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Formulation of Controlled-Release Baclofen Matrix Tablets: Influence of Some Hydrophilic Polymers on the Release Rate and In Vitro Evaluation

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ABSTRACT

This work aims at investigating different types and levels of hydrophilic matrixing agents, including methylcellulose (MC), sodium alginate (Alg), and sodium carboxymethylcellulose (CMC), in an attempt to formulate controlled-release matrix tablets containing 25 mg baclofen. The tablets were prepared by wet granulation. Prior to compression, the prepared granules were evaluated for flow and compression characteristics. In vitro, newly formulated controlled-release tablets were compared with standard commercial tablets (Lioresal and baclofen). The excipients used in this study did not alter physicochemical properties of the drug, as tested by the thermal analysis using differential scanning calorimetry. The flow and compression characteristics of the prepared granules significantly improved by virtue of granulation process. Also, the prepared matrix tablets showed good mechanical properties (hardness and friability). MC- and Alg-based tablet formulations showed high release-retarding efficiency, and good reproducibility and stability of the drug release profiles when stored for 6 months in ambient room conditions, suggesting that MC and Alg are good candidates for preparing modified-release baclofen tablet formulations.

KEYWORDS: Baclofen, modified release, hydrophilic matrix, drug-excipient compatibility.

INTRODUCTION

Many strategies are available for the design and development of modified-release drug delivery formulations. The primary purpose of these drug delivery devices is to improve the state of disease management by modifying the pharmacokinetic profiles of therapeutic agents normally administered as conventional tablets 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.[1] 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.[2] In addition, many reports stated that absorption of baclofen is through facilitated-intestinal transport.[3,4] 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.

Common adverse effects (eg, drowsiness, lethargy, hypotension) are associated with rapid plasma peaking. Consequently, these effects have limited the clinical efficacy of oral baclofen administration.[5,6] Therefore, it is recommended to initiate the therapy with a minimum effective dose,[4] starting at a low dosage and increasing gradually until the optimum effect is achieved (usually 40-80 mg daily).

Similarly, levodopa, the most effective antiparkinsonian agent, shows peculiar peripheral pharmacokinetic features, which contribute to inter- and intrapatient variability in its disposition and complicate long-term administration (highly presystemic metabolism, facilitated intestinal absorption, and fast metabolic elimination).[7] Following the observation that intravenous levodopa infusions could significantly ameliorate response fluctuations by maintaining stable and adequate plasma drug concentrations, controlled-release levodopa formulations have been developed and introduced in clinical practice in an attempt to obtain smoother levodopa plasma profiles and therapeutic response.[8]

Controlled-release levodopa/carbidopa at 4:1 ratio uses a monolithic matrix system to release both active components, through surface dissolution and erosion of the tablet, within 2 to 2.5 hours in vitro, compared with the 30 minutes of the standard-release formulations.[8-11] This controlled release

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Table 1. Composition of 25 mg Baclofen Tablet Formulations*

Formulations	A-2	A-4	A-6	M-2	M-4	M-6	C1-2	C1-4	C1-6	C2-2	C2-4	C2-6
Alg[1]	20	40	60	—	—	—	—	—	—	—	—	—
MC	—	—	—	20	40	60	—	—	—	—	—	—
CMC[3,4]	—	—	—	—	—	—	20	40	60	20	40	60
E-RS100	—	—	—	—	—	—	—	—	—	2	2	2
Mannitol	54	34	14	54	34	14	54	34	14	52	32	12

* One-hundred-milligram tablets containing 1% Mg stearate. Granulation of A with distilled water; of M and C1 with alcohol 50%; of C2 with ethanolic solution of 4% E-RS100. Alg indicates sodium alginate; MC, methylcellulose; CMC, sodium carboxymethylcellulose.

results in a gradual and more protracted levodopa absorption for 4 to 5 hours.[10] The levodopa bioavailability ranged from 70%[10] to 89%[11] relative to that of standard-release combination. Furthermore, controlled-release levodopa-benserazide is a nonerodible delivery system designed to keep the drug carrier in the stomach for an extended time (3-10 hours in healthy volunteers).[8] The active drugs were released by diffusion for up to 8 hours; levodopa bioavailability was 50% to 60% that of the standard-release combination.[12,13]

The use of controlled-release levodopa-carbidopa formulation lessens peak-dose and "wearing-off" responses occurring with conventional carbidopa/levodopa and offers substantial improvement for some parkinsonians. This effect, however, is obtained at the expense of less predictable time-to-plasma levodopa peaks and decreased bioavailability.[7]

Intrathecal baclofen is the reference treatment for severe spasticity. Cruaud et al[14] encapsulated baclofen into poly(lactide-co-glycolide) microspheres. These microcapsules were capable of releasing baclofen over 2 to 4 weeks. Frederic et al[15] improved the previously mentioned encapsulation process for industrial application (scale-up) and set up an animal model to assess the duration of effect of the new formulations.

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.[16-18] 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.[14,19]

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

Lioresal (25-mg tablets, batch number 004, Novartis Pharma, Cairo, Egypt), baclofen (25-mg tablets, batch number 120025, Cairo Pharmaceutical Co, Shoubra, Egypt), methylcellulose (MC) (viscosity of 2% aqueous solution 7000 centipoises [cp]), and sodium alginate (Alg) (viscosity of 2% aqueous solution 4000 cp) were purchased from Sigma Chemical Co (St Louis, MO); sodium carboxymethylcellulose (CMC) (viscosity of 2% aqueous solution 200 cp) was purchased from Shin-Etsu Chemicals (Tokyo, Japan).

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).

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 and drug-excipient physical mixtures (1:1 wt/wt) 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 (50°C-300°C) at a constant scanning speed (10°C/min) in sealed aluminum pans, using nitrogen as purging gas.

Preparation of Hydrophilic Matrix Tablets

Twelve different tablet formulations were prepared using wet granulation technique. The composition of a 25-mg baclofen tablet is given in Table 1. Powder mix was sieved through a No. 60 sieve. Calculated amount (required to prepare a

20-tablet batch) of the drug, polymer (MC, CMC, or Alg), and filler (mannitol) was mixed thoroughly. A sufficient volume of the specified granulating agents was added slowly. After enough cohesiveness was obtained, the mass was sieved portionwise through a 1-mm sieve. The granules were dried at 50°C for 2 hours in a vacuum oven and thereafter kept in a desiccator for 24 hours at room temperature. The dried granules were collected and screened through a 650-μm sieve. Prior to compression, all prepared granules were evaluated for several tests as mentioned below. Magnesium stearate was added as lubricant; the appropriate amount of the mixture was weighed (100 mg) and then compressed using a Shimadzu laboratory hydraulic press equipped with a 6-mm flat-faced punch and die set. The force and time of compression were 2 tonnes and 10 seconds, respectively. All compressed tablets were stored in an airtight container at room temperature for further study. This method of tablet production has previously been described by several authors who provided reproducible experimental results in terms of in vitro release.[20,21]

For comparative reasons, control tablets were prepared without addition of the used hydrophilic polymers, granulated with ethanol 50% vol/vol (control-1) and with 4% Eudragit RS100 (E-RS100) ethanol solution (control-2).

Evaluation of Starting Material and 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,[22] whereby accurately weighed granules (3 g) 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:

$$\text{Tan } \theta = \frac{H}{R} \qquad (1)$$

Bulk Density

Both poured (or fluff) bulk (D_o) and tapped bulk densities (D_F) were determined, according to the method reported by Raghuram et al,[22] whereby a quantity (3 g) of granules from each formula, previously lightly shaken to break any agglomerates formed, 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.[23]

Hausner's Factor

Hausner found that the ratio $\frac{D_F}{D_O}$ was related to interparticle friction and, as such, could be used to predict powder flow properties.[23]

Compressibility Percentage

The compressibility index of the granules was determined by Carr's compressibility percentage[23]:

$$\textit{Compressibility } \% = \frac{D_F - D_O}{D_F} \times 100 \qquad (2)$$

Evaluation of Tablets

Thickness

The thickness of the tablets was determined using a thickness gauge (Mitutoyo, New Delhi, India). Ten tablets from each batch were used. Thickness values were reported in millimeters. Mean and SD were calculated.

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.

Drug Content

Five tablets were weighed individually, then placed in a mortar and powdered with a pestle. An amount equivalent to 25-mg drug (100 mg) 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.

Hardness Test

For each formulation, the hardness of 6 tablets was determined using a hardness tester (VK 200, Vankel, Varian Inc, Palo Alto, CA). Hardness values were reported in kilograms (kg). Mean and SD were calculated.

Friability Test

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

In Vitro Release Studies

In vitro release studies of standard tablets, control tablets, and baclofen matrix tablets were monitored. The release experiments were performed in a 900-mL dissolution medium of hydrochloric acid 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 50 rpm, using US Pharmacopeia dissolution apparatus 2 (perfect sink conditions). 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 preselected intervals up to 8 hours. The amount of the drug was determined as previously mentioned. Each test was performed in triplicate (correlation of variation < 1.5%).

Release Kinetics

Different kinetic equations (zero-order, first-order, and Higuchi's equation) were applied to interpret the release rate of the drug from matrix systems. The best fit with higher correlation ($r^2 > 0.98$) was found with Higuchi's equation for all the formulations. Two factors, however, diminish the applicability of Higuchi's equation to matrix systems. This model fails to allow for the influence of swelling of the matrix (upon hydration) and gradual erosion of the matrix. Therefore, the dissolution data were also fitted according to the well-known exponential Korsmeyer-Peppas equation,[24] which is often used to describe drug release behavior from polymeric systems:

$$\frac{M_t}{M_\infty} = kt^n \qquad (3)$$

M_t/M_∞ is the fraction of drug release at time t, and k is the kinetic constant; n is the release exponent (indicating the general operating release mechanism). In addition, for determination of the exponent n, one must use only the initial portion of the release curve ($M_t/M_\infty < 0.6$).[25,26] Ritger and Peppas[27] have defined the exponent n as a function of the aspect ratio for 1-dimensional to 3-dimensional systems (slabs, cylinders, and discs). The aspect ratio (2a/l) is defined as the ratio of diameter (2a) to thickness (L). For tablets, depending on the aspect ratios, n value between 0.43 and 0.5 indicates Fickian (case I) diffusion-mediated release, non-Fickian (anomalous) release, coupled diffusion, and polymer matrix relaxation occurs if $0.5 < n < 0.89$, purely matrix relaxation or erosion-mediated release occurs for $n = 1$ (zero-order kinetics), and super case II type of release occurs for $n > 0.89$. The release exponent, n, is the slope of log fraction of drug release vs log time curve, using GraphPad Software Version 3.05 (GraphPad, San Diego, CA).

This equation was successfully applied to evaluate the drug release mechanism from hydrophilic,[28] wax,[29] and plastic matrix tablets.[29]

Due to the differences in drug release kinetics, the constant k, though one of the measures of release rate, should not be used for comparison. Therefore, to characterize the drug release rates in different experimental conditions, mean dissolution time (MDT) was calculated from dissolution according to Mockel and Lippold[30] using the following equation:

$$MDT = \frac{n}{n+1} \times k^{-1/n}\ , \qquad (4)$$

where n is the release exponent and k is the kinetic constant calculated from Equation 3.

Effect of Aging on Release of Baclofen From Some Selected Modified-Release Hydrophilic Matrices

The effect of aging on the drug release from some selected matrix tablets was conducted by storing the tablets in amber bottles at ambient room conditions for 6 months. The dissolution studies of the drug from selected matrix tablets followed the same procedure as previously described.

Statistics

To compare the means of all release data and to assess statistical significance between them, either 1-way analysis of variance (ANOVA) or an unpaired 2-tailed *t* test was performed at the 5% significance level, using GraphPad Software Version 3.05.

Results and Discussion

Solubility Studies

Baclofen is an amphoteric drug. In this case, it is worthy to note that first, 2 dissociation constants can be defined: 1 from the amino group (pK_{a1} 9.6) and the other from the carboxyl group (pK_{a2} 3.8).[2] Second, the zwitterions, the least soluble form,[31] exist at the isoelectric point (pH ~7).[1] 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 ascribed to rapid protonation (pK_{a1} 9.6) of the amino group. Consequently, ammonium ions predominantly exist.

Drug-Excipient Interaction

Figure 1 shows thermograms of baclofen and its physical mixtures (1:1 ratio wt/wt) with the excipients used in this study. The DSC analysis of the drug alone elicited an endothermic peak at 210°C, very close to the reported value of

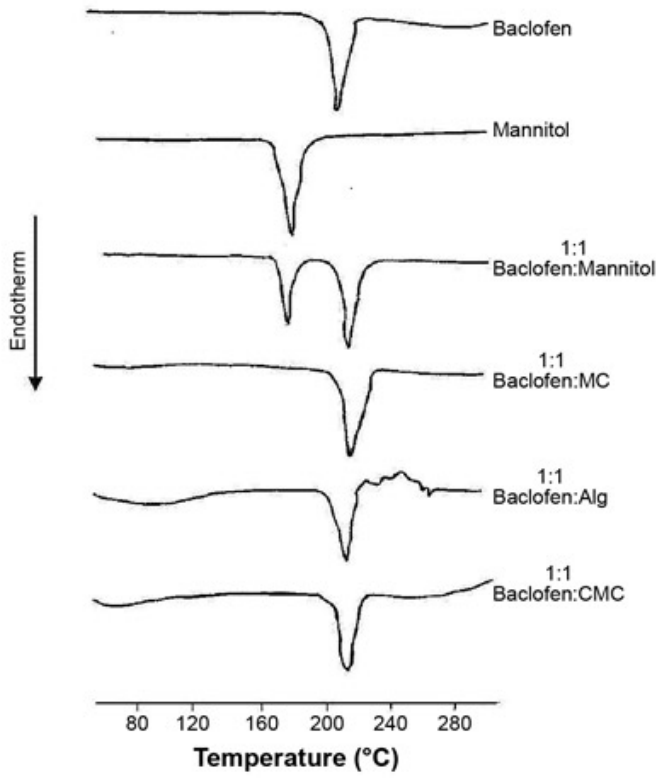

Figure 1. Differential scanning calorimetry thermograms of baclofen and various physical mixtures of baclofen and the used excipients. MC indicates methylcellulose; Alg, sodium alginate; and CMC, sodium carboxymethylcellulose.

baclofen's melting point, which is 208°C,[32] whereas pure mannitol exhibited an endothermic peak at 170°C. Also, it was found that the endothermic peaks of physical mixtures of the drug with mannitol, MC, Alg, or CMC reflected the characteristic features of baclofen alone. Thus, it was thought to indicate that there was no evidence of interactions between baclofen and the used excipients.

Physical Properties of Starting Material and Granules

Baclofen powder and the prepared granules were evaluated for angle of repose, bulk densities, Hausner's factor (HF), and compressibility index (Table 2). The angle of repose could not be measured by the above-mentioned method for baclofen powder. The powder was too cohesive to flow through the funnel, whereas the values of the prepared granules ranged from 20° to 31°. Furthermore, HF measured for baclofen powder was 2.53, indicating the cohesiveness (internal friction between the particles) of the powder and, consequently, the very poor flowability. HF values of the prepared granules ranged from 1.12 to 1.25. The latter was thought to indicate good flow properties of the prepared granules as a result of increasing particle sizes owing to granulation.[22,33] Also, the granulation lowered the tapped density as a result of a relative increase in particle size compared with the untreated drug powder (Table 2). The bulk densities of the granules (M-2 to 6 and C1-2 to 6) granulated by ethanol 50% vol/vol were found to be quite higher than those of A-2, A-4, and A-6 granulated by water. This might be ascribed to the presence of more fines in the granules. These results were in accordance with those obtained by Raghuram et al.[22] Similarly, bulk densities of the granules (C2-2 to 6) granulated by 4% (wt/vol) E-RS100 solution were found to be lower than those granulated by alcohol 50% (vol/vol). This finding might be ascribed to the binding properties of E-RS100 and the presence of fewer fines in the (C2-2 to 6) granules, compared with alcohol of low binding properties. 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,

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

Formulations	Angle of Repose (θ)	Poured Density (g/cm^3)	Tapped Density (g/cm^3)	Hausner Factor	Compressibility (%)
Pure drug	—	0.241	0.611	2.535	60.55
A-2	23	0.282	0.325	1.152	13.23
A-4	25	0.301	0.351	1.166	14.24
A-6	20	0.291	0.332	1.141	12.34
M-2	20	0.501	0.581	1.159	13.76
M-4	22	0.491	0.552	1.124	11.05
M-6	22	0.481	0.541	1.124	11.09
C1-2	27	0.322	0.402	1.248	19.90
C1-4	30	0.401	0.471	1.174	14.86
C1-6	30	0.422	0.483	1.144	12.62
C2-2	26	0.350	0.421	1.203	16.86
C2-4	25	0.330	0.411	1.245	19.70
C2-6	31	0.301	0.378	1.255	20.37

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 (%)
A-2	2	11.23 ± 0.67	0.14	2.11 ± 0.05	100.05 ± 0.98	101.94 ± 0.52
A-4	2	9.64 ± 0.77	0.18	2.22 ± 0.08	102.45 ± 1.88	101.76 ± 0.82
A-6	2	8.56 ± 0.66	0.18	2.33 ± 0.07	99.88 ± 1.75	100.44 ± 0.64
M-2	2	8.35 ± 0.66	0.17	1.94 ± 0.06	100.43 ± 1.66	101.43 ± 0.55
M-4	2	7.53 ± 0.98	0.19	2.43 ± 0.12	100.23 ± 3.23	98.54 ± 0.98
M-6	2	5.34 ± 0.71	0.21	2.71 ± 0.08	101.03 ± 3.87	98.55 ± 0.98
C1-2	2	9.53 ± 0.75	0.17	1.83 ± 0.04	99.45 ± 1.31	99.60 ± 0.82
C1-4	2	9.83 ± 0.99	0.22	1.84 ± 0.03	101.53 ± 1.43	97.77 ± 0.92
C1-6	2	8.24 ± 0.61	0.26	2.27 ± 0.01	98.34 ± 1.13	96.43 ± 0.78
C2-2	2	7.13 ± 0.84	0.18	2.15 ± 0.03	97.52 ± 0.98	99.87 ± 1.47
C2-4	2	7.63 ± 0.55	0.22	2.24 ± 0.98	100.54 ± 2.52	97.45 ± 1.87
C2-6	2	8.23 ± 0.67	0.26	2.31 ± 0.04	99.37 ± 2.58	96.76 ± 0.92

percentage compressibility of baclofen powder was 60.55. 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.[22,33] Finally, both polymer level and polymer type did not affect the physical properties of the prepared granules markedly.

Physical Properties of Tablets

The compression force and the physical properties of the prepared tablets are presented in Table 3. These properties were studied by determining average weight, thickness, drug content, hardness, and friability of the prepared tablets. For all prepared tablets, the relative SD of weight was under 6% and SDs were quite uniform, ranging from 0.98 to 2.58. It was also observed that the variation of thickness was minimal. 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 increase in the thickness of the tablet formulations. These results might indicate that the polymers had low binding properties. Similarly, the thickness of the tablets after incorporating 2% (wt/wt) E-RS100 as a wet blend in formulations C2-2, C2-4, and C2-6, respectively, was significantly increased ($P < .01$, unpaired t test). The friability of the prepared tablets fell into the range 0.14% to 0.26%. The European and US pharmacopeias state that a loss up to 1% is acceptable. The friability of the prepared tablet increased by increasing the polymer level (Table 3). Also, incorporation of 2% (wt/wt) E-RS100 into CMC-based tablet formulations (C2-2, C2-4, and C2-6) slightly raised percentage loss. These findings were in good agreement with the results of thickness measurements, supporting the idea that the used polymers showed quite low binding properties.

Hardness of the prepared tablets fell into the range 5.34 ± 0.71 kg to 11.23 ± 0.67 kg. Tablets granulated by water (A-2 to 6) showed quite higher hardness than those (M-2 to 6 and C1-2 to 6) granulated by ethanol 50% vol/vol. These results might be ascribed to the better binding properties of the former. Irrespective of polymer type, increasing polymer concentration resulted in quite a decrease in the hardness of the tablet. These results were in good agreement with those of thickness and friability. Similarly, the incorporation of 2% (wt/wt) E-RS100 as a wet blend in formulations C2-2, C2-4, and C2-6 slightly decreased tablet hardness. These findings were also in good agreement with those of friability and thickness.

Physical properties of the standard tablets are presented in Table 4. Baclofen tablets had higher mechanical strength than Lioresal tablets. The respective average drug content of baclofen and Lioresal showed 88.80% ± 1.99% and 98.60% ± 42%, whereas the values of the prepared tablet formulations ranged from 98.54% ± 0.98% to 101.94% ± 0.52% (Table 3).

Table 4. Thickness, Diameter, Weight, Drug Content, Hardness, and Friability of Standard Tablets, Expressed as Mean ± SD

Formulations	Thickness (mm)	Diameter (mm)	Weight (mg)	Drug Content (%)	Hardness (kg)	Friability (%)
Lioresal	3.23 ± 0.42	8.43 ± 0.19	202.65 ± 1.98	98.60 ± 0.42	3.61 ± 0.21	0.22
Baclofen	3.16 ± 0.11	9.23 ± 0.09	257.55 ± 2.88	88.80 ± 1.99	6.32 ± 0.09	0.28

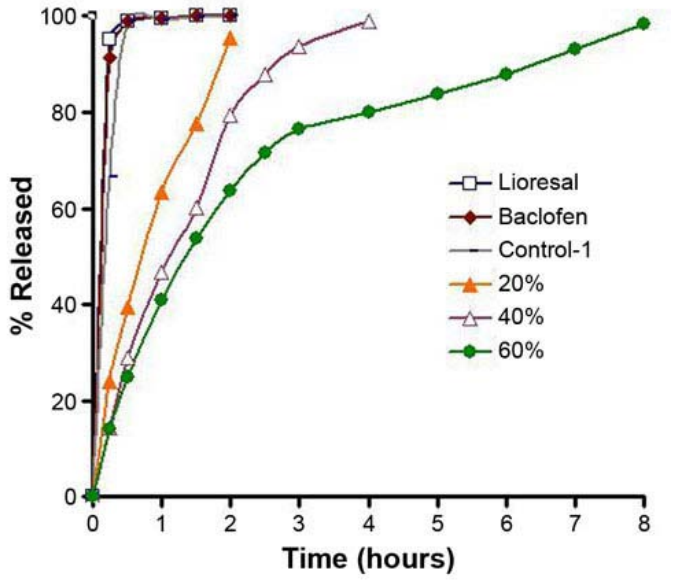

Figure 2. Percentage of baclofen released from standard tablets, control-1 tablet, and methylcellulose matrix tablets, performed in dissolution media of pH 1.2 and 6.8 (n = 3).

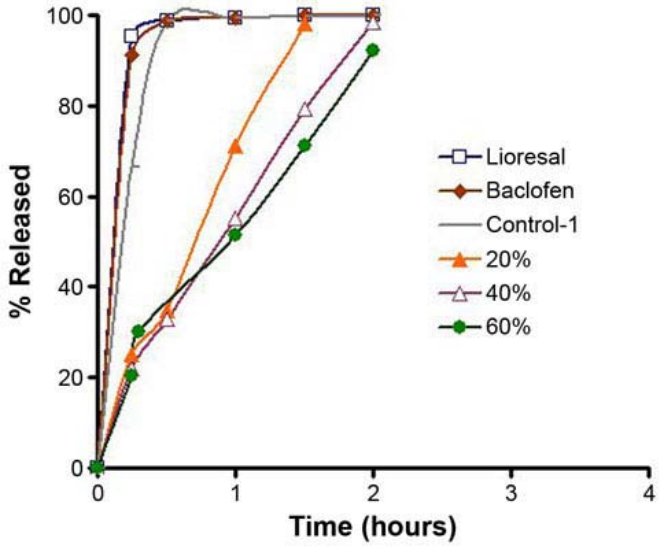

Figure 4. Percentage of baclofen released from standard tablets, control tablets, and sodium carboxymethylcellulose matrix tablets, performed in dissolution media of pH 1.2 and 6.8 (n = 3).

In Vitro Release Studies

Figures 2, 3, 4, and 5 show the in vitro release profile of baclofen from the prepared hydrophilic matrices, standard tablets, and control tablets at pH 1.2 and 6.8. Generally, the drug release rates from the prepared matrix tablets were significantly retarded when compared with the rates from standard tablets (immediate-release commercially available tablets) and control tablets ($P < .0001$, 1-way ANOVA). From Figures 2 and 3, the drug release rate from MC- and Alg-based matrix tablets decreased with the increase in the polymer level. This effect might be ascribed to an increase in the extent of gel formation in the diffusion layer.[34] For instance, Figure 2 shows that formulations containing 20%, 40%, and 60% of MC released ~80% of the drug over 1.5, 2.5, and 5 hours, respectively. Similarly, Figure 3 shows that above 80% of the drug was released over 2, 3, and 5 hours from formulations containing 20%, 40%, and 60% of Alg, respectively. According to Figure 4, CMC-based matrices exhibited significantly lower drug release–retarding efficiency

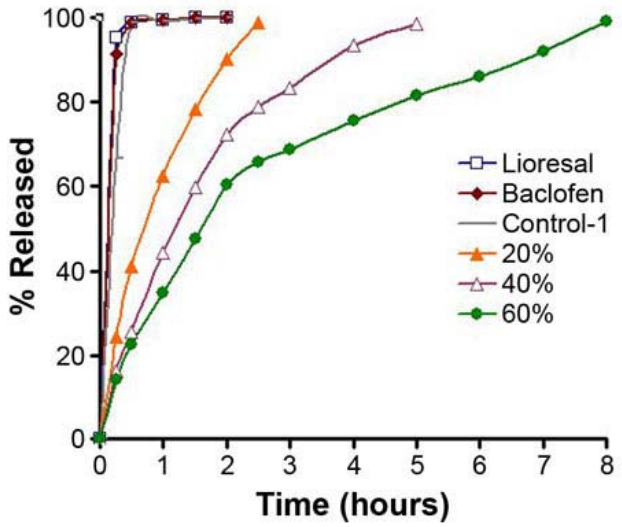

Figure 3. Percentage of baclofen released from standard tablets, control-1 tablet, and sodium alginate matrix tablets, performed in dissolution media of pH 1.2 and 6.8 (n = 3).

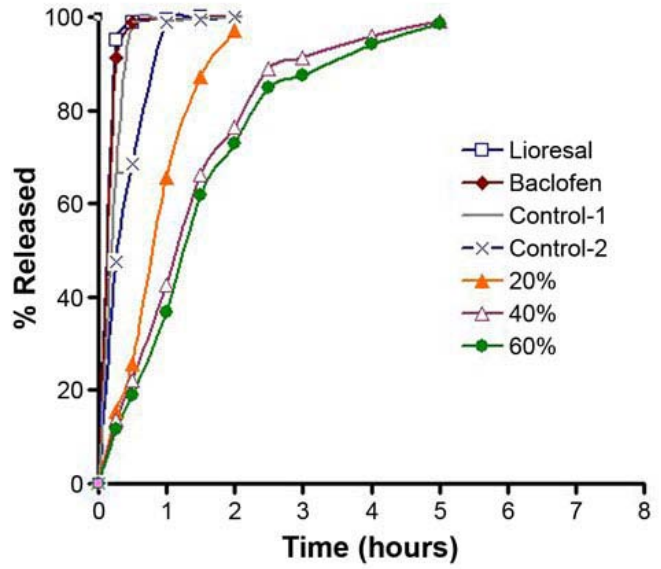

Figure 5. Percentage of baclofen released from standard tablets, control-1 and control-2 tablets, and sodium carboxymethylcellulose matrix tablets, performed in dissolution media of pH 1.2 and 6.8 (n = 3).

than the above-mentioned polymers, for the same polymer level. These results might be attributed to the relatively lower viscosity of CMC, which led to low swellability and rapid dilution and erosion of the diffusion gel layer.[34] Furthermore, the disintegration properties of CMC[35,36] might contribute to that effect. Incorporation of 2% (wt/wt) E-RS100, as a wet blend, into CMC-based matrices markedly increased the drug release–retarding efficiency of CMC (Figure 5). The presence of E-RS100 decreased the solvent molecules' penetration due to the hydrophobicity of the polymer.[22] MC and Alg polymers have higher release-retarding efficiency (Figures 2 and 3). As they have relatively higher viscosity values, they formed a strong viscous diffusion gel layer. However, the drug release from MC-based matrices was slightly higher than that from the Alg-based tablet formulation, irrespective of polymer level; for example, ~90% of the drug was released from M-4 and A-4 within 3 and 4 hours, respectively. These results might be attributed to the better mechanical properties of Alg-based matrices than of MC-based ones (Table 3). As has been found previously, wetting on granulation is another processing factor that could affect the release rate of drug from tablets. Alcohol could not provide sufficient wetting and binding of MC-based granules.[22]

The release studies were performed in perfect sink conditions. Nevertheless, a significant amount of drug was released in dilute hydrochloric acid solution pH 1.2 compared with that released in phosphate buffer pH 6.8 (Figures 2 and 3). Thus, it could be concluded that in vitro release of baclofen is a direct function of its solubility in the dissolution medium.

Release Kinetics

The values of release exponent (n), kinetic constant (k), and MDT calculated from Equations 3 and 4 are presented in Table 5. As observed from the table, correlation coefficients (r^2) of all formulations were high enough to evaluate the drug dissolution behavior using Equation 3 (r^2: 0.98-0.999). Irrespective of polymer level, the prepared hydrophilic tablet formulations showed 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 compound by coupled diffusion and erosion. Alderman[34] reported that when the hydrophilic matrix tablet enters an in vitro dissolution medium, drug particles initially pass into solution from the surface (immediate release). The solid matrix also begins to swell (polymer relaxation) as soon as hydration with solvent molecules, diffusion of the dissolved drug, and erosion of gelatinous viscous polymer layer into aggregates or granules, and these in turn deaggregate into fine particles that also release their drug content by dissolution.

Incorporation of E-RS100 as a wet blend, however, increased the value of n to 1, indicating the tendency toward drug release kinetics nearer to zero-order or case II transport rather than anomalous mechanism. These results were in good agreement with the findings of Raghuram et al.[22] When a hydroxypropylmethylcellulose (HPMC)-nicorandil-based matrix was granulated with pure ethanol, the n value was found to be 0.44; when the same formulation was granulated with Eudragit RS100 (8% wt/vol), the n value increased to 0.6, suggesting alteration of the release mechanism.

Table 5. Values of Release Exponent (n), Kinetic Constant (k), Mean Dissolution Time (MDT), and Correlation Coefficient (r^2) of Baclofen Tablet Formulations

Formulations	Release Exponent (n)	Kinetic Constant (k)	MDT (hours)	Correlation Coefficient (r^2)
A-2	0.674	0.634	0.791	0.986
A-4	0.731	0.440	1.298	0.999
A-6	0.689	0.362	1.781	0.997
M-2	0.692	0.634	0.792	0.998
M-4	0.788	0.459	1.218	0.992
M-6	0.762	0.409	1.393	0.997
C1-2	0.748	0.664	0.738	0.952
C1-4	0.713	0.568	0.907	0.994
C1-6	0.702	0.519	1.133	0.992
C2-2	1.038	0.610	0.819	0.975
C2-4	0.879	0.439	1.190	0.993
C2-6	0.915	0.391	1.331	0.996

MDT is used to characterize the drug release rate from the dosage form and the retarding efficacy of the polymer. A higher MDT indicates a higher drug-retarding ability of the polymer and vice versa. The MDT value was found to be a function of polymer loading. Table 5 shows that the higher the polymer level, the higher the value of MDT. These findings were in accordance with those of Reza et al.[29] They investigated the effect of plastic, hydrophilic, and hydrophobic types of polymers; their content level; and drugs of different aqueous solubility values on MDT. The studies showed that a direct relationship could be found with MDT value and polymer loading irrespective of drug and polymer type, and that this relationship was linear.

Effect of Aging on Release of Baclofen From Some Selected Modified-Release Hydrophilic Matrices

Several studies have demonstrated that drug release from sustained-release dosage forms may change with storage. These changes may involve increase or decrease in dissolution rate or may not occur at all. Al-Hmoud et al[37] noted a decrease in the dissolution rate of propranolol HCl CMC/E-RS100 matrices during storage for 100 days at 60°C. In contrast, Esmail et al[38] found that 19% of amitriptyline was released in 30 minutes from prestored sustained-release capsules; ~90% of the drug was released in the same period

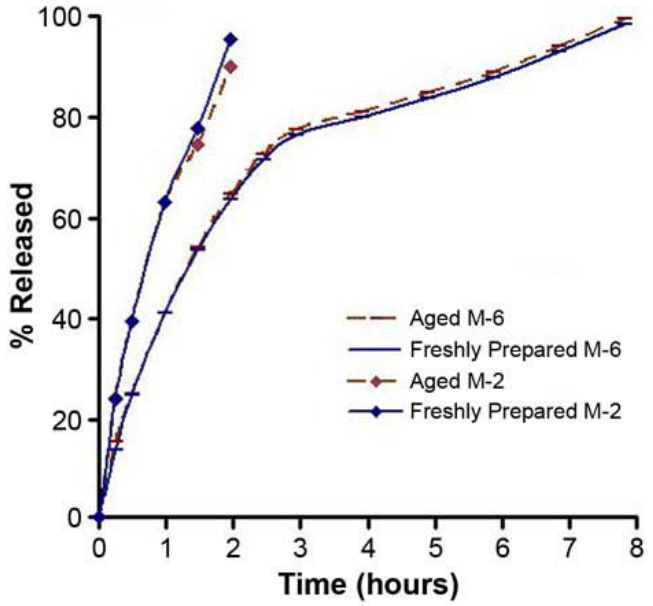

Figure 6. Release profile of baclofen from selected freshly prepared and aged methylcellulose matrices.

after 16 weeks of storage at 40°C/80% relative humidity. Other studies have showed no change in properties with time. For example, the dissolution of diclofenac sodium from HPMC matrices did not alter with storage up to 3 months at ambient temperature, 40°C, and 50°C.[39]

The effect of 6-month shelf aging on the release of baclofen from 7 baclofen hydrophilic matrices was studied (Figures 6, 7, and 8 and Table 6). Formulations M-2, A-2, and C2-2 released their baclofen content within 2 to 3 hours. Formulations M-6, A-4, A-6, and C2-6 were intermediate in their

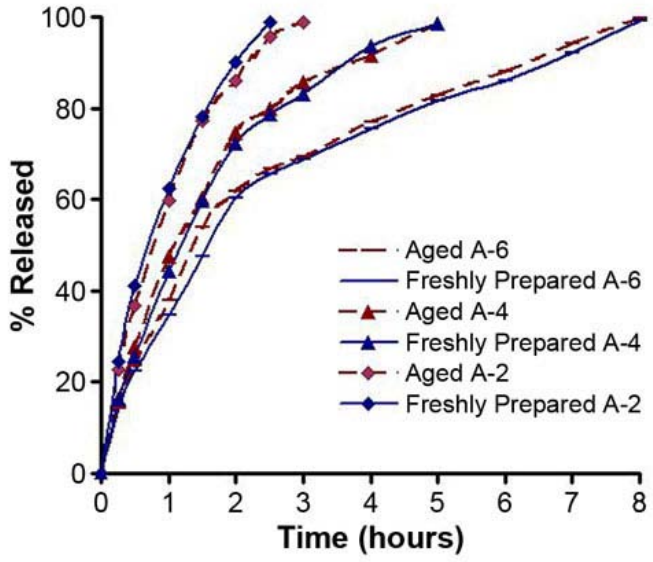

Figure 7. Release profile of baclofen from selected freshly prepared and aged alginate matrices.

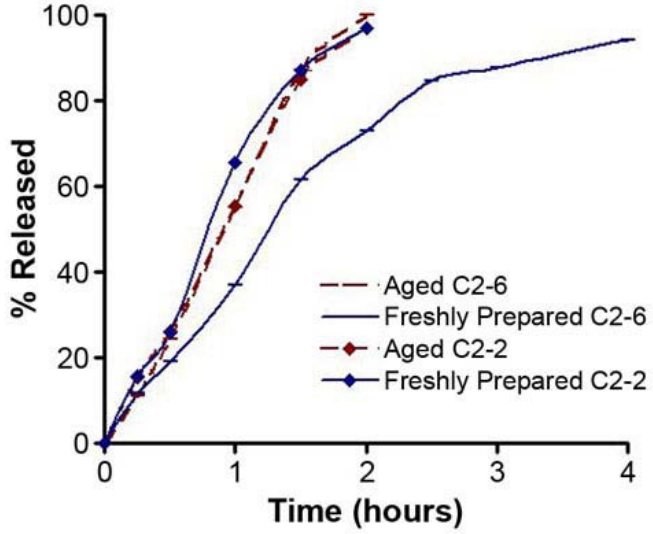

Figure 8. Release profile of baclofen from selected freshly prepared and aged carboxymethylcellulose matrices.

release profiles and released their drug content within 5 to 8 hours. These formulations were chosen for the aging study because they exhibited erosion-mediated release and might be correlated well with gastric and intestinal transient times based on the results of Goetz et al.[40] It was found that during clinical studies, erosion-controlled Sinemet matrix tablets (levodopa-carbidopa) were the most effective formulation for treating Parkinson's disease, ranking CR4 > CR3. CR4 released its levodopa content within 2 hours, while CR3 released its levodopa content within 6 hours. The respective levodopa bioavailability was 89% and 70% relative to that of the standard-release combination.

Figures 6, 7, and 8 show the variation of the release profile of baclofen from formulations M-2 and M-6; A-2, A-4, and A-6; and C2-2 and C2-6 after a 6-month shelf aging. A drastic increase in the release rate from C2-6 was observed. In addition, the dissolution behavior of the stored C2-6 matrix was clearly different from that of the freshly prepared one (Figure 8). The swelling phase of stored matrix lasted for ~0.5 hours, as compared with 3 hours with fresh matrix, after which very rapid erosion occurred, leading to complete disintegration of the matrix within 2 hours, compared with 5 hours with fresh matrix. These results could be ascribed to weakening in the mechanical properties of aged C2-6 matrix and/or moisture penetration through the matrix, dissolving the drug and leading to its migration to the surface, thus disrupting the controlled-release system involved. Comparing the MDT and $T_{90\%}$ of baclofen from fresh and aged tablet formulations confirmed these results (Table 6).

The drug release patterns from formulations M-2 and M-6;, A-2, A-4, and A-6; and C2-2 did not alter apparently on storage (Figures 6 and 7). Confirming these results, MDT

Table 6. Values of MDT and $T_{90\%}$ of Baclofen From Fresh and Aged Selected Hydrophilic Matrix Formulations*

	MDT (hours)		$T_{90\%}$ (hours)	
Code	Fresh	Aged	Fresh	Aged
M-2	0.790	0.802	1.6	2.0
A-2	0.791	0.820	2.0	2.2
C2-2	0.819	0.790	1.5	1.4
M-6	1.393	1.433	7.0	6.2
A-4	1.298	1.278	4.0	4.0
A-6	1.781	1.770	7.0	7.0
C2-6	1.330	0.964	4.0	1.5

*MDT indicates mean dissolution time.

values and $T_{90\%}$ of the aforementioned formulations did not significantly change (Table 6).

CONCLUSION

In vitro release studies demonstrated that the release of baclofen from all prepared matrix tablet formulations was generally sustained. The drug release from matrix tablets containing MC and Alg was non-Fickian. In addition, in vitro release profiles of the drug from the above-mentioned matrix tablet formulations did not alter significantly upon storage at ambient conditions. Therefore, these polymers can be used to modify release rates of baclofen in hydrophilic matrix tablets.

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