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Preparation and Evaluation of Ketoprofen-loaded Sodium Alginate Beads

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Abstract

Ionotropic gelation was used to entrap Ketoprofen in sodium alginate beads. Ketoprofen is NSAIDs category drug; it has a short half life (1.5-2 h) and side effects such as irritation and ulceration in GIT. Beads were characterized for possible sustained drug release .On the basis of differential scanning colorimetry and IR spectroscopy, XRD alginate were found to be compatible with Ketoprofen. SEM showed that the beads were spherical and small. Ketoprofen encapsulation efficiencies were high (>90%), also results showed that, release profile in 0.1M HCl (pH 1) was slow. In phosphate buffer complete drug release was shown for all formulations within 6 h. The mechanism of release depended on swelling of beads. The swelling behavior dependent on pH of the medium; such a pH sensitive swelling could be auspicious for orally administered drug vehicles especially for acid sensitive drugs.

Keywords: Anti-inflammatory, Ketoprofen, alginate beads, ionotropic gelation.

Introduction

Gastroretentive drug delivery is an approach to prolong gastric residence time, thereby targeting site-specific drug release in the upper gastrointestinal tract (GIT) for local or systemic effects[1,2]. GRDDS can bost the controlled delivery of drugs that have an absorption window by releasing the drug for prolong span of time before it passes to its absorption site thus its maximum bioavailability is ensured. Tablets and capsules give an immediate release of the drug; but they fail to maintain the drug concentration within the therapeutically effective range for a required period. To control effective plasma drug concentration, these dosage form must be administered frequently[3-7]. They also have an advantage over the conventional system as it can be used to overcome Floating systems, are low-density systems that have proper tendency to float over the gastric contents & remain in the stomach for a prolonged period. While the system floats over the gastric contents, the drug is released slowly at the needed rate, which results in increased GRT & lessens change in plasma drug concentration[8].

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The benefits of floating drug delivery system includes; Gastric retention time is increased, site specific drug delivery to stomach can be obtained, Drug controlled release for a prolonged period & decreased dosing frequency, Targeted local ailments in the upper GIT, better therapeutic effect short half life drugs can be obtained, increase absorption and first pass metabolism of drugs soluble in stomach & reduced fluctuations of drug concentration could be achieved[9-11]. But the floating drug delivery system are not feasible for drugs having solubility problems in gastric fluid, high level of fluids in the stomach is required for maintaining float, drugs with powerful first-pass metabolism & drugs irritating gastric mucosa are not desirable candidates for floating drug delivery system. Ketoprofen is rapidly and well-consumed orally, with peak plasma levels occurring within 0.5 to 2 hours. No active metabolites have been identified. 80% of an administered dose of ketoprofen is released in the urine after 1day[12,13].

Experimental

Materials

Ketoprofen (KP) was provided by Amriya Pharmaceuticals & Chem. Ind. Co. (Cairo, Egypt).

Sodiumalginate, calcium chloride and gelatin were obtained from Chem. and pharma. Co. LTD (England). Ethyl cellulose (EC) was procured from Hercules, Wilmington, DE. (USA). Hydroxypropyl methylcellulose acetate succinate (HPMCAS) was procured from Shin Etsu, Tokyo (Japan). Potassium dihydrogen orthophosphate, sodium hydroxide, hydrochloric acid were purchased from El-Naser pharm. And chem. Co. (Egypt), and all other ingredients use were of pharmaceutical quality.

Formulation of Sodium Alginate Beads of Ketoprofen

The beads were formulated by ionotropic gelation. Sodium alginate and HPMC E5LV was dissolved in water (9:1 sodium alginate: HPMC E5LV) at a conc. of 1-3 %w/v using gentle heat over water bath. After getting a clear solution, an accurately weighed quantity of drug was added and mixed uniformly into the solution. The bubble free sodium alginate-drug dispersion (20ml) were added drop wise through 22-guage hypodermic needle fit with a 10 ml syringe into 100 ml of calcium chloride solution (1-2%w/v) containing 10% glacial acetic acid and stirred at 400 rpm for 15 min. The droplets from the dispersion directly gelled into discrete matrices upon contact with the solution of gelling agent. Finally, beads were filtered, washed and dried at room temperature[14].

Table 1: Composition of Sodium Alginate Beads

Sr. N.	Formulation Code	Ketoprofen	Sodium Alginate	HPMC	$CaCl_2$
1	F1	100	2%	1%	2%
2	F2	100	2%	1%	2%
3	F3	100	2%	1%	2%
4	F4	100	2%	1%	2%
5	F5	100	2%	1%	2%

Characterization Studies

Estimation of Percentage Yield & Drug Entrapment Efficiency: Beads were crushed and put in 0.1N HCl. After 24 hrs, the solution was filtered and the filtrate was test for drug content[15].

$$\text{Drug Entrapment Efficiency} = \frac{\text{Practical drug content}}{\text{Theoretical drug content}} \times 100$$

Determination of Swelling Index

The swelling index was analysed by studying its weight gain. The swelling index of beads was analysed by put the beads in the basket of dissolution apparatus using media 0.1N HCl (pH 1.2) at 37±0.5° at 50 rpm, After 0.5, one, two, three, four, and five hours intervals,sample was removed and blotted with tissue paper to remove the excess water and weighed on the analytical balance (Shimadzu, AX 120).

$$\text{Swelling Index} = \frac{\text{(Wet weight of beads - Dry weight of beads)}}{\text{Dry weight of beads}}$$

Buoyancy Test

The buoyancy of the beads is done by, soaking 100 beads in 100ml of 0.1 HCl at pH 1.2. The number of floating beads are characterised at fixed time intervals. The floating time is measured as the time at which the 100% of beads floated[16-17].

Morphological Characterization (SEM)

The samples were coated with a thin gold layer with the technique of sputter coater unit Then, SEM photographs were taken by a scanning electron microscope[18-19].

Fourier Transform Infrared Spectroscopy (FT-IR) Studies

The spectra were recorded on Jasco-5300 FT-IR system. Infrared (IR) spectroscopic analysis was carried out on the mixtures to know possible interactions between the drug and the excepients. Samples were prepared by KBr disc technique and. Individual The scanning range was 400–4000 cm^{-1} and the resolution was 1 cm^{-1}.

Differential Scanning Calorimetry (DSC) Studies

DSC is a method to monitor the structure of a material and to obtain information about the physicochemical interaction between drug and polymer. In this technique, samples (8–10 mg) were weighed into aluminum pans and heated in nitrogen from 5 to 250^0C [20-21].

X-ray Diffraction (XRD) Studies

To determine the crystalline state of the drug in the polymer, the X-ray diffraction method of drug loaded beads was determined and compared with that of pure drug.

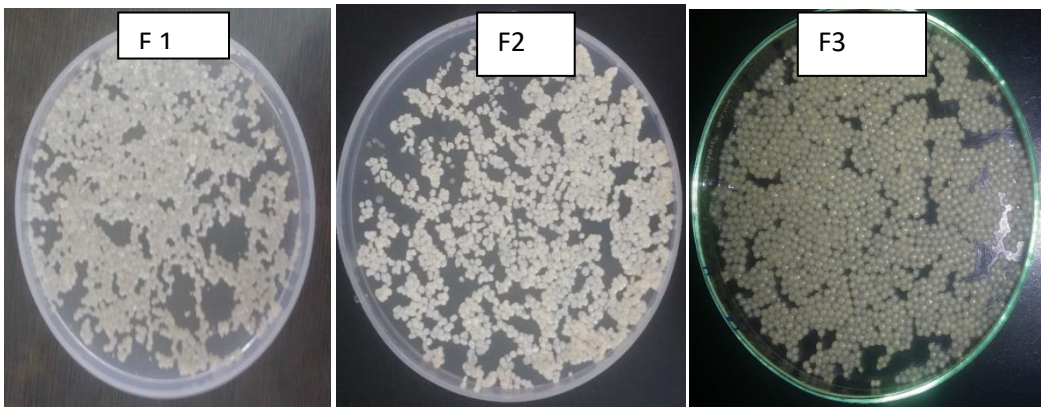
***In-vitro* Drug Release Study**

In-vitro drug release studies were performed in USP type II apparatus at 50 rpm maintained at 37 ± 5°c. A sample was transferred into the dissolution medium of 900 ml of 0.1 N HCl, pH 1.2. Then 5 ml of aliquots was withdrawn from the dissolution vessel at specific time intervals and changed with equivalent volume of fresh medium. Collected dissolution samples were filtered using filter paper and then, used for determination of released KP concentrations by using a UV–Vis spectrophotometer[22].

Results and discussion

Table 2: Evaluation parameters of different floating alginate beads

Formulation code	% Yield	% Entrapment Efficiency	% Floating	Physical Appearance
		Ketoprofen		
F1	86.35	36.26	20	Oval
F2	76.75	38.39	25	Oval
F3	81.89	91.27	55	Round
F4	77.97	73.29	30	Round
F5	78.37	70.29	27	Oval



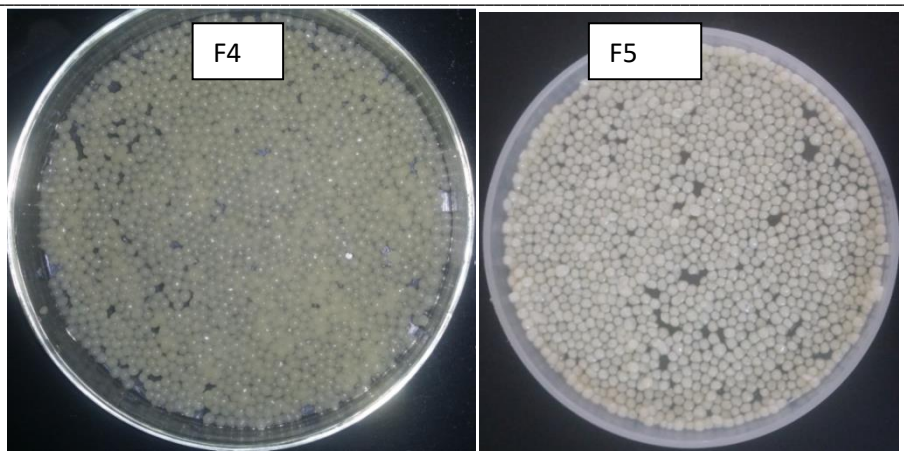


Figure 1: Photographs of different sodium alginate beads formulations

Among of the above formulations, formulation F3 shows good entrapment efficiency but buoyancy is not good so different ratio of calcium carbonate was tried for better buoyancy.

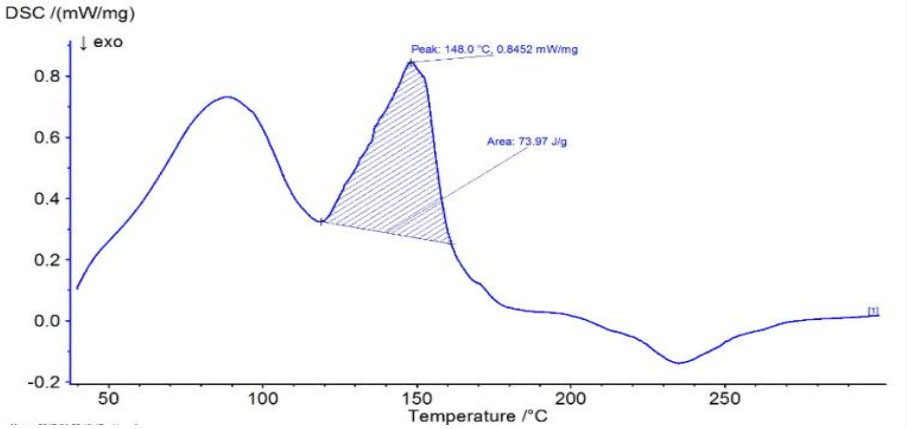


Figure 2: DSC Curve of Ketoprofen + Sodium alginate + Calcium chloride

Samples showed relatively deep melting endothermic peak and pure drug show sharp endothermic peak at 97.1 °C Ketoprofen respectively. The peak power corresponding to the melting of drugs decreased in the thermo grams of mixtures. These results clear that only a small fraction of the drug was present in the crystalline state.

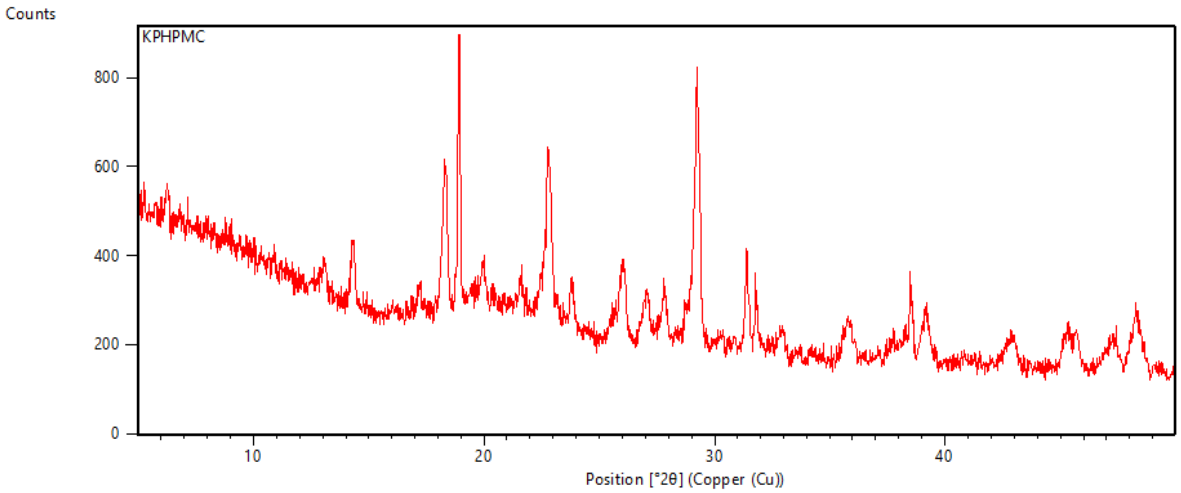


Figure 3: XRD of physical mixture

***In-vitro* drug release studies**

The *in vitro* drug release studies of different formulations and pure drug were controlled to assure the effect of sodium alginate conc. and calcium chloride conc. on the release of Ketoprofen from the formulations. The *in vitro* dissolution studies of the floating formulations were carried out using USP dissolution test apparatus I (basket method). The basket of USP dissolution test apparatus I, each containing an amount of beads comparable to 100 mg Ketoprofen were rotated at 100 rpm in 900 ml of 0.1N HCl maintained at 37°C±0.5 °C. An aliquot of 5 ml of the solution was withdrawn at fixed time intervals.

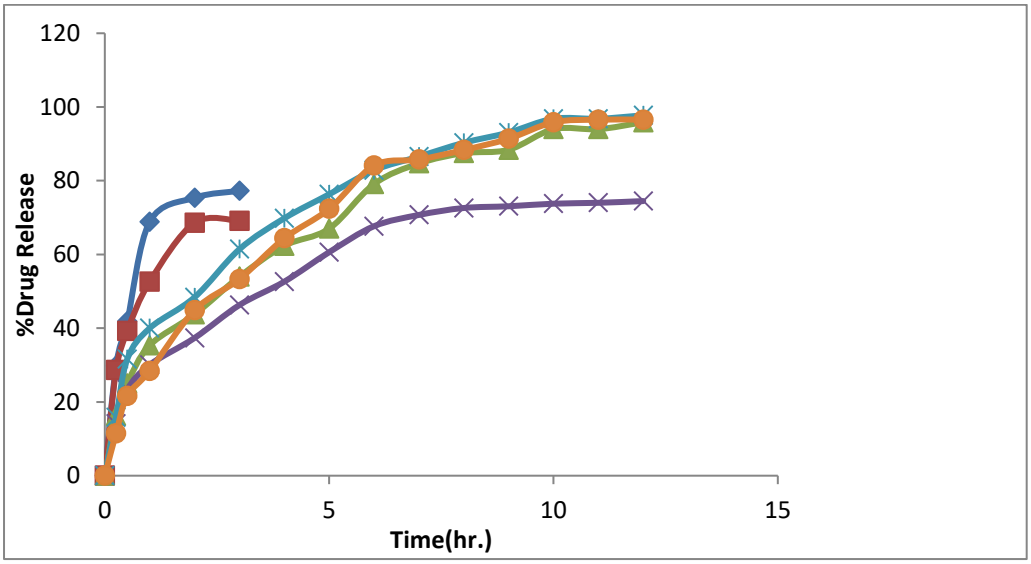


Figure 4: *In-vitro* drug release of different optimized compositions and pure drug in 0.1 N HCl

The *in-vitro* dissolution studies of the formulation formulation-3 shows maximum percent cumulative release with in 12hrs. This shows that Formulation-3 was having the good sustained release of the Ketoprofen up to the 12 hrs.

The morphological characterisationof the optimized beads formulation (Formulation-3) was done by scanning electron microscopy. SEM study revealed that the microspheres almost spherical in shape with rough outer surface.

Scanning electron microscopy (SEM)

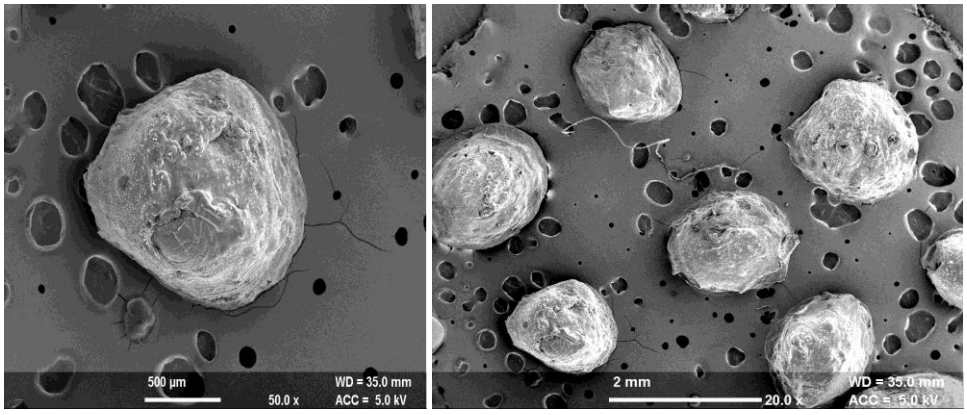


Figure 5: Shape and size of the beads (Formulation-3)

Conclusion

In the present study, a satisfactory attempt has been made to formulate gastroretentive floating beads of Ketoprofen.. From the experimental study result, it was concluded that optimized batch F3 showed good micromeritic properties, entrapment efficiency and releases drug slowly and completely for 12 hours as beads remain in floating condition throughout dissolution study that assures prepared formulation remain floated in stomach without its early passing to lower GIT side. This will help to increase the residence time of Ketoprofen in stomach and achieve sustained release thereby increase the bioavailability of drugs. Finally the prepared floating beads may prove to be potential gastroretentive delivery system for safe and effective controlled release for an extended period of time.

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