65±0.82
F-3	3	70±8	0.15	3.64±0.06	225±3.1	100.22±0.55
F-4	3	75±5	0.21	3.56±0.04	190±2.2	99.82±1.41
F-5	3	90±7	0.24	3.62±0.12	200±1.9	99.68±0.92
F-6	3	90±5	0.11	3.15±0.24	180±2.4	98.97±1.47
F-7	3	85±5	0.13	3.45± 0.36	200±1.8	100.22± 0.82
F-8	3	87±5	0.11	3.48±0.28	200±2.1	99.96±0.91
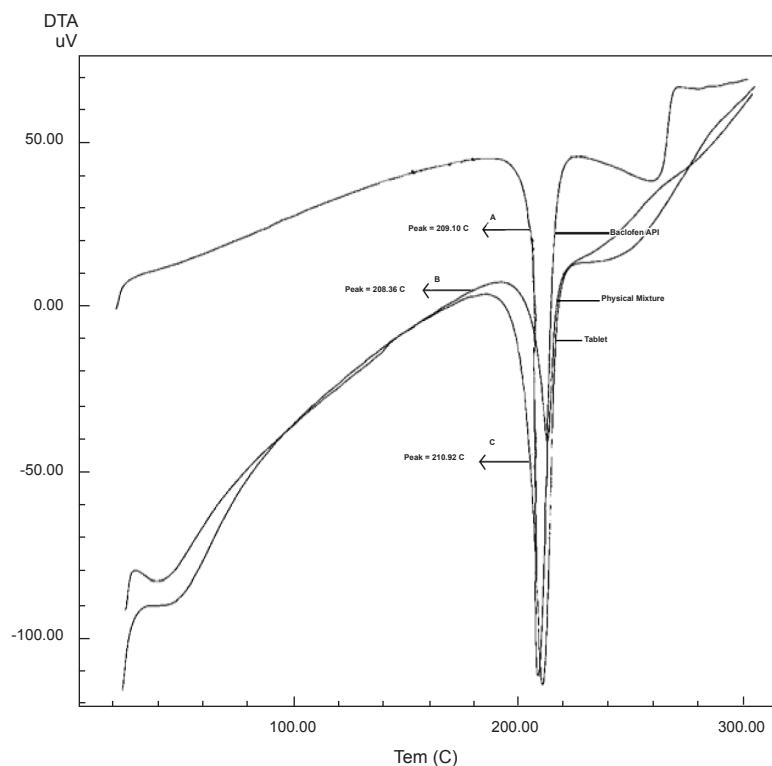
Figure 1. DSC thermograms of pure drug (A) physical mixture (B) and tablet (C).
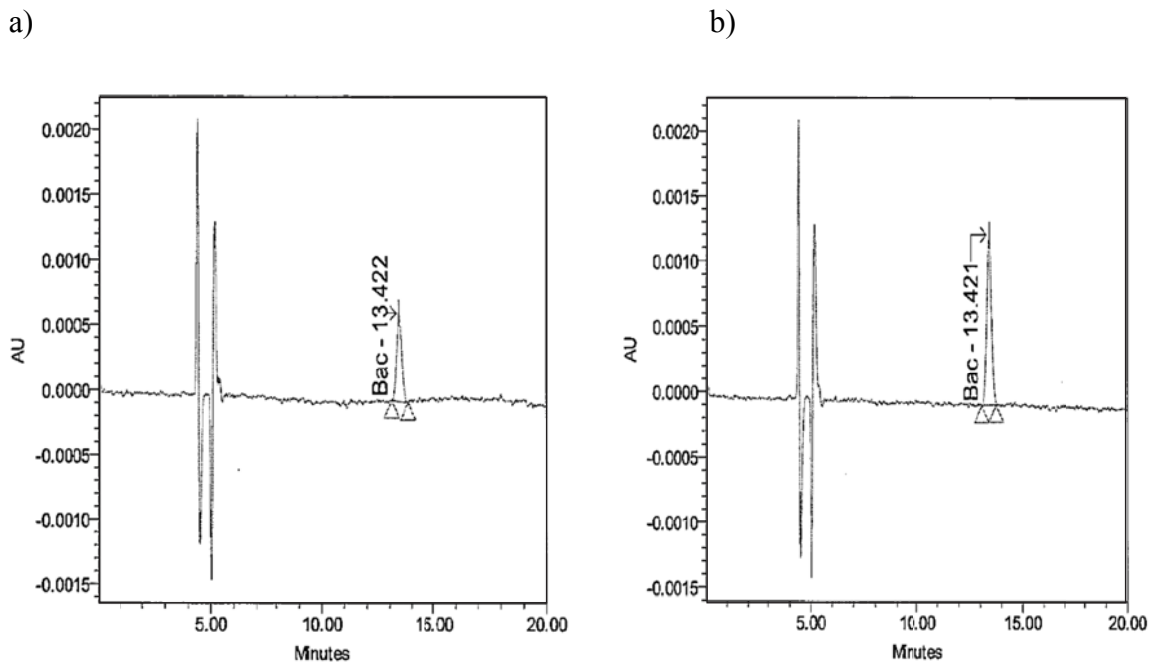
a)

b)

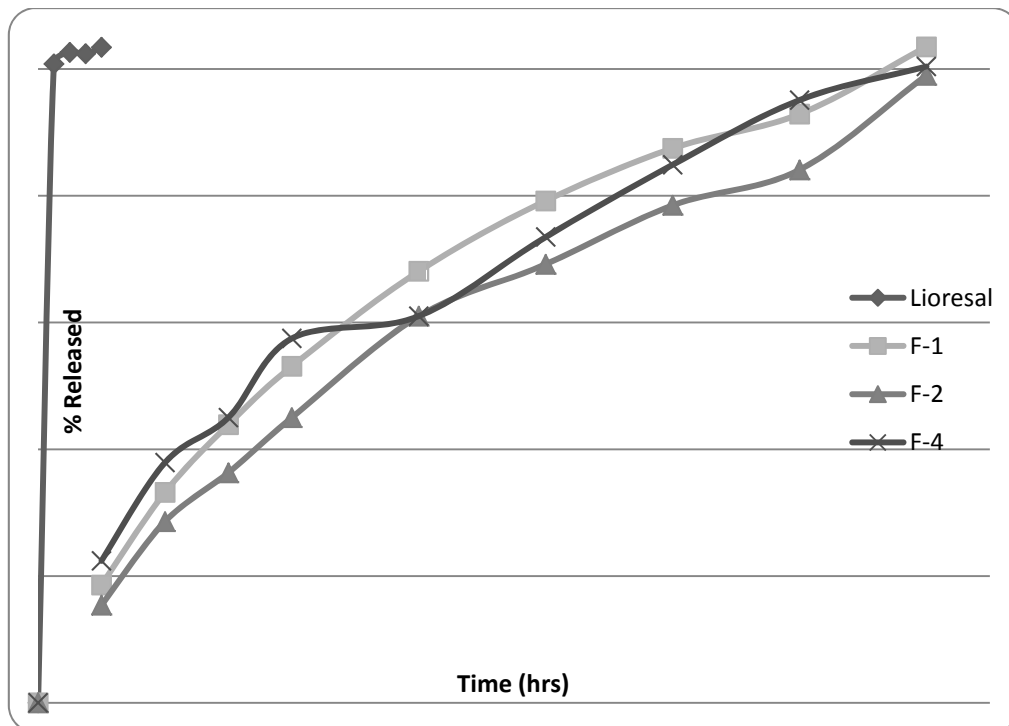**Figure 2.** Chromatograms of baclofen samples. a: Standard 10 µg/ml, b: Sample solutions.

Figure 3. Dissolution profile of lioresal with GRDDS floating tablets F-1, F-2 and F-4.

Table 4. Floating lag time, MDT and % of the release of the prepared baclofen tablets.

Formula	Floating Lag time (Sec)	MDT (10th Hour)	% Release (12 Hour)
F-1	180±20	3.63	93.0
F-2	190±20	3.80	84.1
F-3	ND	ND	ND
F-4	170±30	3.58	95.1
F-5	210±15	3.20	101.1
F-6	200±15	2.90	100.0
F-7	240±15	3.60	105.8
F-8	240±15	3.15	101.5

*ND – Not determined

Table 5. Release parameters of baclofen floating tablets.

Formula	Zero Order (r^2)	K_0	First Order (r^2)	K Values	Higuchi (r^2)	K_h	Peppas (r^2)	N Value
F-1	0.930	6.80	0.353	0.115	0.992	28.8	0.981	0.611
F-2	0.955	6.48	0.387	0.118	0.986	26.9	0.949	0.649
F-3	-	-	-	-	-	-	-	-
F-4	0.923	6.41	0.329	0.108	0.993	27.25	0.966	0.566
F-5	0.891	7.50	0.461	0.235	0.994	29.82	0.969	0.569
F-6	0.886	7.22	0.469	0.235	0.985	28.67	0.980	0.580
F-7	0.926	9.58	0.487	0.303	0.997	33.79	0.955	0.555
F-8	0.887	9.12	0.458	0.294	0.996	32.84	0.927	0.527

Effect of the polymer grade on the release of baclofen

Formulations containing HPMC E6-LV in combination with Methocel K100M or K15M were compared to explore the effect of polymers and amount of the drug release (Table 2). Percent of the release of drug at the end of twelfth hour for F-1, F-2, F-4, F-5 and F-6 were 93.0%, 84.1%, 95.1%, 101.1% and 100.0% respectively (Table 4). These values indicated a decrease of the drug release by increase in polymer. Increasing the weight of tablet (F-3) stopped its floating and hence the in vitro release profile was not studied. R^2 values obtained from zero order equation for F-1, F-2, F-4, F-5 and F-6 were 0.930, 0.955, 0.923, 0.912 and 0.886 respectively (Table 5). The best linearity values found in Higuchi's equation plot were 0.99, 0.986, 0.993, 0.994 and 0.985 respectively indicating the release of drug from matrix as a square root of time dependent process based on diffusion. The n values for korsmeyer and peppas equation (F-1, F-2, F-4, F-5 and F-6) were found to be 0.61, 0.65, 0.56, 0.56 and 0.58 respectively, indicating non-Fickian (anomalous) release, coupled diffusion, and polymer matrix relaxation, 0.5<n<0.89. Thus, it was proposed that these formulations delivered their active compounds by coupled diffusion and erosion (10).

In formulations F-7 and F-8, the percent of the drug release at tenth hour was 105.8% and 101.5%. R^2 values obtained from zero order equations were 0.926 and 0.887 respectively (Table 5). The n values were found to be 0.55 and 0.52 respectively, indicating non fickian (anomalous) release, coupled diffusion. The best linearity was found in Higuchi's equation plot (F-7) which was 0.997 indicating the release of drug from matrix as a square root of time dependent process based on diffusion mechanism. The (F-8) formulation value was near to the zero order release.

The formulations containing HPMC K100M polymer showed zero order release and was found to follow predominantly non fickian (anomalous) release coupled diffusion mechanism.

Immediate release tablets showed 100% drug release within 15 min (11), the drug release rates from the prepared SR matrix tablets were significantly retarded when compared with the rates from standard lioresal 25mg tablets.

No significant change was observed in baclofen release rate (Figure 5) and tablets were buoyant for 12 hrs in 0.1N HCl when subjected to stability study for three months.

The mean gastric retention period
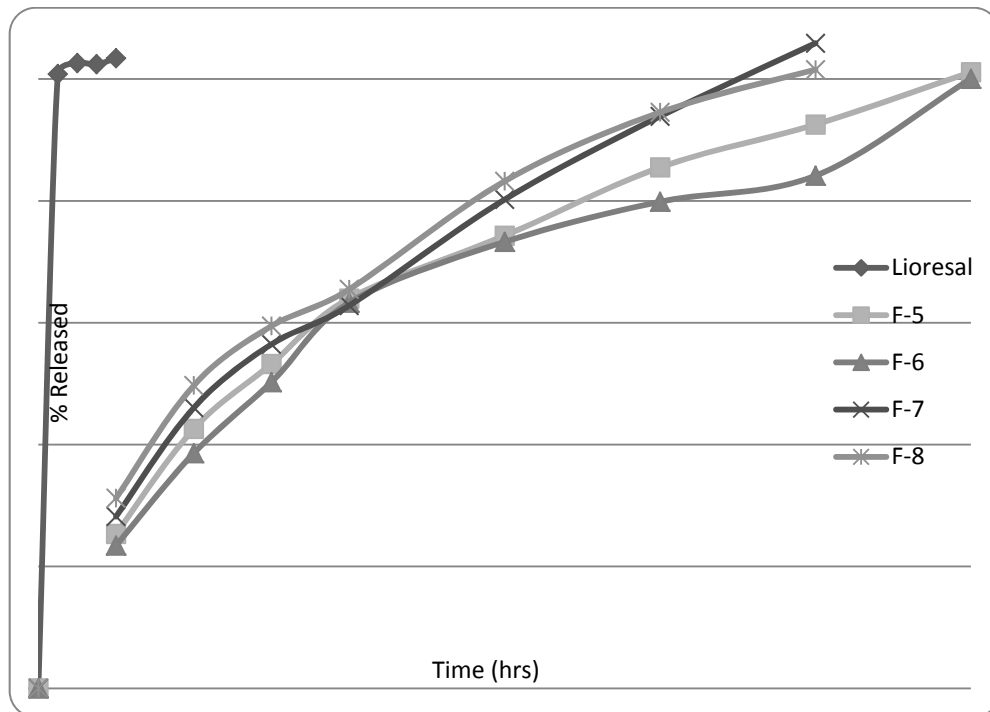
The floating lag time of barium sulfate-loaded

Figure 4. Dissolution profile of lioresal with GRDDS floating tablets F-5, F-6, F-7 and F-8.
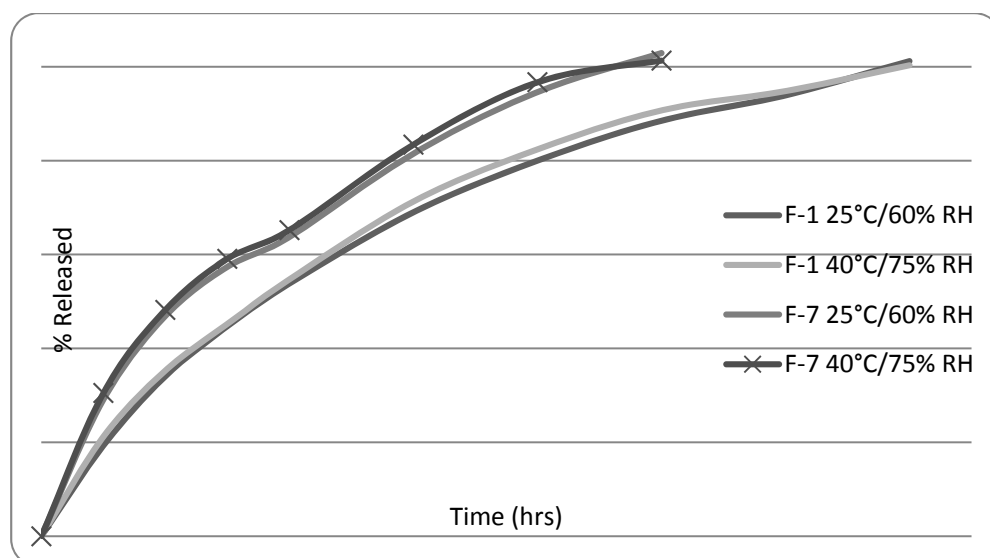

Figure 5. Influence of storage condition on % drug release for 3 months.

tablet was 270±10s. X-ray images taken at different intervals after administration of the barium sulfate-loaded tablets in six healthy human volunteers showed that tablet was more or less at the same position in stomach for the first 3 hrs and moved slightly downwards and remained within the stomach till the end of 6 hrs. The mean gastric retention period was 5.50±0.77 hrs.

From the results of this study may concluded that, drug load, amount of soluble component, type of the polymer and the polymer content of the matrix affected significantly the release profile of baclofen.

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