Preparation and Evaluation of Controlled Release Calcium Alginate Beads Containing Mefenamic Acid

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Abstract:

The present study was designed to investigate the effects of different variables on the release profile of mefenamic acid from calcium alginate beads formulated using modified emulsification method. Five formulations of beads (F1-F5) with different drug: polymer ratios were prepared in which the amount of drug (1g) was kept constant and the amount of calcium alginate was increased from 1 up to 5g. All the formulated beads were evaluated for percentage yield, entrapped efficiency and in vitro release profile at pH 1.2 and 7.2 dissolution media. For further minimize the release of drug from calcium alginate beads, the selected formulation F3 beads were coated separately with 3% and 6% Eudragit S100 solution using dipping method. The coated beads (F6 and F7) minimized the release of drug both in pH 1.2 and 7.2. The study confirms significant effects of two variables, drug:polymer ratio and coating on the release of drug from beads which can be effectively utilized to control the release from prepared calcium alginate formulations.

Key words: calcium alginate, mefenamic acid, Eudrigate S 100, control release, beads

تحضيروتقييم غريزات الجينات الكالسيوم الحاوية على حمض الميفيناميك المسيطرة على تحررها

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الخلاصة:

صُممت الدراسة الحالية للتحقق من تأثيرات المتغيرات المختلفة على تحررحمض الميفيناميك من خريزات ألجينات الكالسيوم التي تمت صياغتها باستخدام طريقة الاستحلاب المعدلة. تم إعداد خمس صيغ من الخرز (F1-F5) بنسب مختلف من دواء: البوليمر التي بقيت فيها كمية الدواء ثابتة (1 جم) وتم زيادة كمية ألجينات الكالسيوم من 1 إلى 5 جرام. تم تقييم جميع الخرزات المحضرة من ناحية النسبة المئوية إنتاجية والكفاءة التحمل وتحرر الدواء في المختبر في محيطات الانحلال ذات الأس الهيدروجيني 1.2 و 7.2. ومن اجل المزيد من الحد من التحرر عن الدواء من حبيبات الجينات الكالسيوم ، تم اختيار الصيغة F3 من الدواء: البوليمر وتم تغليفها باستخدام ايودراجيت س 100 بنسبة مئوية 3% و 6% باستخدام أسلوب الغمس. قللت هذه الخرزات المغلفة من تحرر الدواء في المحيط ذا الأس الهيدروجيني 1.2 و 7.2 على حد سواء. تؤكد الدراسة تأثيرًات هامًا لمتغيرين، وهما نسبة الدواء: البوليمر والتغليف على إطلاق الدواء من الخرز والتي يمكن استخدامها بفعالية لتحقيق السيطرة على تحرر من الصيغ المحضرة لألجينات الكالسيوم.

الكلمات المفتاحية: الجينات الكالسيوم، حمض الميفيناميك، ايودراجيت س 100، تحرر المديد، خريزات.

Introduction:

Several drug delivery systems have been developed to control the release of drugs for oral dosage forms. These systems are designed to release the drug at predetermined time and rate. As a result, plasma drug concentration will be kept within the therapeutic level for a longer period and thus reduces the dosing frequency [1].

In controlled drug delivery systems enteric coating, polymeric reservoir devices and osmotic pumps have been used. Matrix system is also widely used in the development of sustained drug delivery systems because of its ease of manufacturing [2]. Several types of natural and synthetic polymers have been studied. It was found that these synthetic hydrophobic polymers have the ability to extend the release of the drug from the polymeric matrix tablets [3].

The control release of drugs can also be achieved through formulation of polymeric gel or microbeads, which provide a more uniform distribution of drugs within the gastrointestinal tract [4]. Many advantages could be achieved by using beads as a drug delivery system; these include reduced irritation of drugs to the gastrointestinal tract and a low risk of side effects due to dose dumping [5].

Sodium alginate is a natural polysaccharide, which has the ability to form gels by reaction with divalent cations (Ca2+). The gel formation is a result of crossliking of the polymer chains and the formation of the characteristic egg-box structure [6]. Calcium alginate beads are usually used as a drug delivery system to control the release of orally administered drugs. At the low pH of stomach, alginate beads shrink and form insoluble alginic skin, thus the drug inside the beads is not released. Once the beads pass into a higher pH of the intestinal tract, they will be converted into a soluble viscous layer and the drug starts to release. This pH dependent behavior of alginate can be used to modify release profiles of drugs either alone [7] or in combination with other polymers [8].

Mefenamic acid is one of the nonsteroidal anti-inflammatory drugs (NSAIDs) that work by reducing the production of prostaglandins through blocking enzymes involve in the first step of prostaglandins biosynthesis; these enzymes known as COX 1 and COX 2. Prostaglandins are chemicals that promote inflammation, pain and fever. Therefore, the decrease in the production of prostaglandin will reduce inflammation, swelling and pain [9].

The aim of this study is to prepare coated controlled release calcium alginate beads containing mefenamic acid in order to maintain the release of the drug at a specific part of the GIT for long period of time.

To investigate our aim, the following studies were done including preparation five formulations of uncoated beads at various drug: polymer weight ratios and two coated beads then evaluation for the release of the drug in two dissolution media pH 1.2 and 7.2.

Experimental

Materials:

Mefenamic acid was purchased from SDI (Iraq), sodium alginate was purchased from Wuhan Senwayer century, (China), calcium chloride was obtained from Gainland chemical company, (UK), Eudragit S100 was purchased from Evonik Company, (Germany), Dibutyl phthalate was purchased from Fluka Company, (UK), Isopropyl alcohol was obtained from BDH Ind. (China). Acetone was purchased from BDH Ind. (China), talc was obtained from Middle East laboratory Co limited, (Iraq).

Methods:

Preparation of calcium alginate beads loaded with mefenamic acid

Calcium alginate beads were prepared by the simultaneous method [10]; initially sodium alginate (1g) was dissolved in 50 ml distilled water with the help of magnetic stirrer at a constant rotation speed and temperature (800 r.p.m and 50°C) respectively. Mefenamic acid was then added to the prepared sodium alginate solution to form dispersion. Calcium chloride in isopropyl alcohol (10% w/v) was prepared and dropped into the content of the mefenamic acid/ sodium alginate dispersion using a small diameter syringe needle at a rate of 0.5 milliliter per minute to form uniform size beads. Afterwards, formaldehyde solution, a cross linking agent (5 mL) was added to the content of the beaker with continuous stirring for 10 minutes to make the prepared beads rigid enough without collapse. Finally, the beads were collected by decantation, washed repeatedly with distilled water, filtered and kept in a refrigerator for 24 hrs and then left to dry at room temperature for one week. Five different
(core: coat) weight ratios formulas (F1 to F5) were prepared by this method as shown in Table 1.

Table 1: Composition of different formulation beads loaded with mefenamic acid

Ingredients	F1	F2	F3	F4	F5
Mefanamic acid	1g	1g	1g	1g	1g
Sodium alginate	1g	2g	3g	4g	5g
Calcium chloride	5g	5g	5g	5g	5g
Isopropyl alcohol	50ml	50ml	50ml	50ml	50ml
Distilled water	50ml	50ml	50ml	50ml	50ml

Coating of Calcium Alginate Beads Loaded with Mefenamic Acid

Calcium alginate beads (F3) were coated using pH dependent polymer (Eudragit S100). Two coating solutions (3% and 6% w/v Eudragit S100 in a mixture of isopropyl alcohol and acetone) were prepared with the addition of 1% Dibutyl phthalate as a plasticizer. Talc powder was used to facilitate the dispersion of the coating polymer in aqueous media. Formulations F6 and F7 as shown in Table 2 were prepared using 3% and 6% coating solutions respectively by dip coating method [11].

The beads were dipped in the coating solution and then removed out by using a fine sieve. Following this, they were dried for 5 minutes. This process was repeated 4 times to make sure that the whole surface of the beads will be completely coated.

Table 2: Coated calcium alginate beads formulations

Formulation code	Drug: polymer weight ratio	Percentage of coating solution (w/v)
F6	1:3	3%
F7	1:3	6%

Determination of the percentage yield of calcium alginate beads

The percentage yield of the different calcium alginate beads formulations has been calculated using the following formula:

$$\% \text{ Yield of beads} = \frac{\text{Total yield of beads}}{\text{Total weight of (polymers + drug)}} \times 100$$

Determination of Percentage Entrapment Efficiency of Calcium Alginate Beads

Amount of mefenamic acid entrapped in calcium alginate beads was determined by socking a specified weight (10 mg) of the prepared beads in 100 mL phosphate buffer solution pH 7.2 until swollen and completely dissolved. After wards the solution was filtered and suitably diluted to measure its UV absorbance at λ_{max} of 285nm [12].

The % entrapment efficiency was determined using the following formula:

$$\% \textbf{ Entrapment efficiency} = \frac{\textbf{Total amount of drug found in formulation}}{\textbf{Total amount of drug used in formulation}} \times \textbf{100}$$

Dissolution Study

In vitro dissolution study was performed using USP dissolution apparatus type II (paddle). A weighted amount of beads equivalent to (250) mg of mefenamic acid were suspended in 0.1N HCl dissolution media for 1 hr and then in phosphate buffer pH 7.2 for 3 hrs. Samples of 5 ml were withdrawn from the dissolution media every 30 min, filtered and their UV absorbance were measured at λmax of 285 nm [12]. The cumulative percentage of the drug release was calculated according to the calibration curves of mefenamic acid in 0.1 N HCl and phosphate buffer pH 7.2 dissolution media

Results and Discussion

Preparation of Calcium Alginate Beads Loaded with mefenamic acid

All the prepared calcium alginate beads loaded with mefenamic acid showed a uniform spherical shape as illustrated in Figure 1.

Coating of Calcium Alginate Beads Loaded with Mefenamic Acid

Eudragit S100 was selected as pH-dependent coating polymer to minimize the drug release in stomach and small intestine [13]. Two beads formulations F6 and F7 were successfully prepared using dip coating method and subjected for evaluation of the percentage drug release in the dissolution media.

Figure 1. An image of uncoated calcium alginate beads loaded with mefenamic acid (F3).

Determination of Percentage Yield of Calcium Alginate Beads

The percentage yield of different formulations of calcium alginate beads showed reasonable results; the percentage yield is within the range of 90-96% as shown in Table 3.

Determination of Percentage Entrapment Efficiency of Calcium Alginate Beads

The percentage of drug entrapment efficiency was increased with decreasing drug: polymer ratio up to 1:3 (Table 3). This increment in drug load could be related to increase in the amount calcium

alginate that encapsulates the dispersed drug in the media. Similar result was obtained with formulation of ibuprofen in alginate microspheres. It was stated that the high levels of sodium alginate lead to increase encapsulation efficiency [14]. However, a decrease in drug loading efficiency was obtained with further decrease the drug: polymer ratio to 1:4 and 1:6 (F4 and F5). This decrease in drug loading efficiency may be related to the contribution of the saturation concentration effect of the polymer at a certain level, which resulted in reduced drug incorporating efficiency in the beads [15].

Table 3. Percentage yield and drug load of different coated and uncoated calcium alginate beads loaded with mefenamic acid.

Formulation code	Drug: polymer weight ratio	Percentage yield (w/w)	Percentage entrapment efficiency (w/w)
F1	1:1	90%	78%
F2	1:2	93%	83%
F3	1:3	95%	89%
F4	1:4	96%	87%
F5	1:5	92%	85%

Dissolution study

Percentage of a drug released from uncoated calcium alginate beads in 0.1 N HCl pH 1.2 and phosphate buffer pH 7.2 dissolution media is shown in Figure 2. The drug release is decreased with increasing the concentration of sodium alginate. It was reported that the decrease in the drug release with increase in the concentration of alginate was due to increase in the cross-linking between sodium alginate and calcium chloride, thus more drug remained entrapped and the percentage of drug release decreased [16].

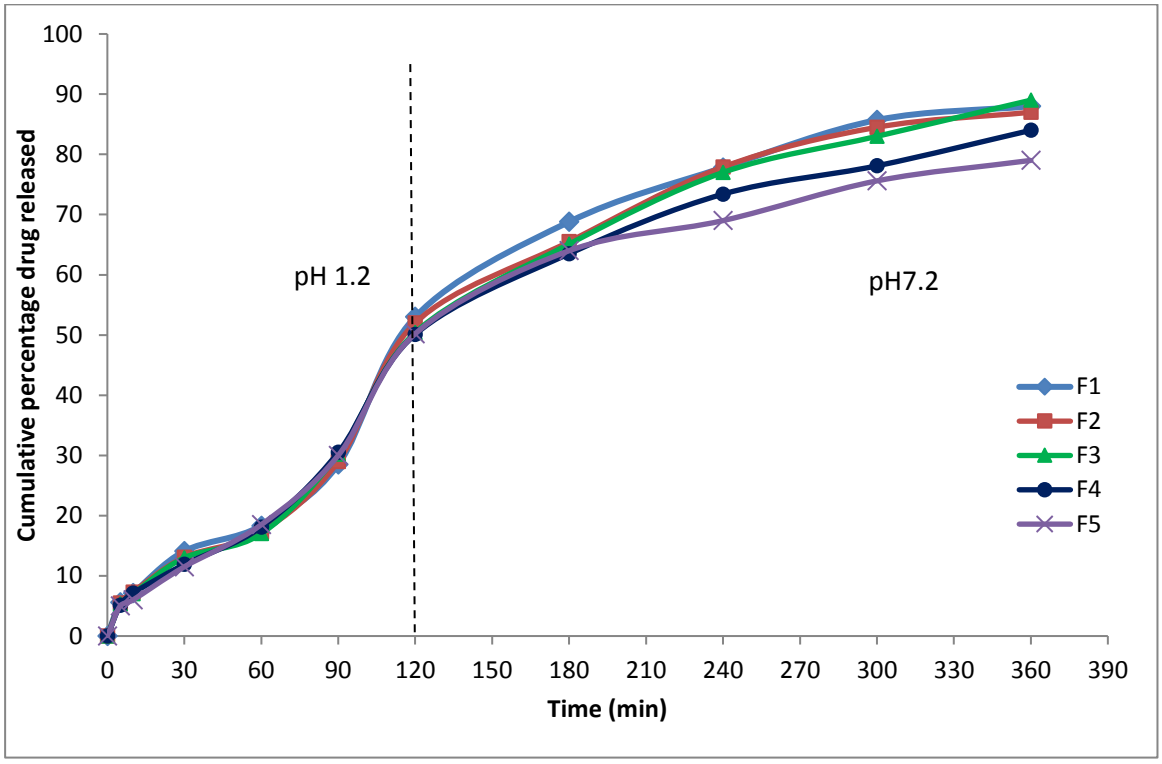

Figure 2. Percent drug released of mefenamic acid from different uncoated calcium alginate beads in pH1.2 and 7.2

The percentage of drug released was decreased upon coating the beads with Eudragit S 100 as shown in Figure 3. At the end of two hrs dissolution in acidic pH 1.2, approximately 30% and 20% of the drug were released from coated beads (F6 and F7) respectively compared to 50% drug released from uncoated beads of the same drug: polymer ratio (F3). Eudragit S100 is known to dissolve at pH above 7 therefore these percentages of drug released from F6 and F7 in pH 1.2 could be related to release of the drug from beads that were incompletely coated with Eudragit S100. On the other hand, it was found that at the end of 6 hrs dissolution in pH 1.2 and 7.2, the cumulative percentage of drug released from beads was also reduced upon coating; about 76% of the drug was released from F6 coated with (3%) coating solution compared to 90% of the drug released from uncoated beads (F3). Beads coated with (6%) polymer coating solution (F7) further decreased the cumulative percentage drug release; about 70 % of the drug was released at the end of dissolution test. This retardation in the release could be related to an increase in the thickness of the coating layer applied on the beads. Similar slower release profile of naproxen was obtained with applying high coating concentration of Eudragit S-100 coating on sodium alginate microspheres of naproxen sodium than from lower concentration of Eudragit S-100 coating [17].

Coated bead formulation F7 was selected as an optimum formulation, since it showed both reduced in percentage of mefenamic acid released in pH1.2, and slow constant release profile at pH 7.2 compared with other coated and uncoated formulations of calcium alginate beads.

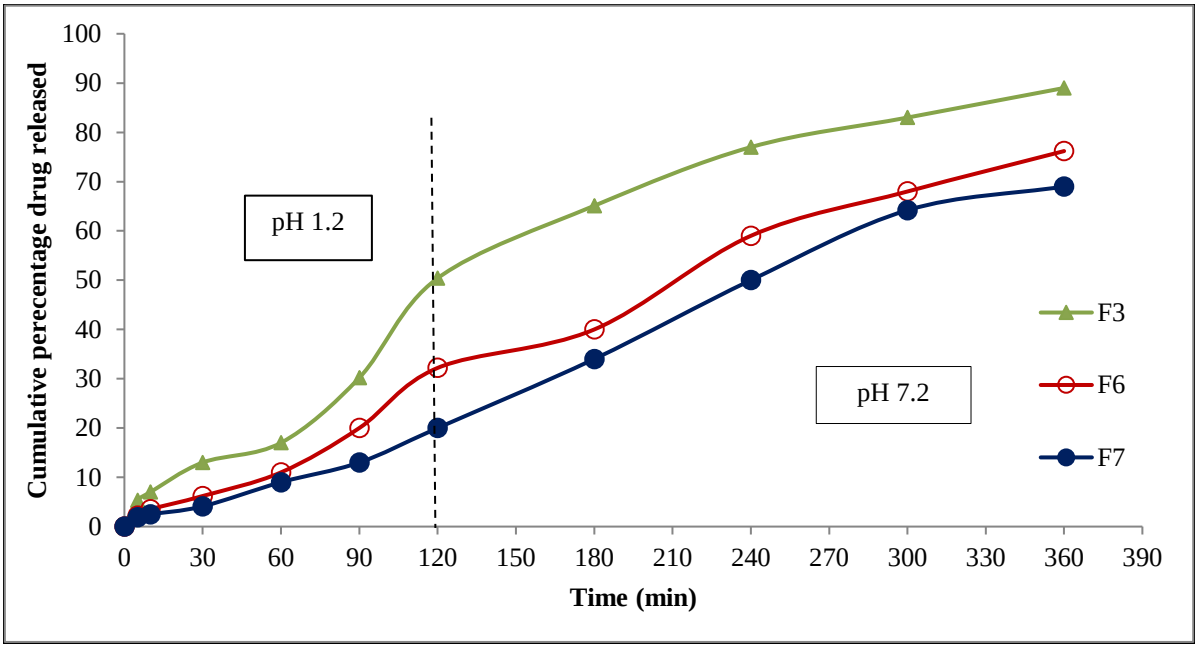

Figure 3. Percentage drug released of mefenamic acid from calcium alginate beads coated with Eudragit S100 (F6 and F7) compared with uncoated, beads F3

Conclusions:

From the results of this study**,** it is concluded that calcium alginate beads loaded with mefenamic acid can be prepared with a high efficiency drug load and with an acceptable percent yield. The method used for the preparation of beads showed spherical shape beads. Both drug: polymer ratio and coating of the beads with Eudragit S100 solution could effect on the release profile of mefenamic acid from calcium alginate beads; the drug release decreases with increase the ratio of polymer and with the application of a coat on the beads. In addition, the drug release retarded with an increase in the percentage of the coating solution.

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