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COMMUNICATION

Formulation and Release Behavior of Diclofenac Sodium in Compritol 888 Matrix Beads Encapsulated in Alginate

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ABSTRACT

Sustained-release polymer beads containing diclofenac sodium (DNa) dispersed in Compritol 888 and encapsulated in calcium alginate shell were prepared utilizing 2^3 factorial design. The effect of sodium alginate concentration, drug:Compritol 888 weight ratio and $CaCl_2$ concentration on drug content (%), time for 50% and 80% of the drug to be released, and mean dissolution time (MDT) were evaluated with analysis of variance (ANOVA). An increase in the level of all these factors caused retardation in the release, and $t_{50\%}$, $t_{80\%}$, and MDT were increased. The drug release was dependent on the pH of the release media. A formula that gives a release comparable to commercial products was prepared.

Key Words: *Alginates; Beads; Compritol 888; Diclofenac sodium.*

INTRODUCTION

Alginates are cell-wall constituents of brown algae (Phaeophycota). They are chain-forming heteropolysaccharides made up of blocks of mannuronic and guluronic acid (1). Regions of guluronate monomers in one alginate molecule can be linked to a similar region in another molecule by means of calcium or other divalent cations. The divalent Ca^{2+} cation fits into the guluronate structure like eggs in an egg box. This binds the alginate polymer together by forming junction zones, thus leading to the gellation of the solution. The higher porosity of alginate beads results in somewhat faster release of lower molecular weight drugs. Therefore, to sustain the release of diclofenac sodium (DNa), we dispersed the drug in a waxy matrix (Compritol 888) and then coated it with alginates (2).

Compritol 888 (glyceryl behenate) is a mixture of glycerides of fatty acids, mainly behenic acid (1). It consists of about 28–32% tribehenate, 52–54% dibehenate,

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and 12–18% monobehenate (3). Pharmaceutical formulations and processes were investigated and developed simply by trial and error while varying one factor at a time; this approach is both time and energy consuming and costly. Furthermore, misleading conclusions can be drawn, particularly when different variables interact. Factorial designed experiments are intended to avoid such problems and separate those factors that are important from those that are not (4–6).

EXPERIMENTAL

Materials

Compritol 888 ATO was a gift from Gattafosse (Paris, France). Sodium alginate was purchased from Sigma Chemical Company (St. Louis, MO). DNa was a gift from Dar Al-Dawa Development and Investment Company (Jordan). Olfen® retard and Diclogesic® retard were purchased from the market.

Methods

Preparation of the Beads and Experimental Design

To prepare the beads, 60 ml of deionized water was added to a weighed quantity of sodium alginate powder, and the mixture was stirred with a magnetic stirring bar in a beaker until complete dissolution was achieved. This solution was warmed to 70°C on a water bath. The desired quantity of Compritol 888 was weighed in a beaker and slowly heated on a water bath to 80°C (mp ~70°C). DNa powder (<150 mesh) was added to the molten vehicle and mixed well for 10 min. The hot alginate solution was added portionwise to the Compritol and DNa at 80°C and mixed well for 10 min. The mixture was brought to 100 ml with deionized water and mixed for another 10 min using a vortex mixer. This resulted in the formation of a crude emulsion. This emulsion was dropped using a peristaltic pump (Harvard, Germany) with a polyethylene tubing nozzle (i.d. 0.6 mm, o.d. 2 mm, falling distance 4 cm, pumping rate 2 ml/min) into 100 ml of calcium chloride solution, which was gently agitated with a magnetic stirrer. The stirring speed was kept constant. The formed beads were allowed to stand in solution for 1 hr to be cured and then collected by filtration. These beads were washed with 20 ml of deionized water twice before drying in air for 72 hr and then in a desiccator over silica gel to constant weight. The dried beads were sieved, and beads with a diameter of 1–2 mm were used.

Beads without Compritol 888 were also prepared. DNa (<150 mesh) was added to sodium alginate solution. The DNa alginate mixture was stirred with a vortex mixer for 10 min and then dropped into calcium chloride solution using the same conditions as above.

The effects of three formulation variables (alginate concentration, drug : Compritol 888 weight ratio, and calcium chloride concentration) on drug content and drug release were studied in a conventional 2^3 factorial design. All processing variables were kept constant. All experiments were performed in duplicate to allow estimation of the experimental error. The experiments were performed in randomized order as follows: c, bc, a, I, abc, ac, ab, b. The response parameters were the times for 50% ($t_{50\%}$) and 80% ($t_{80\%}$) of the drug to be released and mean dissolution time (MDT). The responses are given as mean values of three readings. The estimated effects of increasing the factors from a low to a high level were tested for significance by analysis of variance (ANOVA) using the Statistica® computer program.

Release Studies

The drug concentration in the beads was determined spectrophotometrically at 280 nm (Cecil Instruments, England). The release of DNa from alginate beads (equivalent to 100 mg DNa) was examined according to the USP 22 paddle method at 37°C ± 1°C and 50 ± 1 rpm (Erweka DT-D6, Germany). The dissolution medium was 900 ml phosphate buffer at pH 6.6, 6.8, or 7.4 (USP 21). At predetermined time intervals, 5-ml aliquots were withdrawn and immediately filtered through a 0.45-μm Millipore filter. The same volume of fresh medium was added to the test medium. The concentration of DNa in the filtrate was determined in three replicates. Compritol 888 and alginates did not interfere with the assay. The same procedure was followed to measure the release from the commercial products, Diclogesic capsules, and Olfen-100 retard.

RESULTS AND DISCUSSION

Choice of the Factor Levels of the Factorial Design

Since the only intent of the study was to screen for the most important formulation variables, each factor was studied at two levels. The responses were thus assumed to be approximately linear over the factor levels chosen.

From preliminary experiments, it was found that an alginate concentration less than 1.5% w/v did not give

Table 1

Measured Time Responses and the Result of Analysis of Variance as Produced by the 2^3 Factorial Design

	$t_{50\%}$ (hrs)			$t_{80\%}$ (hr)			MDT (hrs)		
Experiment	Replicate I	Replicate II	*P*	Replicate I	Replicate II	*P*	Replicate I	Replicate II	*P*
(1)	1.38	1.52	—	2.68	2.89	—	1.22	1.68	—
a	2.14	1.71	.0053	3.86	3.57	.0001	2.77	1.93	.0026
b	2.05	1.64	.0023	3.95	3.46	.0000	2.37	1.63	.0000
ab	1.86	2.07	.0343	4.14	4.26	.2288	2.18	2.82	.9111
c	2.57	1.99	.003	4.64	3.99	.0000	2.86	2.2	.0000
ac	2.81	2.99	.0144	6.2	6.9	.0022	2.45	4.1	.1584
bc	3.24	3.78	.0045	13.78	15.13	.0000	6.1	7.35	.0001
abc	9.46	8.91	—	18.92	18.38	—	8.68	8.12	—

spherical beads. Badwan et al. (7) found that when a 1% w/v solution of sodium alginate was used, the yield was irregular beads. Increasing the concentration to 3% w/v was difficult to manipulate. In addition, tear-shaped beads were produced when the amount of alginate loading exceeded 3% w/v (8). A concentration between 1.5% and 2.5% gave reproducible spherical beads. Consequently, 1.5% w/v was chosen as the lower level, and 2.5% w/v was chosen as the upper level of factor A. The levels of factor B were chosen after the release studies at pH 6.8 from beads containing 2% sodium alginate and different drug:Compritol weight ratios (1:1, 1:2, 1:3). For a 1:4 drug:Compritol weight ratio, the release was negligible up to 8 hr, and 65% of the drug was released after 24 hr (this system can be optimized for colonic drug delivery). Therefore, the lower and upper levels were set to 1:1 and 1:3 drug:Compritol weight ratio. Factor C levels were also chosen after the dissolution studies at pH 6.8 from beads containing 2% sodium alginate, (1:2) drug:Compritol weight ratio, but gelled in different concentrations of $CaCl_2$ (0.1, 0.3, 0.5, or 0.6 M). Beads gelled in 0.6 M $CaCl_2$ released only 15% of the drug after 8 hr. Therefore, the lower and upper limits were set to 0.1 and 0.5 M, respectively.

Factors Affecting $t_{50\%}$, $t_{80\%}$, and Mean Dissolution Time

Since DNa is an acidic compound (pK_a 4) with very low solubility in an acidic medium (<2 mg/ml) and is not expected to dissolve in the stomach, release of the drug from the beads was studied only at pH 6.6, 6.8, or 7.4. The time for 50% ($t_{50\%}$) or 80% ($t_{80\%}$) of the drug to be released and MDT were response parameters. MDT was calculated from the equation suggested by Tanigawara et al. (9).

The area under the curve was calculated the by TopFit® computer program. The responses and their ANOVA results are listed in Table 1. All factors investigated in the 2^3 factorial design had a significant effect on $t_{50\%}$, $t_{80\%}$, and MDT. The most important factor was the calcium chloride concentration ($P < .001$). It is well known that increasing the $CaCl_2$ concentration in the counterions solution produces beads with higher levels of Ca^{+2} ions (10,11), consequently increasing the cross-linking of the polymer and compactness of the formed insoluble matrix. The release of sulfamethaxazole from alginate beads in 0.1 N HCl decreased with increasing $CaCl_2$ concentration (7). Theophylline release in water from alginate beads was also shown to be dependent on concentration of $CaCl_2$ used for gel bead production (12). Increasing the ratio of Compritol 888 also had a significant effect ($P < .005$). This may be attributed to higher partitioning of the drug in the waxy and hydrophobic material when it is in the high level.

Release Studies at Different pH

The effect of pH on the dissolution profile of beads containing (1:3) drug:Compritol, 2% sodium alginate, and gelled either in 0.5 M (formula 1) or 0.3 M $CaCl_2$ (formula 2) was studied. As the pH increased, the release increased. This is due to the pH-dependent solubility of DNa. In addition, alginates are polyelectrolytes that exhibit swelling properties that are sensitive to the pH. Maximum swelling was observed at pH 6.8. At pH 7.4, although the beads initially swelled, erosion was fast. The dissolution studies were also carried out at pH 1.2 for 2 hr, followed by pH 6.8 for 6 hr. The release of DNa was negligible at pH 1.2. This was due to the lower solubility of DNa in acidic medium (<2 mg/ml). No disintegration or swelling was observed at pH 1.2, and when the pH was changed to 6.8, the release was faster than when the dissolution was performed at pH 6.8 alone. This may be due to the fact that calcium ions in alginate beads were

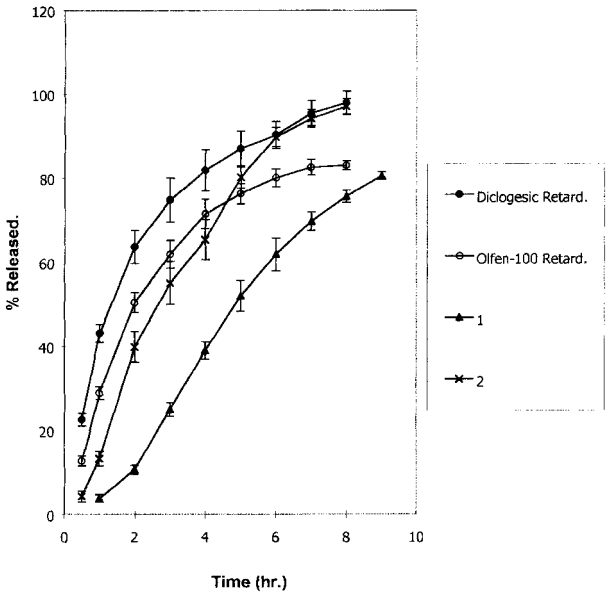

Figure 1. Release profile of DNa at pH 6.8 from two commercial products, Diclogesic capsules, Olfen-100 Retard, and beads containing (1:3) DNa:Compritol and 2% sodium alginate and gelled in either 0.5 M (1) or 0.3 M calcium chloride (2).

totally discharged in an acidic environment, and the carboxyl groups were shifted to an un-ionized form. As mentioned above in this section, the bc interaction is very important in controlling the release of DNa. Also, there is no significant difference in the release profiles of DNa although the beads were gelled in different $CaCl_2$ concentrations, further confirming that the matrices were entirely depleted of calcium ions. The release from beads of formulas 1 and 2 was compared with release from two commercial products, Diclogesic retard and Olfen-100 retard, at pH 6.8 (Fig. 1). The release of DNa from formula 2 was comparable to the above-mentioned commercial products. Formula 1 had somewhat lower release than the two commercial products when examined visually, but statistically there is no significant difference between the two commercial products and the two formulas at the 5% level of significance.

CONCLUSION

Spherical beads were formulated using DNa as a model drug, Compritol 888 as a waxy matrix, and sodium alginate cross-linked with $CaCl_2$ as the sustained-release polymer. An optimized formula was found with the help of factorial design. Factor B decreased the drug content, but retarded drug release and improved the sphericity of the beads; therefore, optimum formulas contain factor B at the higher level.

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