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Porous Floating Beads of Ornidazole: Formulation and In Vitro Characterization

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Research Article

Porous Floating Beads of Ornidazole: Formulation and In Vitro Characterization

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Abstract

The aim of the present study was to develop a floating drug delivery system using Ornidazole porous beads with sodium alginate and cetyl alcohol. Sodium alginate beads containing cetyl alcohol was prepared by ionotropic gelation technique using calcium chloride solution (5% w/v) as coagulation fluid. The embedded wax was removed by heating the beads at 50-55°C. The influence of wax amount on drug release and buoyancy was studied. The prepared beads were evaluated for morphological changes, bead size, encapsulation efficiency, floating properties and in vitro drug release. Bead sizes ranged from 1.142±0.062 mm to 1.274±0.05 mm. In simulated gastric fluid, the beads remained afloat for > 24 h. The quantity of wax and curing time of bead did not affect *in vitro* drug release.

Key words: Ornidazole, sodium alginate, wax removal, porous floating beads.

Introduction

Administration of drugs orally is a convenient route for drug delivery due to its advantages such as less cost, good patient compliance and ease of use. But, oral drug delivery has several demerits i.e rapid gastric emptying, reduced bioavailability due to its low absorption and deterioration in the alimentary tract [1]. Approaches like bioadhesion, low density system, high density system, expanding system and modified - shape system may delay the gastric emptying time [2]. One of the novel approaches for enhancing the gastric retention time in the stomach is non-effervescent low density system. [1]

The polymers like Eudragit®, low methoxylated pectin, cellulose acetate phthalate, agar and alginic acid derivatives are used as carries in various floating approaches[3]. Instant floating can be achieved by the low-density system (density < 1 g/cm^3), for example entrapment of the air in the dosage form or by incorporation of oil or waxes [1]. Many methods have been developed for the low-density floating systems, solvent evaporation, including a gas forming agent or making the system porous [2].

In this work an effort is made to formulate the floating beads containing anti-protozoal drug (Ornidazole). Ornidazole is an anti- protozoal drug use to treat some protozoal infection and also stomach infections [4]. It is soluble in ethanol, acetone and its water solubility is 3.34 mg/ml. Dosage range from 400-500 mg daily for adults and 125-150 mg daily for children.

Materials

Ornidazole was received as a gift sample from Micro Labs Pvt Limited, Bangalore. Sodium alginate was procured from SD Fine Chem, Mumbai. Cetyl alcohol was obtained from Alpha Chemika, Mumbai, Maharashtra. Calcium chloride and acetone were received from Alpha Chemika, Mumbai.

Methods

Preparation of porous floating beads [1,5]:

Wax removal technique was used to prepare porous floating beads. The polymer was dissolved in

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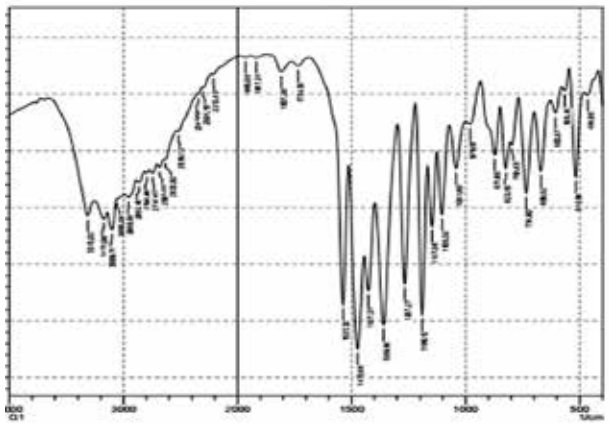
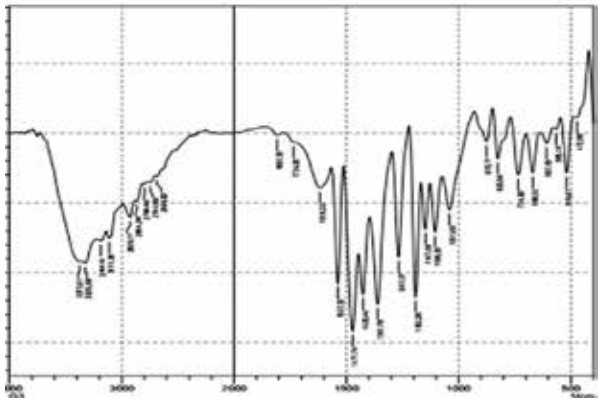
Table 1: Different batches with formulation variables

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Ornidazole (mg)	125	125	125	125	125	125	125	125	125	125
Sodium alginate (%)	1	1	1	1	1	2	2	2	2	2
Cetyl alcohol (mg)	250	500	750	250	250	250	500	750	250	250
Acetone (ml)	2	2	2	2	2	2	2	2	2	2
Curing time (min)	5	5	5	10	15	5	5	5	10	15

distilled water. Then drug, acetone and cetyl alcohol was added polymeric solution as given in Table 1. Then mixing was done homogenously by using magnetic stir. The dispersion containing wax was then extruded through 18 gauges needle into 5% of calcium chloride solution. The formed beads were cured by gentle stirring at room temperature and filtered. The wax (cetylalcohol) removal was induced by heating the beads at 50-55 °C for about an hour.



(a)



(b)

Figure 1: FTIR images of (a) pure drug and (b) formulation

Fourier Transform Infrared (FTIR) spectroscopy:
The FTIR spectra of pure and the final one (F2) were obtained by scanning the samples within the range of 400-4000 cm^{-1} using the FTIR spectrometer (Shimadzu 84000S, Japan).

Differential Scanning Calorimetry (DSC):
Differential scanning calorimeter (DSC-60 Plus, Shimadzu, Japan) was used to obtain DSC peaks of pure drug and the prepared beads. The DSC thermogram was obtained by sealing the drug or formulation in hermetically in an aluminum pan and kept under nitrogen purging (atmosphere). The samples were scanned from room temperature to 300 °C and with 10 °C rise/ min.

Size determination of porous floating beads:
The diameter of the 100 beads were determined using calibrated eye piece micrometer by optical microscopy.

Morphology of porous floating beads:
Scanning electron microscopy was used in analysis of the surface and internal structure of the floating beads. The prepared beads were subjected to sputter coating where ultra-thin coating of electrically conductive metal such as gold is applied onto a bead. Next, scanning electron microscope (JSM 6380LA, Joel India) was used to observe the sputter coated beads.

Drug content and encapsulation efficiency:
It was determined by crushing the beads in a glass mortar and pestle and shaking the crushed beads with 100 ml of 0.1N HCl for 48 hours. After crushing, filtration was done using Whatman filter paper and suitably diluted. It was then analysed using UV spectrophotometer (1601, Shimadzu, Japan) using suitable blank at 277 nm.

$$\textbf{Encapsulation efficiency} = \frac{\text{Acutacl drug content}}{\text{Theoritical drug content}} * 100$$

The studies were performed in triplicate and results are given as mean ± SD.

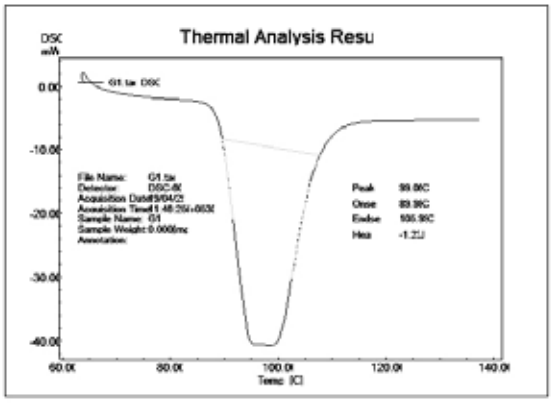
Table 2: Physico-chemical parameters of the prepared formulations

Formulation code	Diameter ±SD (in mm)	Drug content (mg)	% Encapsulation efficiency
F1	1.252±0.09	88.892±0.06	71.11±0.01
F2	1.220±0.061	97.821±0.08	78.25±0.03
F3	1.274±0.05	94.964±0.026	75.97±0.07
F4	1.251±0.047	82.125±0.04	65.70±0.09
F5	1.266±0.35	59.982±0.02	47.98±0.15
F6	1.208±0.065	73.535±0.05	58.82±0.17
F7	1.225±0.073	67.107±0.14	53.68±0.27
F8	1.224±0.095	69.607±0.19	55.68±0.20
F9	1.142±0.062	61.767±0.11	49.41±0.11
F10	1.227±0.074	54.607±0.05	43.68±0.21

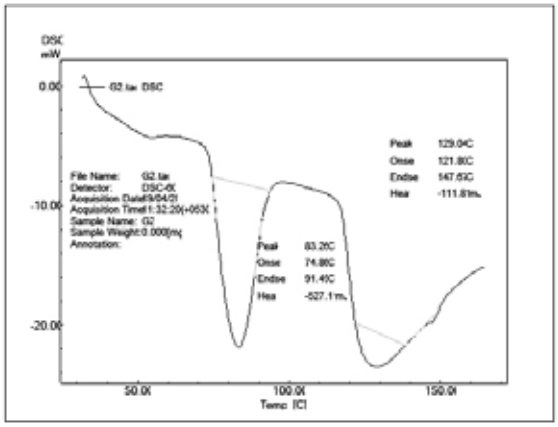
All the prepared batches of beads were buoyant instantaneously and remained buoyant for over 24 hours in the test medium.

Floating properties of the beads [6]:

Paddle type USP dissolution apparatus II was employed to assess the floating capacity and lag time of the prepared beads. Twenty beads were kept in the vessel and the paddle was rotated at a speed of 50 rpm in 900 mL of 0.1 N HCl. The floating ability was measured by visual observation.



(a)



(b)

Figure 2: DSC thermograms of (a) pure drug and (b) formulation

***In vitro* dissolution studies [7]:**

It was studied by paddle type USP dissolution apparatus II. Floating beads were kept in vessels as previously. The temperature of the media was maintained at 37±0.5°C and paddle was rotated at 50 rpm. At specific time intervals, the sample was withdrawn (5 ml) and replaced with the fresh media. The sample was filtered with 0.45 um membrane filter. The amount of the Ornidazole in each sample was estimated by using UV-Spectrophotometer (UV-1601, Shimadzu, Japan) at 277 nm. The samples were analyzed triplicate and the mean (±S.D) reading was taken.

Drug release kinetic [8]:

Various models were used to understand the kinetics and drug release mechanism by analyzing the *in vitro* release data. The experimental data was fitted to different kinetic models of drug release.

Results and Discusiion

Fourier Transform Infrared spectroscopy (FTIR):

The FTIR spectra of Ornidazole and final formulation are displayed in the Figure 1. Figure 1(a) exhibits the characteristic peak at 3313 cm^{-1}, 2955cm^{-1}, 1267cm^{-1}, 1147 and 1103 cm^{-1} as a result of stretching vibration of the O-H, C-H stretching for CH_3 (methyl), C-O (Carbonyl) and C-N (cyanide) groups respectively. Peaks also appeared at 1473 cm^{-1} and 1427 cm^{-1} due to the deformation of C-H and O-H of the pure drug sample. Figure 1 (b) showed the characteristic peaks at 3325 cm^{-1}, 2926 cm^{-1}, 1267 cm^{-1}, 1147 cm^{-1} and 1105 cm^{-1} due to the stretching vibration of the O-H, C-H stretching for CH_3, C-O,

C-N respectively. Peaks were also visible at 1471 cm^{-1} and 1425 cm^{-1} because of deformation of C-H and O-H for final formulation. This confirms that no interaction between the used drug and polymer was present.

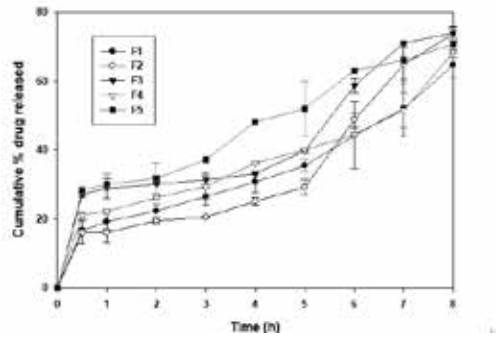


Figure 3: In vitro drug release profiles of Ornidazole of formulations F1 to F5

Differential Scanning Calorimetric Analysis

The obtained Differential Scanning Calorimetric (DSC) thermograms of Ornidazole and final formulation are shown in Figure 2. It showed an endothermic peak at 99.06°C with onset and endset temperatures of 89.98°C and 105.99 °C respectively. The latent heat of fusion (ΔHfus) was found to be -1.23 J/g, indicating crystallinity of the drug. Similarly, the final formulation DSC thermogram showed endothermic peak at 83.26°C with onset and endset temperatures of 74.86 °C and 91.49 °C, respectively. The latent heat of fusion (ΔHfus) was found to be -527.11 J/g. There was no considerable change in the melting endotherm of final formulation compared to that of pure drug sample. This confirms that no interaction between the used drug and polymer was present.

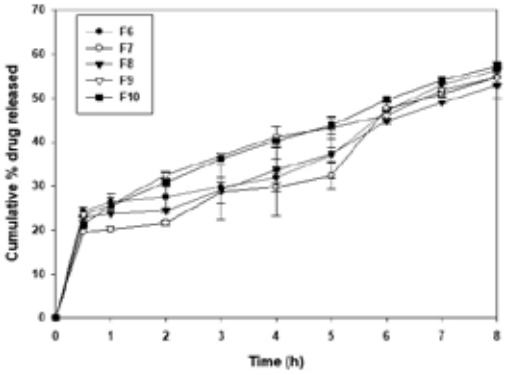


Figure 4: In vitro drug release profiles of Ornidazole of formulations F6 to F10

Particle size analysis

The mean surface diameter of 10 formulations is showed in Table 2.

Encapsulation efficiency and drug content:

The calculated drug content and the encapsulation efficiency are showed in Table 2. Drug content in

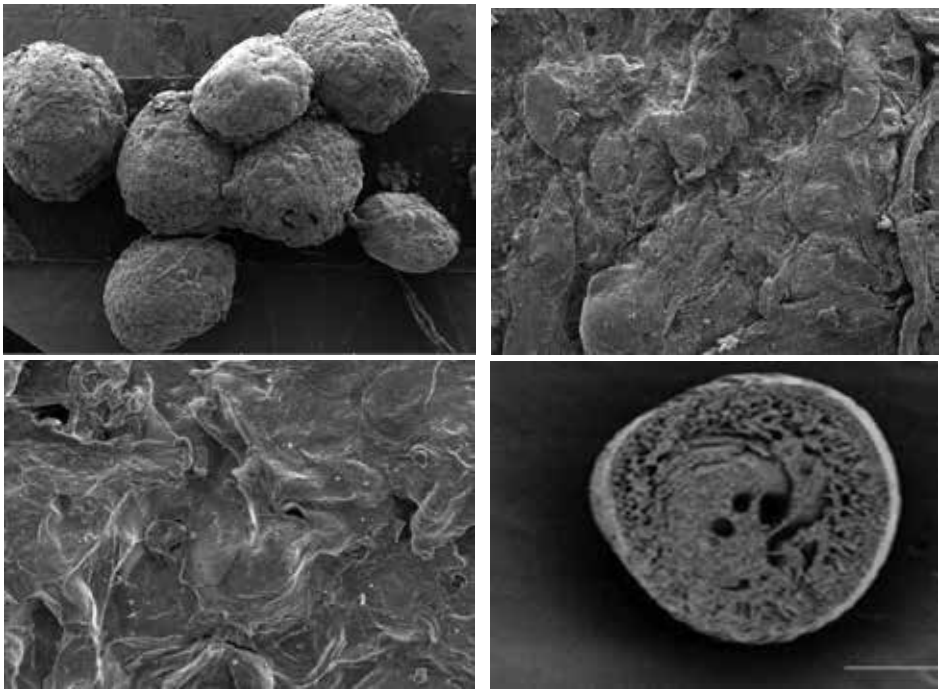


Figure 5: Scanning Electron Microscopy images of final formulation.

the beads ranged from 54.60 ± 0.05 mg to 97.82 ± 0.08 mg and entrapment efficiency was found between 43.68 ± 0.21% to 78.25 ± 0.03%. F2 and F3 formulations showed maximum amount of drug content 97.821 ± 0.08 mg and 94.964 ± 0.026 mg and drug encapsulation efficiency 78.25 ± 0.03% and 75.97 ± 0.07% respectively. The amount of the wax used did not influence the drug content and entrapment efficiency. Ornidazole is an aqueous soluble drug and during the preparation it may be diffused from the beads that reduced the drug content and entrapment efficiency. The curing time played an important role in the drug entrapment efficiency, increased curing time reduced the drug content and entrapment efficiency this is may be because of aqueous solubility of the drug.

Floating properties of the beads

The beads instantly floated in 0.1N HCl and remained in the floating state for 24 hours. Incorporation of the various amount of the wax did not significantly influence floating behaviour. The floating behaviours of the alginate beads may be due to the porous structure created during wax removal.

***In vitro* drug release study**

0.1 N HCl used to carry out *in vitro* drug release studies mimicked the gastric environment and it was helpful in understanding the applicability of the beads as gastro-retentive low-density system for drug delivery. Different amount of waxes were used in *in vitro* drug release studies as shown in figure 3 and 4. Initially there was burst release which is probably due to the tendency of drug to move to the bead surface during the preparation or drying period. The drug release also enhanced due to removal of the wax from the beads. Drug release of all the prepared formulation ranged from 52.89 ± 3.01% to 74.02 ± 1.49% at 8 hours. The formulations F2 and F3 showed 73.73 ± 2.11% and 74.02 ± 1.49% drug release respectively. Formulation F8 showed low drug release about 52.89 ± 3.01%, because of polymer used in higher concentration (2%).

***In vitro* kinetic studies**

Various kinetic models were used to fit the drug release data like Higuch diffusion, zero order, first order and Korsmeyer–Peppas release models. R^2 value was used to define accuracy of all kinetic models. Formulations F2, F5 and F8 followed the first order drug release kinetics. Formulations F6, F7, F9 and F10 followed Higuchi's model of diffusion and Formulation F1 followed zero order drug release kinetics. Kosemeyer-Peppas model is used to analyze drug release mechanism from the beads. If the release exponent (n value) is less than 0.45 it indicates Fickian model, n value between 0.45 to 0.89 indicates anomalous or non-Fickian diffusion, and if n values is more than 0.89 it indicate super case II drug release mechanism. Formulations F1, F2, F3, F4, F5 and F8 followed non-Fickian diffusion and formulations F6, F7, F9 and F10 followed Fickian diffusion as n value was found to be 0.644, 0.737, 0.778, 0.533, 0.456, 0.510 and 0.384, 0.054, 0.354 and 0.395 respectively. From the evaluation data, it was concluded that porous beads with desired buoyancy can be developed by wax removal technique with selective modification of formulation variables.

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