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Research Article

INFLUENCE OF HYDROPHILIC POLYMERS ON RELEASE PROFILE OF BACLOFEN FROM BILAYER TABLET

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ABSTRACT

This work was done to investigate the influence of hydrophilic polymers on release profile of Baclofen from bilayer tablet. The sustained release layer comprised of matrix of different types and concentration of hydrophilic polymers as retardants . Immediate release layer consisted of sodium starch glycolate and directly compressible microcrystalinecellulose (MCC). Hydrophilic polymers like Hydroxy propylmethyl cellulose-K4M (HPMC-K4M), Carboxymethylcellulose (CMC), Methylcellulose (MC), Polyethleneoxide (PEO) were chosen for formulation of controlled release matrix layer containing Baclofen. Precompression evaluation for flow properties and compression characteristics was carried out for granules. The flow and compression characteristics of the prepared granules significantly improved by virtue of granulation process. Also, the prepared bilayer tablets showed good mechanical properties. Formula H2 containing HPMC K4M (40mg) gave sustained release profile after 12 hr with cumulative drug release of 99.20% drug with release pattern of Higuchi's pharmacokinetic model showing correlation coefficient of 0.981.

Keywords: Baclofen, Bilayer Tablet, Hydrophilic matrix.

INTRODUCTION

Many strategies are available for the design and development of bilayer tablet. The primary purpose of these drug delivery is to improve the state of disease management by modifying pharmacokinetic profiles of therapeutic agents normally administered as conventional tablet or capsules. Conventional oral dosage forms often produce fluctuations of drug plasma level that either exceed safe therapeutic level or quickly fall below the minimum effective level; this effect is usually totally dependent on the particular agent's biologic half-life, frequency of administration, and release rate. It is recognized that many patients can benefit from drugs intended for chronic administration by maintaining plasma levels within a safe and effective range. 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. It shows peculiar pharmacokinetic characteristics. The half-life of the drug is ~2.5 to 4 hours in plasma.[1] In addition, many reports stated that absorption of baclofen is through facilitated-intestinal transport.[2,3] Therefore, gastric and intestinal transient times have a significant effect on the rate and extent of oral absorption of the drug. As a result, variable oral bioavailability may be expected with conventional tablets.

Adverse effects (eg, drowsiness, lethargy, hypotension) are associated with rapid plasma peaking. Consequently, these effects have limited the clinical efficacy of oral baclofen administration.[4,5] Therefore, it is recommended to initiate the therapy with a minimum effective dose,[3] by loading dosage and maintaining therapeutic level concentration by matrix layer.

Bi-layer tablets containing Metformin HCl as sustained release and Pioglitazone HCl as immediate release layer. Sustained layer were prepared by wet granulation method using different viscosity grade of HPMC (HPMC K4M & HPMC K100M) as polymers and immediate release layer were prepared by direct compression method using superdisintegrants such as sodium starch glycolate and crosscarmellose sodium. It followed by Higuchi's kinetic model. Optimized formula gave burst release of Pioglitazone HCl followed by sustained release of Metformin HCl for 8 hr.

The direct application of baclofen into the spinal subarachnoid space avoids the dose-limiting adverse effects of its oral administration and can eliminate spasticity of spinal cord origin even at low efficient doses.[7-9] This drug has to be injected chronically in the intrathecal space by implanted pumps, which are very expensive, are uncomfortable, and sometimes lead to side effects.[6,9]

Therefore, this work aims at modifying oral baclofen release, in an attempt to minimize dose fluctuation and improve therapeutic response for patients suffering from spasticity and chronic musculoskeletal conditions. Moreover, different tablet formulations were tested to endow the formulator with a higher degree of flexibility during scaling up.

MATERIALS AND METHODS

Materials

Baclofen (Gifted from Sun Pharmceuticals industries ltd., Vadodara.), Sodium starch glycolate, Microcrystalinecellulose (MCC), Hydroxy propylmethyl cellulose-K4M (HPMC-K4M) , Carboxymethylcellulose (CMC), Methylcellulose (MC), Polyethleneoxide (PEO), Mannitol, Magnesiulm steareate (), Polyvinlypyrolidine (PVP) (Obtained from local market).

Drug-Excipient Interactions

Powder blends (50mg) of drug and polymer *i.e* HPMC K4M, CMC, MC, PEO were prepared using geometric dilution method. Differential scanning calorimetry was conducted first with samples of the pure polymers and pure polymers. The DSC profiles thus obtained were compared for possible drug-polymer interactions.

Solubility Studies

The equilibrium solubility of baclofen was measured in 0.1 M hydrochloric acid (pH 1.2), acetate buffer (pH 5), and phosphate buffers (pH 6.8 and pH 7.4). Excess amounts of the drug were added to 50 mL-stoppered conical flasks (n = 2). The flasks were shaken mechanically at 37°C ± 0.5°C for 24 hours. After another 2 days of equilibrium, aliquots were withdrawn and filtered (0.22-µm pore size filter paper). Then, the filtered samples were diluted with an appropriate amount of 0.1 M hydrochloric acid to obtain final solutions of pH 1.2. The final solutions were measured by first derivative (D_1) spectrophotometry at 226.5 nm, adopting the peak height method (Shimadzu-UV 160A spectrophotometer, Shimadzu, Kyoto, Japan).

Preparation of Bilayer Tablets

A) Immediate Release Layer

The composition of 13mg Baclofen immediate release layer is given in Table 1. Powder was sieved through a No. 80 sieve. Calculated amount (for 180 tablet batch) of the drug, super disintegrant (sodium starchglycolate) and filler (MCC) was mixed in geometric proportion.

B) Modified Release Layer

Nine different tablet formulation were prepared using wet granulation technique. The composition of Baclofen matrix layer of bilayer tablet is given in Table 1. All powder components were sieved through a No. 80 sieve. Calculated amount (required to prepare a 20 tablet batch) of the drug, Polymer (HPMC-K4M, CMC, MC, PEO) and filler (mannitol) were weighed and mixed thoroughly. A sufficient volume of granulating agent (10%w/v PVP in IPA) was added to the powder mix to obtain a cohesive mass which was sieved through a No. 12 sieve. The granules were dried at 60° C for 15 min in tray dryer. The dried granules were collected and screened through No. 22 sieve. The granules were evaluated for derived properties after addition of magnesium stearate and fines.

An appropriate amount of the mixture of both the individual layer was weighed and then compressed using a rotary tablet compression machine (B tooling).

Table 1: Composition of 40 Mg Baclofen Bilayer Tablet Formulations

Formulations	H1	H2	H3	C1	C2	C3	P1	P2	P3
A. Immediate release layer									
Baclofen	13	13	13	13	13	13	13	13	13
Sodiumstarchglycolate	20	20	20	20	20	20	20	20	20
MCC	67	67	67	67	67	67	67	67	67
B. Sustained release layer									
Baclofen	27	27	27	27	27	27	27	27	27
HPMC-K4M	20	40	60	-	-	-	-	-	-
CMC	-	-	-	10	20	30	-	-	-
MC	-	-	-	10	20	30	-	-	-
PEO	-	-	-	-	-	-	10	20	40
Mannitol	151	131	111	151	131	111	161	151	131
Magnesium stearate	2	2	2	2	2	2	2	2	2

Evaluation of Granules

Angle of repose

Static angle of repose was determined according to the fixed funnel and freestanding cone method, according to the method reported by Raghuram et al,[11] whereby granules were carefully poured through the funnel with its tip at 2-cm height, H, until the apex of the conical heap so formed just reached the tip of the funnel. The mean diameter, 2R, of the base for the powder cone was measured and the angle of repose (θ) was calculated using the following equation:

Equation: 1 $\tan\theta = H/R$

Bulk density and tapped density

Both bulk density (D_o) and tapped densities (D_T) were determined, according to the method reported by Raghuram et al,[11] whereby a quantity of granules from each formula, was introduced into a 10-mL measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at 2-second intervals. The tapping was continued until no further change in the volume was noted.[12]

Compressibility percentage

The compressibility index of the granules was determined by Carr's compressibility percentage[12]:

Equation: 2 $\text{Compressibility \%} = (D_T\text{-}D_0)/D_T \times 100$

Hausner's ratio

Hausner found that ratio of D_T/D_0 was used to predict powder flow properties as well as study of interparticle friction.

Evaluation of Tablets

Average weight of the dosage unit

To study weight variation, 10 tablets of each formulation were weighed using an electronic balance (Mettler Toledo, Basel, Switzerland). Weight values were reported in milligrams. Mean and SD were calculated.

Thickness

The thickness of the tablets was determined using a thickness gauge. Ten tablets from each batch were used. Thickness values were reported in millimeters. Mean and SD were calculated.

Drug content

Five tablets were weighed individually, then placed in a mortar and powdered with a pestle. An amount equivalent to 40-mg drug was extracted with 100 mL of 0.1 M hydrochloric acid and sonicated for 15 minutes. The solution was filtered through a filter paper (0.22-µm pore size), properly diluted with 0.1 M hydrochloric acid, and then the drug content was measured as previously mentioned.

Friability test

For each formulation, 6 tablets were weighed. The tablets were placed in a friabilator (Roche's Friabilator) and subjected to 100 rotations in 4 minutes. The tablets were then dedusted and reweighed. The friability was calculated as the percentage weight loss.

Hardness test

For each formulation, the hardness of 6 tablets was determined using a hardness tester (Pfizer hardness tester). Hardness values were reported in kilograms (kg). Mean and SD were calculated.

In vitro release studies

In vitro release studies of baclofen matrix tablets were monitored. The release experiments were performed in a 900-mL dissolution medium of 0.1N HCl (pH 1.2) for the first 2 hours, then replaced with the same volume of a phosphate buffer solution (pH 6.8) kept at 37°C ± 0.5°C and stirred at 75 rpm, using US Pharmacopeia dissolution apparatus 2 (perfect sink conditions). A 5-mL sample was withdrawn at desired time interval and replaced with another 5 mL of a suitable fresh dissolution medium, for up to 12 hours. The amount of the drug was determined as previously mentioned.

Release kinetics

Different pharmacokinetic models (First-order, Zero-order, Higuchi's model and korsmeyer-peppas model) were applied to interpret the release kinetic of the drug from different matrix systems.

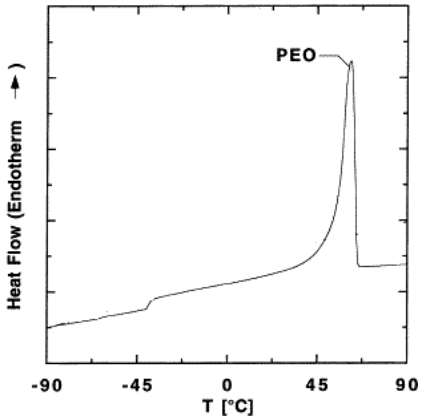
RESULT

Solubility study

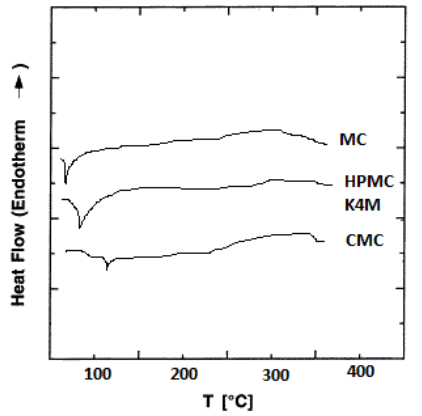
Baclofen is a amphoteric compound. The results of baclofen solubility in physiological solutions of pH 1.2, pH 5, pH 6.8, and pH 7.4 were 26, 6, 5.2, and 5.1 mg/mL, respectively, at 37°C. These pH values, rather than pH 1.2, were nearly closer to the isoelectric point (pH 7), and thus the predominant form was zwitterions, the least soluble form. The higher solubility value from pH 1.2 can be shows to rapid protonation (pK_{a1} 9.6) of the amino group. Consequently, ammonium ions predominantly exist.

Physical properties of granules

Baclofen powder and the prepared granules were evaluated for angle of repose, bulk density, tapped density, Hausner's factor (HF), and compressibility index (Table 2). Angle of repose of baclofen powder was not possible because of high cohesiveness of powder.



Drug-excipient interactions: As per the DSC graph of pure drug and pure polymer shows that there is no interaction between them.



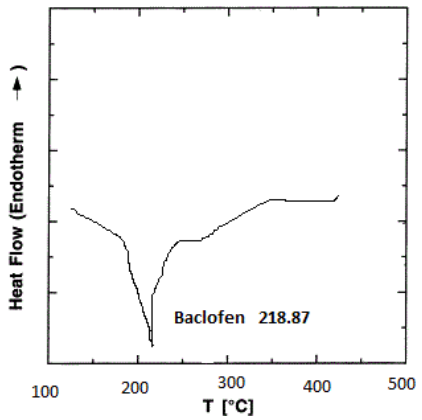


Table 2: Physical Properties of the Prepared Granules, Using Sodium Alginate, Methylcellulose, and Sodium Carboxymethylcellulose, as Matrix-Forming Polymers

Formulations	Angle of Repose (θ)	Bulk Density (g/cm³)	Tapped Density (g/cm³)	Hausner Factor	Compressibility (%)
Pure drug	—	0.241	0.611	2.535	58.98
H1	22	0.282	0.325	1.152	13.23
H2	23	0.301	0.351	1.166	14.24
H3	25	0.291	0.332	1.141	12.34
C1	21	0.501	0.581	1.159	13.76
C2	22	0.491	0.552	1.124	11.05
C3	26	0.481	0.541	1.124	11.09
P1	25	0.322	0.402	1.248	19.90
P2	29	0.401	0.471	1.174	14.86
P3	30	0.422	0.483	1.144	12.62

Furthermore, HF measured for baclofen powder was 2.53, indicating the cohesiveness of the powder and, consequently, the very poor flowability. HF values of the prepared granules ranged from 1.12 to 1.25 indicating good flow property. Also, the granulation lowered the tapped density as a result of a relative increase in particle size compared with the simple drug powder (Table 2). The bulk densities of the granules (C1 to C3 and P2-P3) found to be quite higher than those of H1 to H3 granules. The percentage compressibility, an indirect method of measuring powder flowability from bulk densities developed by Carr, was calculated according to Equation 2. From Table 2, percentage compressibility of baclofen powder was 58.98. This result was in good agreement with the results of angle of repose and HF, whereas the values of the prepared granules ranged from 11.05 to 20.37, supporting the idea that granulation improved both flowability and compressibility.[11,12] Finally, both polymer level and polymer type did not affect the physical properties of the prepared granules markedly.

Physical properties of tablet

Various physical properties of tablets were measured. Compression force was kept constant for all formulations. Average weight with standard deviation for each batch is shown in table-3. Standard deviation obtained between 0.89 to 2.87 shows weight uniformity of tablets. The thickness of the prepared tablets ranged from 1.83 ± 0.04 mm to 2.71 ± 0.08 mm. Also, it was observed that increasing polymer concentrations resulted in a slight decrease in the thickness of the tablet formulations. Friability data of tablets in table-3 indicates decrease in friability with increase in polymer concentration. The friability values obtained between 0.15 to 0.20 % are within the accepted limit as per EP and USP. As per USP hardness of sustained release tablet should be between 6-10kg. In this study hardness obtained was between 8-10 kg. Hardness increase with increase in polymer concentration because of high binding capacity of hydrophilic polymer. Drug content ranged between 96.43 to 101.94 %.

Table 3: Compression Force, Hardness, Friability, Thickness, Weight, and Drug Content of the Prepared Hydrophilic Matrix Tablets, Expressed as Mean ± SD

Formulations	Compression Force (tonnes)	Hardness (kg)	Friability (%)	Thickness (mm)	Weight (mg)	Drug Content (%)
H1	2	8 ± 0.57	0.18	2.33 ± 0.05	100.05 ± 0.97	101.94 ± 0.52
H2	2	9 ± 0.77	0.17	2.22 ± 0.08	102.45 ± 0.89	101.76 ± 0.82
H3	2	10 ± 0.62	0.15	2.11 ± 0.07	99.88 ± 2.00	100.44 ± 0.64
C1	2	8 ± 0.65	0.20	2.71 ± 0.06	100.43 ± 1.57	101.43 ± 0.55
C2	2	9 ± 0.93	0.17	2.43 ± 0.12	100.23 ± 3.15	98.54 ± 0.98
C3	2	9 ± 0.83	0.15	1.94 ± 0.08	101.03 ± 2.87	98.55 ± 0.98
P1	2	8 ± 0.48	0.19	2.27 ± 0.04	99.45 ± 1.85	99.60 ± 0.82
P2	2	9 ± 0.87	0.16	1.84 ± 0.03	101.53 ± 1.78	97.77 ± 0.92
P3	2	10 ± 0.61	0.15	1.83 ± 0.01	98.34 ± 1.78	96.43 ± 0.78

Table 4 : %cumulative baclofen release from various formulation tablets performed in 900ml dissolution media first 2 hour 0.1N HCl (pH 1.2) and after replace with Phosphate buffer (pH 6.8) using USP apparatus – II at speed 75 rpm.

% Cumulative drug release									
Time (hr)	H1	H2	H3	C1	C2	C3	P1	P2	P3
0.25	28.68	27.88	28.68	28.00	26.22	27.56	26.98	29.00	28.66
0.5	31.85	30.55	31.00	28.98	29.65	30.12	29.35	30.00	29.98
2	33.08	32.56	33.00	33.09	31.65	32.99	32.85	33.20	33.75
3	33.30	33.68	34.20	34.12	33.23	34.65	34.62	34.22	34.12
4	40.00	41.56	40.12	52.32	39.12	40.32	41.25	39.67	40.32
5	48.65	51.85	42.35	65.62	46.23	44.32	45.32	48.35	49.12
6	56.24	59.69	50.65	75.95	51.35	55.33	59.78	57.16	55.62
7	68.26	67.24	55.86	86.52	60.45	62.35	64.26	62.64	62.39
8	75.66	76.00	61.35	90.32	69.89	69.35	72.85	71.64	70.34
9	79.98	82.36	68.75	95.32	78.62	74.62	81.23	79.89	77.64
10	85.65	89.68	75.32	99.32	84.61	80.32	89.32	82.56	81.62
11	91.26	94.85	81.20	95.32	89.65	85.64	92.32	88.65	87.64
12	98.99	99.20	85.65	90.36	94.62	89.64	96.32	95.78	92.89

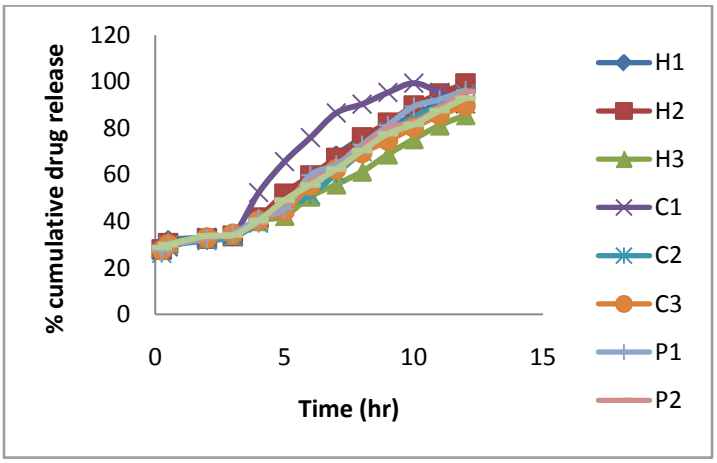


Fig. 1: Percentage cumulative baclofen release profile of various formula

In vitro drug release study

From Figures 1 the drug release rate from HPMC K4M, CMC, and PEO based hydrophilic matrix tablets decreased with the increase in the polymer level in case of formula C1-C3 and P1-P3. Due to retardation of drug release from matrix containing high concentration of polymer. In formula H2 shows maximum release 99.20% after 12 hr. also it shows immediate release within the first half an hour from the immediate release layer.

Release Kinetic

Different Pharmacokinetic models like First-order, Zero-order, Higuchi model and korsmeyer peppas model was applied to optimized formula H2. Zero order release kinetic obtained with highest correlation coefficient (r^2) 0.978 Figure-2. Higuchi model was excellent fit for this formula, described good sustained release profile.

Table 5: Release parameters of Optimized formula H2 of Baclofen matrix bilayer tablet

Zero order		First order		Higuchi model		Korsmeyer peppas	
r^2	K_o	r^2	K_1	r^2	K_H	r^2	n valule
0.978	5.844	0.757	0.1386	0.891	26.9	0.783	0.69

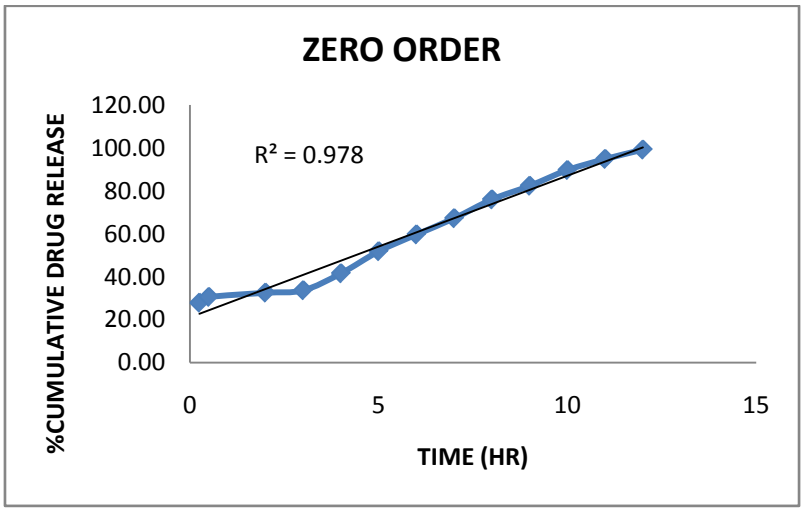


Fig. 2: Zero order release kinetic of optimized formula H2

CONCLUSION

In vitro release studies demonstrated that the release of baclofen from optimized formula H2 matrix tablet formulations was generally sustained. The best linearity values found in Higuchi's equation plot were 0.891 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 for H2 were found to be 0.69 indicating non-Fickian (anomalous) release, coupled diffusion, and polymer matrix relaxation, 0.5<n<0.89. Thus, it was proposed that these formulation delivered their active compounds by coupled diffusion and erosion Therefore, these polymers can be used to modify release rates of baclofen in hydrophilic matrix tablets.

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