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Original Research Article

Sustained Delivery of Propranolol By Using Multiparticulate Gastroretentive Drug Delivery System

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Abstract

PURPOSE: Gastroretentive systems can significantly prolong the gastric residence time of drugs. If a drug is stable in gastric acid, prolonged gastric retention improves bioavailability. The objective of the present investigation was to develop an extended and controlled release composition and formulation of propranolol using expandable, gelling, swellable hydrocolloid polymer along with mineral oil.
METHODS: A formulation was prepared without using mineral oil by conventional ionotropic gelation method. All other formulations of oil entrapped floating gel beads of propranolol hydrochloride were prepared by using emulsion gelation method in which sodium alginate was used as a gelling agent and mineral oil was used to impart buoyancy to the formulation Spherical gel beads were formed instantaneously. The prepared beads were evaluated for diameter, surface morphology, encapsulation efficiency and drug release.
RESULTS: Low concentration of oil containing formulation exhibited greater release of drug. As the concentration of oil increases, drug release decreases to certain extent**.** Percentage buoyancy of floating propranolol hydrochloride gel beads was found satisfactory. The highest mean diameter was observed in the formulation with 30% of mineral oil. The formulation with 35% of mineral oil had the highest drug loading and scanning electron microscopy revealed that the beads were spherical in shape with rough surfaces.
CONCLUSION: Oil entrapped gel beads can be used as floating drug delivery system for extended drug release for both local and systemic drug delivery.

Keywords: Floating drug delivery system; Emulsion gelation; Sodium alginate; Mineral oil; Propranolol hydrochloride.

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Introduction

Absorption window in the proximal gut can limit the bioavailability of orally administered compounds and can be a major obstacle in the development of controlled release formulations of drugs. Two main approaches are presently being explored: (i) bioadhesive microspheres that have a slow intestinal transit; and (ii) the gastroretentive dosage system, which is based on multiparticulates or large single unit systems. A good understanding of gastrointestinal transit in humans and the effect of factors such as food can be helpful in the design of rational systems that will have clinical benefit[1].

Gastric retentive delivery systems potentially allow increased penetration of the mucus layer and therefore may increase drug concentration at the site of action. These systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention may improve bioavailability and dissolution for drugs that are less soluble in a high pH environment, provided that the drug is stable in gastric environment. This has applications for local drug delivery to the stomach and proximal small intestines. Gastroretention helps to provide better availability of new products with new therapeutic possibilities and substantial benefits for patients.

With the aim of the development of oral-controlled release dosage forms, gastoretention has attracted much attention on the polymers that can control the release of drugs such as polymeric hydrogels, which are being increasingly investigated for controlled release applications because of their good compatibility. In addition, the ability of hydrogels to release an entrapped drug in aqueous medium and to regulate the release of such drug by control of swelling and by cross-linking makes them particularly suitable for controlled release applications. Hydrogels can be applied for the release of both hydrophobic and hydrophilic drugs and charged solutes [2].

Gastroretentive microparticles have been investigated[3] but few studies have demonstrated success in clinical investigations. Pivotal studies in Nottingham University, UK have revealed that oral dosage forms containing finely divided ion-exchange resins can provide prolonged gastric residence and uniform distribution within the stomach[3]. For such an effect, the particles will need to be small from a mechanical consideration and of low density so that they might be able to float[3]. Several approaches like floating multiparticulates system using ion exchange resin loaded with bicarbonate[4], floating beads of riboflavin using sodium alginate solution containing $CaCO_3$ or $NaHCO_3$ as gas generating agents[5], piroxicam in hollow polycarbonate (PC) micro spheres[6], hollow microspheres (microballoons) loaded with either Translit or Ibuprofen in an outer enteric acrylic polymer[7], air compartment multiple-unit system for prolonged gastric residence[8], microspheres by core solubilization technique[9], wax and fat embedded floating micro spheres of ibuprofen[10], floating microspheres by different solvent evaporation technique[11], floating-bioadhesive microspheres containing acetohydroxamic acid by quasi-emulsion solvent diffusion method[12] were developed and studied for there gastroretentive properties.

In the present investigation we developed an extended and controlled release composition and formulation of propranolol hydrochloride using expandable, gelling, swellable hydrocolloid polymer along with the mineral oil. The polymer used was sodium alginate, which is an inexpensive, nontoxic product extracted from kelp. Sodium alginate has been used as thickening and gelling agent. Additionally it also reduces interfacial tension between an oil and water phase and is efficient for preparation of emulsion.

EXPERIMENTAL

Materials

Sodium alginate was purchased from Sigma-Aldrich Chemicals (Mumbai, India). Propranolol hydrochloride was a generous gift sample from Natco Pharmaceuticals Ltd, Hyderabad, India. Light mineral oil was of standard pharmaceutical grade and all other chemicals used were of analytical grade.

Ionotropic gelation method

Propranolol formulation (PF1) was prepared by conventional ionotropic gelation method, which was previously described[13] without using mineral oil. In brief sodium alginate (4% w/w) was dissolved in distilled demineralized water with agitation to produce 100 g of solution. The resultant solution was extruded using 21G needle into 1% calcium chloride (10 ml) containing propranolol hydrochloride (80 mg) and left at room temperature for 2 hr. The resultant hydrogel beads were washed twice with distilled water and kept for drying at room temperature up to 12 hr.

Emulsion gelation method

Seven other different formulations of the propranolol, PF2-PF8, were prepared by emulsion gelation method using sodium alginate (4% w/w) and different concentrations of mineral oil (Merck Ltd, Mumbai). The emulsion (2.5 g) containing oil (0-40 % (w/w)) was prepared prior to adding the propranolol. It was passed through 21G needle into 1% calcium chloride (10 ml) containing propranolol hydrochloride (80 mg) and left at room temperature for 2 hr. Hydrogel beads formed were washed twice with distilled water and kept for drying at room temperature up to 12 hr.

Buoyancy of prepared floating gel beads

Percentage buoyancy of all formulation was calculated by spreading 50 beads over the surface of a USP XXIV dissolution apparatus Type II (Labindia Mumbai, 8 ST). Simulated gastric fluid without enzymes (900 ml) of pH 1.2 was used as medium and was maintained at 37±0.5 ^{o}C for 12 hr. The paddle speed was controlled at 100 rpm. The floating portion of beads and the settled portion of beads were recovered separately. Buoyancy percentage was calculated as the ratio of the number of beads that remained floating and total number of beads taken (50).

Size analysis of floating gel beads

The mean diameter of 10 dried beads was determined by optical microscopy (Metzer, India) fitted with a stage micrometer.

Drug loading and encapsulation efficiency

Accurately weighed quantities of approximately 100 mg beads were dissolved in 25 ml phosphate buffer pH 7.4. The solution was centrifuged at 4000 rpm for 45 min and drug concentration was assayed at 229 nm using a spectrophotometer. The drug concentration in the sample was used to calculate the percentage drug loading by dividing the weight of beads initially dissolved and the encapsulation efficiency was calculated as[14]

$$\frac{\text{\% drug content} \times \text{amount (dried matrices produced)}}{\text{Amount drug added} - \text{amount drug remaining in apparatus}}$$

Scanning electron microscopy (SEM)

Morphological examination of the surface and internal structure of the dried beads was performed by using a scanning electron microscope (SEM). For examination of the internal structure of the beads, they were cut in half with a steel blade.

In vitro release study

In vitro release rate studies were carried out using USP XXIV dissolution apparatus Type II (Labindia, Mumbai 8 ST). Simulated

gastric fluid without enzymes (900 ml) of pH 1.2 maintained at 37±0.5 ^{o}C was used as dissolution medium. Approximately 0.5 g beads were used for each experiment. The paddle speed was controlled at 50 rpm. Aliquots of 5 ml were withdrawn at different time intervals for up to 10 hr. Each time, a 5 ml of fresh medium was added to replace the sample that was withdrawn. Drug content of the beads was determined in triplicates using a UV/Visible spectrophotometer at 229 nm, after suitable dilution of the samples.

Permeability

The amount of drug released at time (M_t) was plotted against square root time and the slope of the resultant plot was used to estimate the diffusion coefficient (D) as permeability parameter. This was considered a useful parameter to study hydrogel drug delivery.

Drug release mechanism and kinetics

In order to establish the mechanism of release of the drug from the gel beads, the experimental data was fitted to different kinetic models including zero order and first order as well as Higuchi and Korsmeyer's models. The release exponent (n) was then calculated.

Statistical method

Analysis of variance (ANOVA) was applied to experimental drug release data to identify the significance of factors that influence drug release. At 95% confidence interval, 2-tailed p values less than 0.05 were considered to be significant.

Results

Eight formulations of propranolol hydrochloride containing different concentrations of oil (0-35% w/w) were successfully prepared by the emulsion gelation method. Spherical gel beads were formed instantaneously, in which intermolecular cross-links were evident between the divalent calcium ions and the negatively charged carboxyl group of alginic acid. The gel beads were easily manufactured without any sophisticated equipment.

The emulsifying property was limited when the oil concentration was increased. As a consequence, oil began to leak from the beads at 35% w/w of oil. The resultant gel beads were spherical, having rough surfaces and brownish color.

As shown in Table I, the formulation without oil (PF1) showed 0% buoyancy but the others (PF2-PF8) had percentage buoyancy between 84.7% and 95.7%. The results of size analysis study revealed that the size distribution of propranolol hydrochloride beads was between 0.52 mm and 1.66 mm. Formulation PF8 (35% oil) showed highest drug loading (9.88% w/w) and PF2 (5% oil) showed lowest drug loading (7.98 w/w). PF3 (10% oil) showed highest encapsulation efficiency (96.1 %) while PF6 (25%) showed lowest encapsulation efficiency (79.7%).

When the experimental data was also fitted to Higuchi and Korsmeyer's models, the 'n' values obtained for gel beads after fitting into Korsmeyer and Peppas equation were approximately 0.5. All the formulations except PF1 and PF2 followed Higuchi's equation proving that the release is by diffusion mechanism. As shown in Table 2, release kinetic equation values of the prepared formulations followed Higuchi type of drug release profile. Formulations PF1 and PF2 were in close approximation with first order release kinetics.

Figure I shows entire (A), surface (B), section (C) and enlarged section (D) of propranolol hydrochloride floating gel bead under the scanning electron microscope.

The effect of concentration of oil on drug release from gel beads is presented Figure 1D. The low concentration of oil containing formulation exhibited greater release of drug.

Table 1: Characterization of prepared calcium alginate gel beads

Formulation	Concen-tration of oil (%)	Diameter (mm)	% drug Loading	Encapsula-tion efficiency	Drug diffusion coefficient – D	Value of n	% Buoyancy (n^{*} = 50)
PF1	0	0.52 ± 0.03	9.02	83.00	3.49	0.2444	0
PF2	5	0.84 ± 0.05	7.98	94.77	3.47	0.2887	90.66
PF3	10	1.01 ± 0.07	8.34	96.14	4.57	0.4189	94.66
PF4	15	1.22 ± 0.09	8.85	94.59	4.22	0.3759	95.33
PF5	20	1.34 ± 0.05	8.97	91.21	4.49	0.4085	91.33
PF6	25	1.54 ± 0.08	9.02	79.74	4.19	0.3625	84.66
PF7	30	1.66 ± 0.08	9.56	87.08	4.60	0.3649	88.00
PF8	35	1.60 ± 0.07	9.88	90.85	3.82	0.3190	85.33

Mean±sd, n^{*} = 10, n = Korsmeyer's release exponent

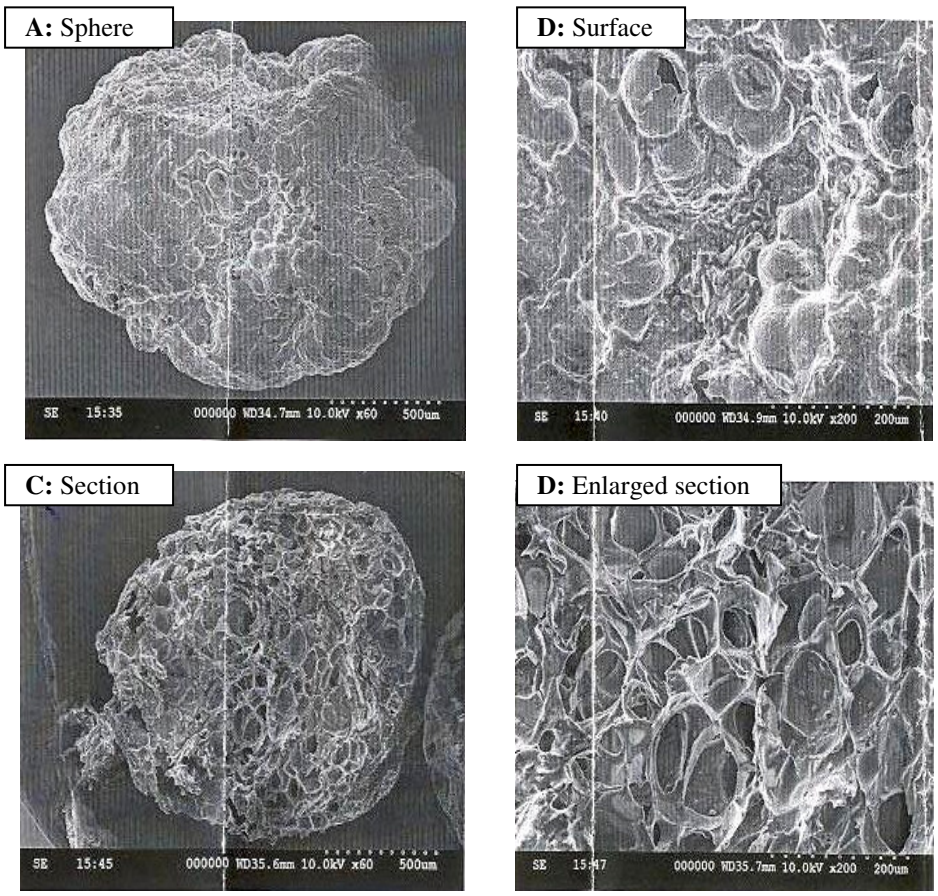

Figure I: Structure of the dried beads under a scanning electron microscope

Table 2: Release kinetic equation values of the prepared formulations

Formulation	Zero – Order R^2 value	First – Order R^2 value	Higuchi R^2 value
PF1	0.7183	0.9619	0.9107
PF2	0.7591	0.9552	0.9335
PF3	0.9210	0.9518	0.9918
PF4	0.9156	0.8414	0.9760
PF5	0.8971	0.8921	0.9932
PF6	0.8894	0.9059	0.9754
PF7	0.8849	0.9622	0.9828
PF8	0.8452	0.9419	0.9680

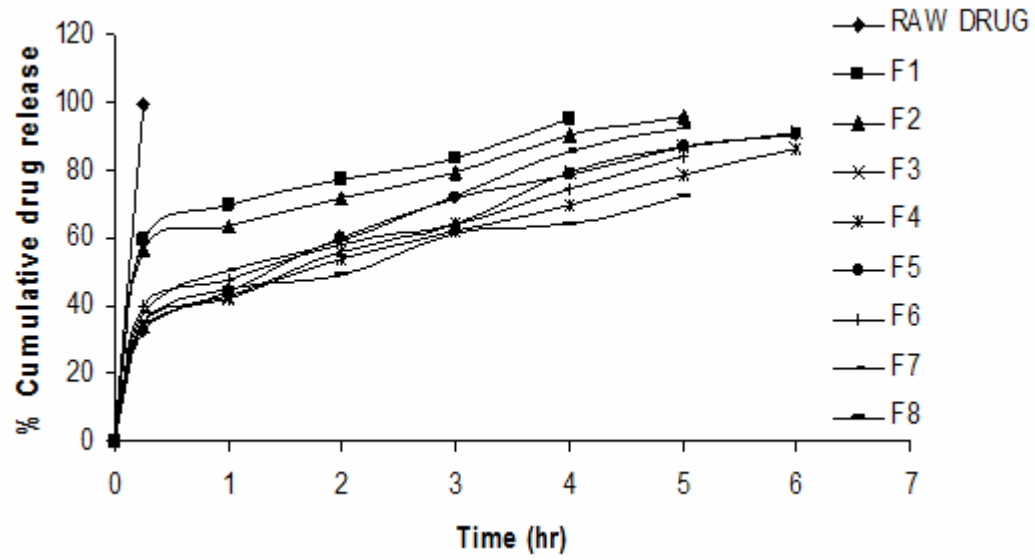

Figure 2: Propranolol release from alginate gel beads

Discussion

Buoyancy is an important characteristic in sustained drug delivery. The absence of buoyancy in the formulation without oil is indicative of the important of oil in buoyancy of proporanolol formulation as it was concentration related. Although the buoyancy increased with increasing concentration of oil, the increase was not sustained beyond 15% w/w as the percentage buoyancy declined at oil concentration above 20%. The increase in buoyancy paralleled simultaneous increase in the sizes of the resultant gel beads.

The dissolution profiles obtained for propranolol hydrochloride floating gel beads (figure 1) made with different concentration of oil, showed that the use of different concentration of oil permit efficient control of the release of the drug. Low concentration of oil containing formulation exhibited greater release of drug. In fact, as concentration of oil increases, drug release decreases to certain extent implying that oil permits efficient control of the release of the drug.

Analysis of dissolution profiles on the basis of Higuchi's model and that of Korsmeyer et al's model suggested that drug release was basically Fickian diffusion controlled (Table I). However, statistical analysis revealed that there was a significant difference between concentration of oil and dissolution rate. The observed between-formulation difference in dissolution rate can be attributed to differences in the concentration of oil since the gel beads were formulated by keeping a uniform ratio of the drug and polymer and only the concentration of oil was changed.

Upon air-drying, the conventional calcium alginate beads (AF1) formulations became small and dense. Morphological examination indicated roughly spherical and brownish oil entrapped alginate gel beads with internal large pores formed due to oil. The sponge-like structure where the oil was entrapped is demonstrated in figure I.

Conclusion

A new gastroretentive multiparticulate floating type drug delivery system of oil entrapped alginate beads was designed and prepared by an emulsion gelation method and it's morphological and release characteristics were studied. The prepared beads were easy to prepare and the mean diameter of beads increased with increase in the amount of the oil phase. The pore size of oil-entrapped beads was affected by concentration of the oil. The beads showed excellent sustaining properties as compared to the conventional beads. Thus, oil entrapment technique novel approach towards the development of multiparticulate system for sustained drug delivery.

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