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Investigations on mefenamic acid sustained release tablets with water-insoluble gel

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Abstract

Mefenamic acid (MA) has analgesic, anti-inflammatory and antipyretic properties. Available conventional dosage forms are capsules and film-coated tablets. No commercial sustained release preparation of MA exists in the market. The usual oral dose is 250 or 500 mg and reported half-life is 2 h. Sodium alginate (NaAL) is the sodium salt of alginic acid, a natural polysaccharide extracted from marine brown algae. It has the ability to form a water-insoluble gel with a bivalent metal ions as calcium. Therefore, NaAL has been studied for preparing sustained release formulations in pharmaceutical technology. In this study, tablet formulations containing different ratios of NaAL and calcium gluconate (CaGL) were prepared by direct compression method. In vitro release studies were carried out using USP 23 basket method and release data were kinetically evaluated. According to release studies, it can be emphasized that NaAL and CaGL can be used for design of sustained release preparation of MA.

Keywords: Mefenamic acid; Sodium alginate; Calcium gluconate; Sustained release

1. Introduction

Mefenamic acid (MA), 2-[(2,3-dimethylphenyl)amino]benzoic acid, is a nonsteroidal anti-inflammatory agent possessing analgesic and antipyretic activities [1,2]. It is an inhibitor of prostaglandin synthetase. The usual oral dose is 250 or 500 mg, being administered three times daily and reported half-life is 2 h [2]. Sustained release MA beads based on κ-carrageenan [3] and cellulose acetate phthalate [4] and prolonged released MA microcapsules prepared with acrylic acid polymers [5,6] have been reported in the literature. However, no commercially long acting product exists in the market.

The use of natural polymers as drug carriers is one of the main objectives of researchers dealing with long acting dosage forms [7–9]. Sodium alginate (NaAL), the sodium salt of alginic acid, a natural polysaccharide having high biological safety is extracted from brown algae. It has been widely used as a stabilizer, thickener, dispersing agent and gelation agent [10]. NaAL has the ability of forming rapid viscous solutions and gels by its contacts with aqueous media. Its wide application involves the preparation of hydrophilic matrix type sustained release oral dosage forms [11–13]. In addition, NaAL also has the ability to cause water-insoluble gelation in the presence of bivalent metal ions as calcium [14]. Therefore, NaAL has been widely used for design of novel drug delivery systems [15–18].

In this study, tablets containing different ratios and amounts of NaAL and calcium gluconate (CaGL) as a bivalent metal were prepared by direct compression method. In vitro release of MA from tablets was evaluated by using USP 23 basket method and release data were fitted to kinetic models.

2. Experimental

2.1. Materials

Mefenamic acid was kindly supplied from Nobel Pharm. Comp., Turkey. Sodium alginate (A-2033) was

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purchased from Sigma, USA. Calcium gluconate (CaGL), magnesium stearate and talc were purchased from Merck, Germany. Avicel pH 101 was obtained from Selectchemie AG, Germany and all other chemicals were of analytical grade.

2.2. Preparation of tablets

The unit formula of the tablet formulations is given in Table 1. The ratio of NaAL (1% w/v 260±35 cps at 25 °C) and CaGL in the formulations A, B and C was 1:1, but these ingredients were used in different amounts for each formulation. Formulation D and E were prepared adding NaAL and CaGL at the ratios of 1:2 and 2:1, respectively. The formulation F was prepared without CaGL to assess the influence of CaGL on the release of drug. Avicel pH 101 was used as diluent, magnesium stearate and talc as lubricants in the all formulations.

For tablet preparation, MA (< 63 mesh) and all the auxiliary ingredients except lubricants were mixed in V-type mixer for 15 min. Then, talc and magnesium stearate were added and mixed for a further 5 min. The mixtures were sieved through ASTM sieve (0.710 mm). Then, the blends were directly compressed on a single station tablet machine (Korch, Berlin) using 1.3 cm diameter flat-faced punches, to a weight of 500 mg and such a compression force that give tablets with minimum 5 kg hardness. Ten tablets were weighed one by one and weight variation of tablets were calculated. Friability of all tablet formulations was determined using 20 tablets by Roche Friability Tester.

2.3. Mefenamic acid contents of the prepared tablets

Five tablets were powdered and 500 mg of this mixture was accurately weighed. It was suspended in 50 ml of 0.1 N NaOH and sonicated in the ultrasonic bath for 30 min. The volume of the suspension was adjusted to 100 ml with a 0.1 N NaOH and filtered (S&S 589[3]). 0.2 ml of the filtrate was diluted to 100 ml with 0.1 N NaOH and absorbances were determined spectrophotometrically at 285 nm. Preliminary studies have shown that the presence of the tablet ingredients has no interference with the spectrophotometric method. The MA contents of tablets were calculated using standard curve which was plotted in the range of 1–10 mcg ml^{-1} ($r^2 = 0.998$). The experiment for each formulation was repeated three times.

Table 1
The unit formula of the prepared tablets

Ingredients [a]	Formulation code					
	A	B	C	D	E	F
MA	250	250	250	250	250	250
NaAL	25	50	75	50	100	100
CaGL	25	50	75	100	50	–
MS	12.5	12.5	12.5	12.5	12.5	12.5
TC	12.5	12.5	12.5	12.5	12.5	12.5
AV	175	125	75	75	75	125

Abbr.: MA, mefenamic acid; NaAL, sodium alginate; CaGL, calcium gluconate; MS, magnesium stearate; TC, talc; AV, Avicel pH 101.

[a] Amount of ingredients was given as milligram.

2.4. Dissolution studies

Dissolution studies of the sustained release tablets in comparison with pure drug (powder MA) were carried out employing USP 23 basket method at 37±0.5 °C [19]. Basket rotational speed was held at 50 rpm. The dissolution medium was chosen as 900 ml phosphate buffer (0.2 M, pH 7.4) containing 0.5% of Tween 80. Phosphate buffer containing 27.22 g mol^{-1} potassium dihydrogene phosphate was prepared according to USP 23 [19]. At predetermined intervals (1–8 h), 1 ml samples were taken and diluted to 10 ml with 0.1 N NaOH. Subsequently, released amount of MA was determined spectrophotometrically at 285 nm. Each measurement was repeated three times for each formulation.

2.5. Kinetic assessment

Drug release mechanism was investigated in comparison with modellings according to the equations of zero order, first order and Higuchi's square root of time [20,21]. The following plots were made: Q_s versus t (zero order kinetic model); $\log(Q_0 - Q_t)$ versus t (first order kinetic model), and Q_t versus $\sqrt{t}$ (Higuchi's square of root kinetic model), where Q_t is the percentage of drug released at time, t and Q_0 is the initial amount of drug.

The release constants (k), determination coefficients (r^2) and sum the weighed squared deviations (SWSD) were calculated by means of a computer programme which was written in Gw-Basic 3.10 for the kinetic assessment of the dissolution data. The percent of released drug were input. The programme fits these dissolution data to kinetic models and prints kinetic parameters, together with goodness of fit [22].

2.6. Statistical analysis

The determined dissolution data was subjected to statistical analysis using a computer programme, PC-Instat, for a one-way analysis of variance (ANOVA) following Student–Newman–Keuls multiple comparisons test. A comparison between two formulations was performed by using a Student's t-test. $P < 0.05$ was considered as evidence of a significant difference.

3. Results and discussion

The results indicated that all the tablets prepared in this study meet the USP 23 requirements for weight variation tolerance [19]. The amounts of MA in the all tablet formulations were found in the range of 98.0–102.0%. The friability results showed that all formulations satisfied the *Ph. Eur.* fourth ed. requirements [1].

The release profiles which represent the percent released of pure drug (MA powder) and MA from the sustained release tablets as function of time are shown in Fig. 1(a and b). It is seen from that figure $96.70 \pm 2.2\%$ of pure drug was released in 2 h. According to release data, while about 50% of MA from formulations A, B, D and E was released in 5 h, only about 20% of MA was released from formulations C and F (Fig. 1(b)). When the release data were evaluated statistically (ANOVA), formulations C and F significantly ($P < 0.001$) decreased the extent of drug release in comparison with the other formulations (A, B, D and E).

As can be seen from Fig. 1(b) that formulation A and B showed similar release patterns. At the end of 8 h, 69.25 ± 2.1 and $73.30 \pm 1.8\%$ of MA was released from formulations A and B, respectively. On the other hand, only $39.76 \pm 1.7\%$ of MA was released from formulation C in 8 h. Although the ratio of NaAL and CaGL was 1:1 in the formulations A, B and C, the extent and rate of drug release from formulation C was significantly slower than from formulations A and B ($P < 0.001$), this could be attributed to the presence of higher amount of NaAL and CaGL in formulation C (Table 1). The decreased in drug release may be explained by the fact that insoluble

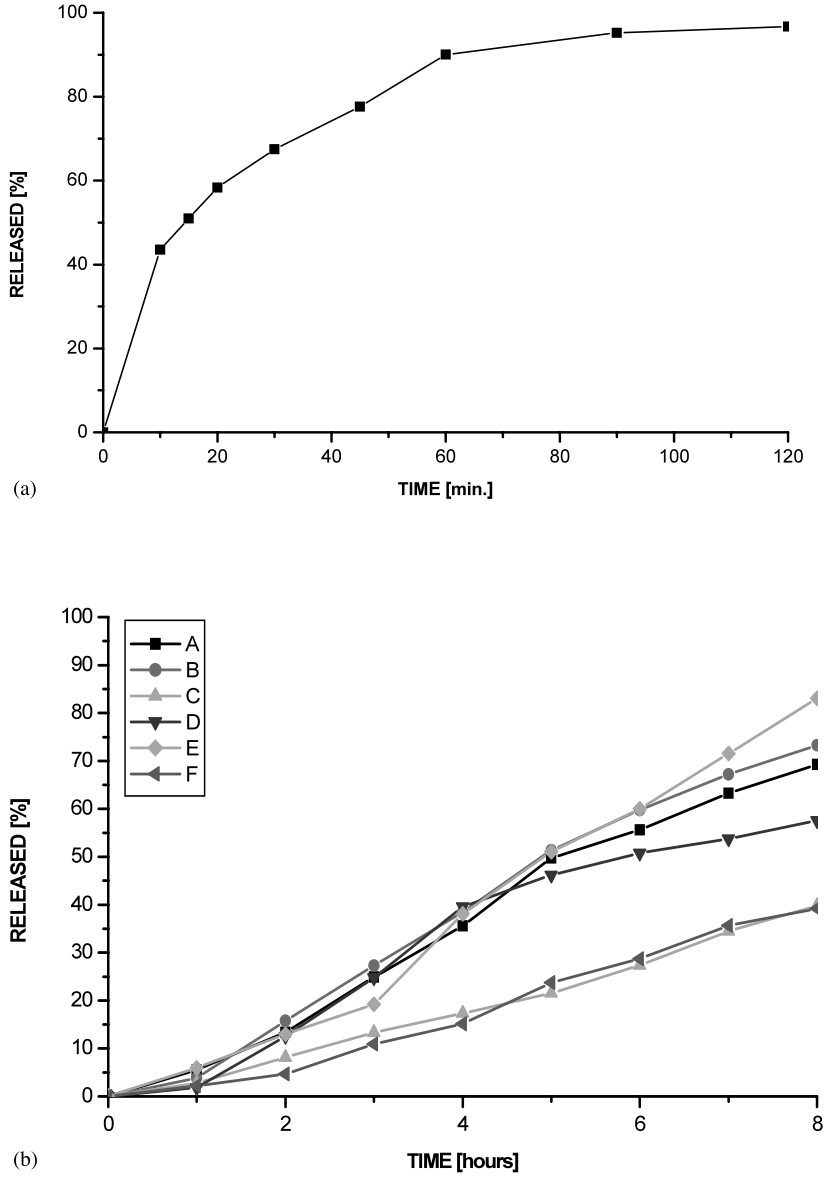

Fig. 1. In vitro release profiles of: (a) pure drug, and (b) mefenamic acid from sustained release tablets.

Table 2
Kinetic assessment of dissolution data

Formulation code	Zero-order			First-order			Higuchi		
	k_0	r^2	SWSD	k_1	r^2	SWSD	k_h	r^2	SWSD
A	9.544	0.986	0.0174	0.336	0.866	0.1517	37.182	0.985	0.1390
B	10.165	0.988	0.0210	0.364	0.802	0.2010	39.741	0.994	0.1599
C	5.202 [a]	0.994	0.0059	0.337	0.883	0.0250	19.963	0.964	0.0372
D	8.109	0.933	0.1261	0.402	0.699	0.0419	32.331	0.976	0.0868
E	11.523	0.989	0.0435	0.365	0.919	0.2010	44.225	0.959	0.3028
F	5.668 [a]	0.990	0.0199	0.401	0.909	0.0531	21.723	0.957	0.0530

k_0, release rate constant of zero order kinetic (mg h^{-1}), k_1, release rate constant of first order kinetic (h^{-1}), k_h, release rate constant of Higuchi's square root of time (mg $h^{-0.5}$); r^2, determination coefficient; SWSD, sum of weighed squared deviations.
[a] Significantly slower than that of the other formulations ($P < 0.001$).

CaGL was formed by cation exchange between Na^+ and Ca^{2+}.

In vitro release pattern of MA from formulation F was appeared similar to that of release from formulation C (Fig. 1(b)). Although no bivalent calcium ion existed in the formulation F (Table 1), a significant decrease ($P < 0.001$) in the extent of drug release was observed by the effect of hydrogel matrix formed as a result of the gelation of NaAL by exposing to aqueous media.

In order to investigate the release mechanisms, the release data were fitted to the models representing zero order, first order and Higuchi's square root of time [20,21]. The goodness of fit was evaluated by the SWSD and determination coefficients were given in Table 2. Except formulation D, all tablet formulations followed zero order release kinetic, since the highest determination coefficients and the lowest SWSD were obtained for this kinetic model (Table 2).

According to zero-order kinetic model, the release rate constants of the formulations C and F were found to be 5.202 and 5.668 mg h^{-1}, respectively (Table 2). Release rates of MA from formulations C and F were significantly lower ($P < 0.001$) than that of other formulations (A, B, D and E). However, there was no statistically significant difference between two formulations (C and F) with respect to release rates ($P > 0.05$).

In conclusion, based on the data it can be suggested that sustained release MA tablets can be prepared using NaAL and CaGL by direct compression method.

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