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Study of Drug Release from the Multiunit Floating System Beads Bearing Metronidazole using Hydrophilic Polymer by Ionotropic Gelation Technique

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ABSTRACT

In our present investigation we developed the multiunit gastro retentive beads bearing Metronidazole (MTZ) (log p=0.0) and sodium alginate (SA). This gastroretentive system can remain in the gastric region for a prolonged period of time and increases the gastric retention time which significantly increases the bioavailability, reduces drug waste and improves the solubility for the drugs that are less soluble in high pH environment.In this we developed beads system which comprises of MTZ, SA, buoyancy imparting agents and cross linking agents. These beads are prepared by ionotropic gelation technique and evaluated for the particle size, drug content, % buoyancy and *in-vitro* release. Percentage buoyancy of the beads was found excellent and they remain afloat for 12 hours and also show release characteristics for 12 hours. As the concentration of polymer increases (M4) the drug release extends upto 12 hours. This result however reveals that this system can be employed for the treatment of upper GI tract infection as well as system drug delivery.
Keywords: multiunit gastroretentive beads, Metronidazole base, Sodium alginate, ionotropic gelation, % buoyancy, GI tract infection.

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INTRODUCTION

Floating beads are one of the multiple unit dosage forms. The growing interest for multiple unit dosage forms and their increasing share of the pharmaceutical product market are claimed by their proponents to stem from some advantages. Floating beads for oral use offer following advantages as compared to single unit dosage forms [1] like- floating beads spread out more uniformly in the gastro-intestinal (GI) tract, thus avoiding exposure of the mucosa to high concentrations of drug, thereby ensuring more reproducible drug absorption, the risk of dose dumping also seems to be considerably lower than with a single unit dosage form [2], preparation of the multiple unit dosage form of drug which has nonlinear pharmacokinetic characteristics as verapamil provides an advantage as regards to its decreasing inter and intra subject variability of absorption [2,3], multiple unit beads dosage forms avoid the vagaries of gastric emptying and different transit rates, and thereby, release the drugs more uniformly.

Encapsulation of drugs in hydrocolloid beads for prolonged/ modified/site specific release of drugs is a very popular, simple and old method. A number of naturally occurring as well as biotechnology derived hydrocolloids has been explored as bead system for the above mentioned purpose [4]. However, these beads systems often suffered from poor drug encapsulation/leaching of drug in the curing medium and in some cases very fast drug release. Although a number of efforts have been made in past to overcome these disadvantages by using various crosslinking agents but these modifications often leads to the systems which are difficult to reproduce or scale up [5,6].

In this our present investigation, technology used that is use of cross linking agent like calcium chloride. Drug of choice is the Metronidazole, and it is a nitroimidazole compound with broad spectrum activity against protozoa and anaerobic bacteria. It acts by inhibition of DNA synthesis. Metronidazole is bactericidal at low concentrations for most anaerobes, it is most active against Gram-negative anaerobic bacilli. It is used in the treatment of trichomonal genital infections, as a prophylactic agent before abdominal surgery and in the management of severe anaerobic infections. Although it is rapidly, completely absorbed (>80%) after oral administration. The peak plasma concentrations are achieved after 1-3 hours. The plasma half life is 6-8 hours, which makes frequent dosing necessary to maintain the therapeutic blood levels of the drug for a long term treatment. Therefore, Metronidazole is an ideal drug candidate for formation multi unit floating beads formation. The present investigation was under taken to develop and evaluate multi unit floating beads of Metronidazole.

MATERIALS AND METHODS

Materials and method

Metronidazole (MTZ) was gifted by Simpex Laboratories Kotdwar, India. Sodium alginate was purchased from Sigma-Aldrich (St. Louis, USA). Water used in the formulations was of HPLC grade (Merck) and all other chemicals used were of analytical grade.

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Method

Preparation of MTZ and SA loaded multi unit floating systems

Floating beads were prepared by using formulation given in (Table 1) by extruding an SA containing $CaCO_3$ with drug with the help of 25 ml hypodermic syringe, into $CaCl_2$ solution (4%w/v) at room temperature (28^0C). The beads formed instantaneously, were cured for 10 minutes in gelation medium at 37 ^{0}C with mild agitation. Prepared beads were separated by filtration, washed thrice with deionized water and dried in an oven at 35 ^{0}C for 12 hours than kept in a desiccator for another 12 hours before further experiments.

Table 1 Formulation composition for gel beads containing Metronidazole

Formulation code	MTZ (mg)	S A (% w/v)	$CaCl_2$ (%w/v)	$CaCo_3$ (mg)	Curing time (min.)
M1	100	1.5	4	100	10
M2	200	1.5	4	100	10
M3	100	2.0	4	100	10
M4	200	2.0	4	100	10

Total volume of the formulation was 10 ml

RESULT AND DISCUSSION

Microscopic characterization of the MTZ beads

The beads size of the prepared formulation varies from 0.96 ± 0.02 mm to 1.16 ± 0.02mm in range and it is estimated by using optical microscope (Olympus Japan). The reason for this broad range particle size due to use in different concentration of drug and polymer, curing time of formulation also affect the particle size. Formulation M4 is having the largest size of 1.16 ± 0.01 mm where as there is little bit gradual decrease in the size of particle in formulation M3 due decrease in drug ratio as compared to the polymer. Smallest particle is of 0.96 ± 0.02 mm particle size which is of formulation M1.

Drug entrapment efficiency

The drug entrapment efficiency of each formulation was determined by extracting the crushed beads with 0.1M HCl (pH 1.2) for 180 min at 37 ^{0}C and then centrifuged at 5000 rpm. The supernatant layer was taken and suitably diluted with 0.1M HCl (pH 1.2) buffer, quantifying the amount of drug UV spectrophotometrically at 278 nm (Shimadzu UV-1800, Japan). The entrapment efficiency (EE) was calculated according to relationship:

$$EE = \frac{\text{Actual drug content}}{\text{Theorectical drug content}} \times 100$$

The entrapment efficiency varies from 60.91 to 68.56%. This can be well explained by the basis polymer : drug ratio. In formulation M1, M2, M3, M4 the entrapment efficiency was found to be 67.47%, 68.56%, 60.91% and 64.34% respectively with low standard deviation value. This type of result is due to the improper mixing of the drug in the polymer due to nature of the drug and may be also due to the drug loss in the curing media, this

leads to the improper mixing of the drug in the sodium alginate solution which leads to the unfruitful result of the entrapment efficiency results.

Table 2 Particle size analysis and % drug entrapment efficiency

Formulation code	Particle size ± S.D (mm)	% EE ± S.D	% buoyancy
M1	0.96 ± 0.02	67.47 ± 0.04	92
M2	1.06 ± 0.03	68.56 ± 0.05	94
M3	1.10 ± 0.02	60.91 ± 0.02	100
M4	1.16 ± 0.01	64.34 ± 0.01	100

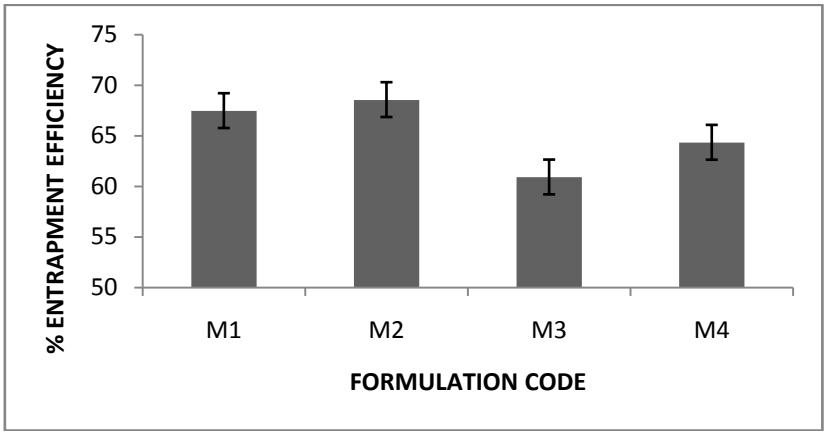

Fig. 1 Histogram representing % entrapment efficiency

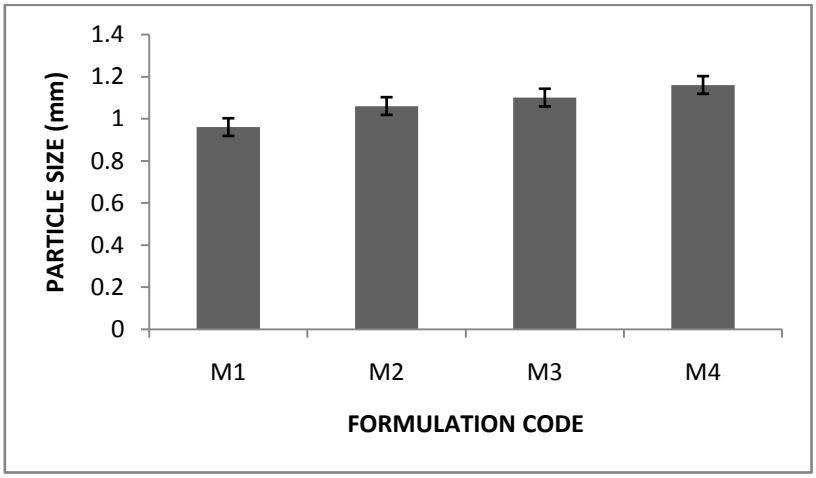

Fig. 2 Histogram representing particle size

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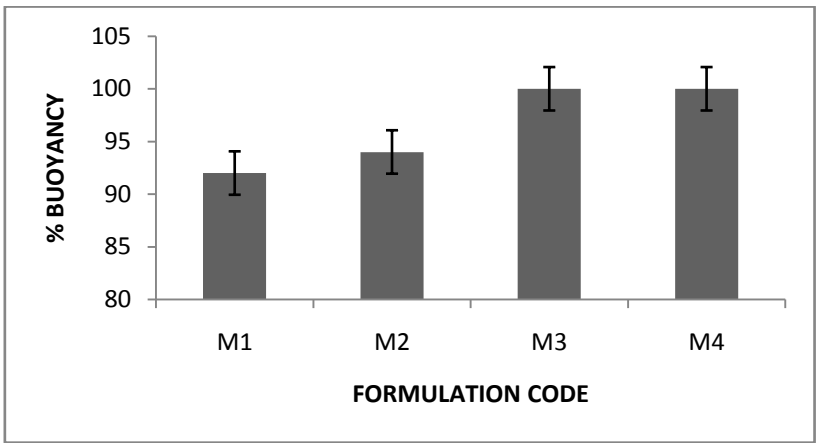

Fig. 3 Histogram representing % buoyancy

Assessment of *in vitro* buoyancy of the floating beads

The buoyancy of the beads was not dependent upon the hydrophilic polymer i.e sodium alginate concentration. Beads prepared with gas-generating agent remained buoyant on 0.1 M HCl for sufficiently long duration of time. Floating beads remained buoyant for upto 12 hours on 0.1 M HCl with no floating lag time. Upon contact with an acidic medium, the $CaCO_3$ effervesced, releasing CO_2. The released CO_2 was entrapped in the gel network producing buoyant formulation and thus, prolonged floating of beads for upto 12 hours.

In vitro drug release

In vitro release profile was performed in the 0.1 M HCl (pH 1.2) in dissolution apparatus type II at 50 rpm (Electrolab India,). In this release study we found that in all the formulation there is slow release profile in first few hour of dissolution run. After there is progressive and continuous release of drug from the hydrophilic polymer matrixes. In our present investigation we find out that the in M1 formulation the drug release continuously releases for almost 8 hours with loading of drug to 67.47%. This is attributed due to the concentration of drug and concentration of polymer. The drug is uniformly distributed in both the phases and extent the release the drug from these matrixes of polymer.

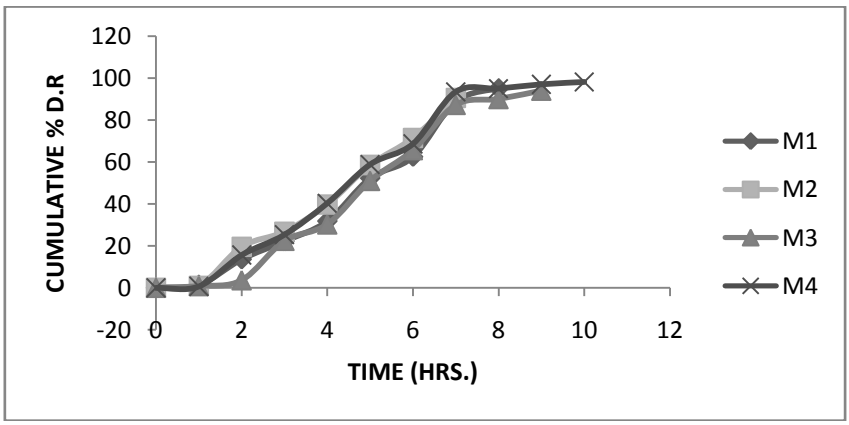

Fig 4. Release profile of formulations

In M2 formulation the same concept behind this is that the distribution of the drug in both the phases but only the difference of drug loading in it. Due to the high drug content in this formulation leads to the high entrapment efficiency. In formulation M3 in this case the drug releases for almost 10 hours due to the increase in the concentration of the hydrophilic polymer concentration which acts as a barrier for the release of the drug from the formulation to the extended period of time and showing the entrapment efficiency of 64.34%. In formulation M4 the extent of release is upto 12 hours which is well described on the basis of drug and polymer ratio. The ratio of the polymer incorporated is high which leads to the release of the drug due to the rapid distribution of the drug between the polymer strands and diffuses the drug from the oozes of strands when it comes to contact with the dissolution media and showing the entrapment efficiency of almost 65%.

Drug release kinetics

Table 3 Release kinetics of MTZ from fabricated beads

Formulation Code	r^2 Value				n value
	Zero order	First order	Higuchi	Korsmeyer-Peppa's	
M1	0.9954	0.7302	0.9106	0.9227	0.76
M2	0.9891	0.6188	0.9627	0.9269	0.60
M3	0.9791	0.5787	0.9781	0.9777	0.60
M4	0.9957	0.7915	0.9107	0.9897	0.77

Release kinetics was well explained when different values were putted on Ms excel 07 to give the value of r^2, *in vitro* release pattern of various formulations was analyzed by fitting the dissolution data into various kinetic models (Table 3.4). In case of MTZ loaded beads, It was observed the for the formulations M1, M2, M3 and M4, the r^2 values were higher when fitted to zero order kinetics, which describes that the drug release rate from the formulations is independent of the concentration of the drug.

The n values from drug release experiment ranged from 0.60-0.77, indicated anomalous non-Fickian transport, which suggest that mechanism and kinetics of drug release were dependent on the solubility of MTZ in dissolution medium, with MTZ being predominantly released by diffusion and anomalous behaviour resulting from the relaxation of macromolecular polymeric chains in sodium alginate beads.

CONCLUSION

In this study, we have prepared sodium alginate based floating beads formulations and examined their drug encapsulation efficiency and release characteristics by loading water soluble (MTZ). Prepared beads showed high drug encapsulation efficiency; excellent buoyancy and released the model drug MTZ gradually in 0.1 M HCl. These properties are not only applicable to the sustained release of the drugs with absorption window in the upper

GIT but also to the stomach specific drug delivery. We propose that the prepared alginate based beads thought to be able to sustain the release of hydrophilic drug over 12 h, while remaining afloat in gastric fluid.

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