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Study OF Multiparticulate Floating Drug Delivery System prepared by Emulsion Gelation Technique

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Abstract: Gastroretentive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility for drugs that are less soluble in a high pH environment. The present work describes the formulation and evaluation of gastroretentive system of an antibacterial agent, amoxicillin trihydrate, based on the concept of altered density. Different formulations of oil entrapped floating gel beads were prepared by using sodium alginate as gelling agent. The prepared beads were evaluated for diameter, surface morphology and encapsulation efficiency. Percentage buoyancy of floating amoxicillin trihydrate gel beads was found satisfactory, highest mean diameter was observed in formulation AF9. Formulation AF6 showed highest drug loading and scanning electron microscopy reveled that the beads were spherical in shape with rough surface. These results demonstrate that the oil entrapped gel beads can be used as floating drug delivery system for local as well as systemic drug delivery.

Key-words: Floating drug delivery system; Emulsion gelation; Calcium alginate; Mineral oil;

Inttroduction

Absorption window in the proximal gut can limit the bioavailability of orally administered compounds and can be a major obstacle to the development of controlled release formulations for important 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 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 improves bioavailability, reduces drug waste, and improves solubility for drugs that are less soluble in a high pH environment. It has applications also 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, it 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, 3].

Gastroretentive microparticles have been investigated, 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. 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[4]. Several approaches like floating multiparticulates system using ion exchange resin loaded with bicarbonate[5], floating beads of riboflavin using sodium alginate solution containing $CaCO_3$ or $NaHCO_3$ as gas generating agents[6], piroxicam in hollow

polycarbonate (PC) micro spheres[7], hollow microspheres (microballoons) loaded with Ibuprofen in an outer enteric acrylic polymer[8], air compartment multiple-unit system for prolonged gastric residence[9], microspheres by core solubilization technique[10], wax and fat embedded floating micro spheres of Ibuprofen[11], floating microspheres by different solvent evaporation technique[12], floating-bioadhesive microspheres containing acetohydroxamic acid by quasi-emulsion solvent diffusion method[13], Dry Coated Drug Delivery System With Floating-Pulsatile Release[14] were developed and studied for there gastroretentive properties.

In the present investigation we developed an extended and controlled release composition and formulation of amoxicillin trihydrate 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.

Materials

Sodium alginate was purchased from Sigma-Aldrich Chemicals (India); amoxicillin trihydrate was generous gift sample of Sun Pharmaceuticals, Baroda. Light mineral oil was of standard pharmaceutical grade and all other chemicals used were of analytical grade.

Methods

Preparation of oil-entrapped beads

1. Ionotropic gelation method

Formulation AF1 was prepared without using mineral oil by conventional ionotropic gelation method, which was previously described[14].

2. **Emulsion gelation method**

Formulations AF2-AF9 were prepared by emulsion gelation method. Sodium Alginate (4%) was dissolved in distilled demineralized water with agitation. Amoxicillin Trihydrate and different concentrations of mineral oil were added to the solution. This solution (2.5g) containing Amoxicillin Trihydrate (125 mg) and oil (0-40 % (w/w)) was dropped through 21 G needle in to 1% calcium chloride (10 ml) and left at room temperature for 2 h. The resultant hydrogel beads were washed twice with distilled water and kept for drying at room temperature up to 12 hours.

Percentage buoyancy of prepared floating gel beads

50 beads were spread over the surface of a USP XXIV dissolution apparatus Type II. Simulated gastric fluid without enzymes of pH 1.2 was used as medium (900 ml) and was maintained at $37^{o}C \pm 0.5^{o}$ C for 12 hrs. The paddle speed was controlled at 100 rpm. The floating 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). The optical microscope was fitted with a stage micrometer by which the size of beads could be determined.

Percentage drug loading and encapsulation efficiency

Accurately weighed quantities of approx. 100 mg beads were dissolved in 25 ml phosphate buffer pH 7.4. The solution were centrifuged at 4000 rpm for 45 min and assayed at 228 nm.

A) Percentage Drug Loading:

The drug concentration in the sample was used to calculate the loading by dividing the weight of beads initially dissolved.

B) Encapsulation Efficiency:

The encapsulation efficiency was calculated according to the following relationship.

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

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 of pH 1.2 was used as dissolution medium (900 ml) and was maintained at $37^{o}C \pm 0.5^{o}$ C. 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 up to 10 h and a 5 ml of fresh medium was added to replace the sample that was withdrawn. Drug content of the beads was determined by UV/Visible spectroscopy at 228 nm, after suitable dilution of the samples. Dissolution studies were performed three times and the mean values were taken.

Permeability

It is a useful parameter to study hydrogel drug delivery. Since the drug is dispersed in the hydrogel, the slopes of plot of M_t versus square root time will yield D, the drug diffusion coefficient, where M_t is the amount released at time 't'.

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.

Results

Nine formulations of amoxicillin trihydrate containing different concentration of oil (0%-40%) were prepared by emulsion gelation method. Spherical gel beads were formed instantaneously, in which intermolecular cross-links were formed 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 40 % w/w of oil; the beads were spherical, smooth and yellowish in color. As shown in Table II, percentage buoyancy was found between 84.66% to 95.33%, size distribution was found between 0.56 mm to 1.36 mm, formulation AF6 showed highest drug loading (33.15% w/w) and AF3 showed lowest drug loading (16.39 w/w) while AF7 showed highest encapsulation efficiency (97.42 %) and AF2 showed lowest encapsulation efficiency (83.42 %), the 'n' values obtained for gel beads after fitting into Korsmeyer and Peppas equation are closely approximate with n = 0.5. Morphological examination of the surface and internal structure of the dried beads was performed by using a scanning electron microscope (Fig. I - IV).

Discussion

There was gradual increase in floating percentage as the concentration of oil goes on increasing i.e. from 5%-15% w/w but as the concentration of oil goes above 20 % the percentage buoyancy decreased, the results were reported (Table-II). It suggests that the size of the gel beads increased as the concentration of oil used was increased. As shown in Table- II, optical microscopy reveled that there was gradual increase in bead diameter as concentration of oil increases. Morphological examination of the surface and internal structure of the dried oil entrapped calcium alginate gel beads was performed by using a scanning electron microscope. Upon air-drying, the conventional calcium alginate beads (AF1) formulations became small and dense. The oil-entrapped beads were spherical, the section showed sponge-like structure where the oil was entrapped (Fig. III). The effect of concentration of oil on drug release from gel beads is presented Fig-V, the low concentration of oil containing formulation exhibited greater release of drug. In fact, as concentration of oil increases, drug release decreases to certain extent, it implies that the use of different concentration of oil permit efficient control of the release of the drug. All the formulations followed Higuchi's equation proving that the release is by diffusion mechanism (Table-III). The 'n' values are closely approximate with n = 0.5, indicating Fickian diffusion (Table- II).

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 can become a useful tool for the development of multiparticulate system for gastroretention.

Fig. I: Scanning electron microscope (SEM) photograph of amoxicillin trihydrate floating gel bead (Sphere)

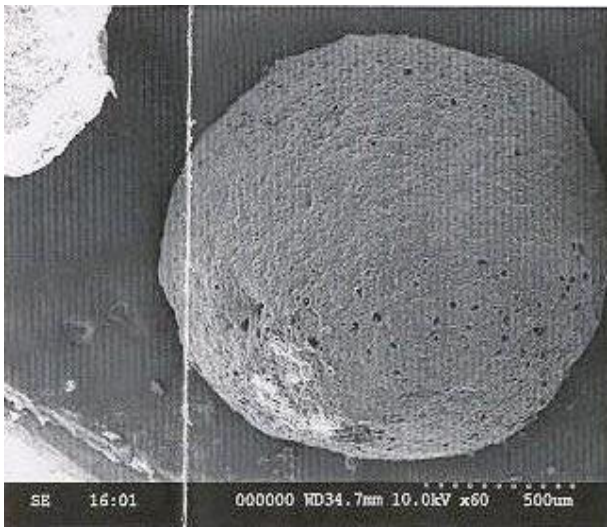

Fig. II: Scanning electron microscope (SEM) photograph of amoxicillin trihydrate floating gel bead (Surface)

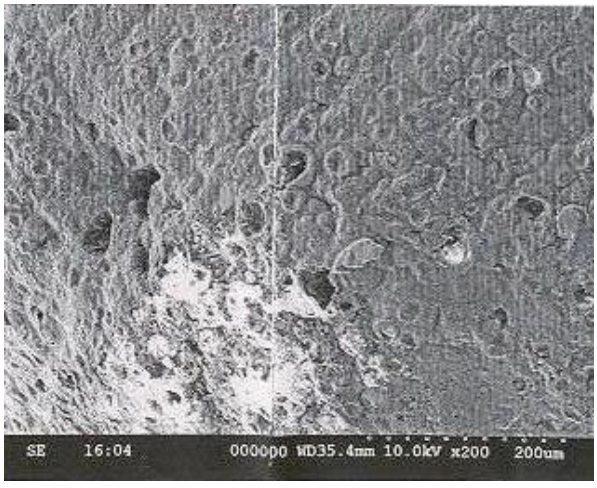

Fig. III: Scanning electron microscope (SEM) photograph of amoxicillin trihydrate floating gel bead (Section)

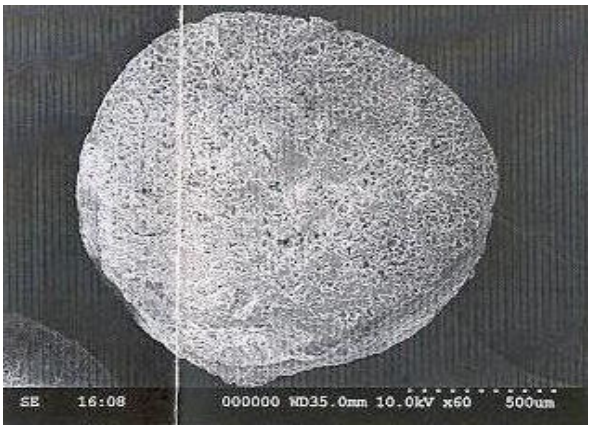

Fig. IV: Scanning electron microscope (SEM) photograph of amoxicillin trihydrate floating gel bead (Section Enlarged)

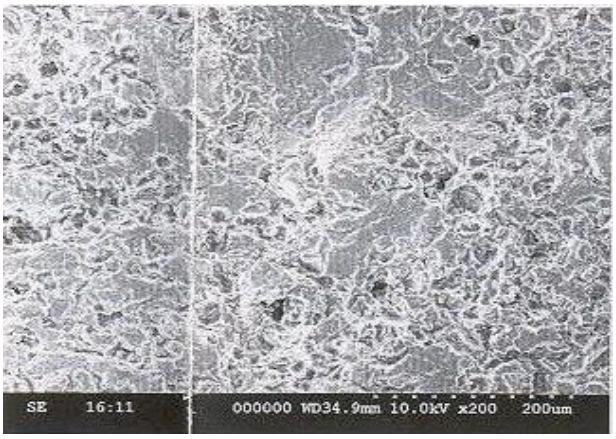

TABLE – I: FORMULATION OF CALCIUM ALGINATE GEL BEADS

Formulation	Amoxicillin Trihydrate (g)	Sodium alginate (g)	Liquid Paraffin (g)	Distille Water (to make)
AF1	2.5	2	0	50 g
AF2	2.5	2	2.5	50 g
AF3	2.5	2	5	50 g
AF4	2.5	2	7.5	50 g
AF5	2.5	2	10	50 g
AF5	2.5	2	12.5	50 g
AF7	2.5	2	15	50 g
AF8	2.5	2	17.5	50 g
AF9	2.5	2	20	50 g

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TABLE – II: CHARACTERIZATION OF PREPARED CALCIUM ALGINATE GEL BEADS

Formulation	Concentration of oil (%)	Diameter * (mm)	%Drug Loading	Encapsulation Efficiency	Drug Diffusion Coefficient – D	Value of n	% Buoyancy ($n^1 = 50$)
AF1	0	0.56 ± 0.02	32.68	95.71	4.49	0.3330	0
AF2	5	0.87 ± 0.09	16.39	83.42	2.53	0.2166	88.66
AF3	10	0.93 ± 0.04	19.21	87.14	2.84	0.3075	93.33
AF4	15	1.08 ± 0.05	20.30	94.00	3.37	0.3936	95.33
AF5	20	1.17 ± 0.06	22.52	90.57	4.15	0.4189	97.33
AF6	25	1.26 ± 0.06	33.15	95.14	2.82	0.2790	94.66
AF7	30	1.31 ± 0.03	31.37	97.42	2.87	0.3524	87.33
AF8	35	1.32 ± 0.04	27.41	93.14	2.97	0.2951	86.66
AF9	40	1.36 ± 0.11	27.80	90.85	1.85	0.2782	84.66

***Values are Mean ± S.D. of ten determinations**
n = Korsmeyer's release exponent
n^1 = Number of beads taken.

TABLE – III: RELEASE KINETIC EQUATION VALUES OF THE PREPARED FORMULATIONS

Formulation	Zero – Order R^2 value	First – Order R^2 value	Higuchi R^2 value
AF1	0.7644	0.8208	0.8277
AF2	0.5694	0.8145	0.7945
AF3	0.8363	0.9314	0.9136
AF4	0.8534	0.9625	0.9646
AF5	0.8511	0.9704	0.9677
AF6	0.7110	0.8589	0.9056
AF7	0.8529	0.9552	0.9771
AF8	0.8127	0.9674	0.9557
AF9	0.7795	0.8722	0.9319

References

1. Stanley S D., Formulation strategies for absorption windows, Drug delivery tech., 2005, 10, 249-257.

1) Kudela V., editor. Encyclopedia of polymer sciences and engineering, New York, John Wiley., 1987.

2) Graham N.B, Mc Neill M.E., Hydrogels for controlled drug delivery, Biomaterials., 1984, 5, 27-36.

3) Burton S., Intragastric distribution of ion-exchange resins: a drug delivery system for the topical treatment of the gastric mucosa, J. Pharm. Pharmacol., 1995, 47, 901–906.

4) Atyabi F, Sharma H.L, Mohammad H.A, Fell J.T., Controlled drug release from coated

5) floating ion exchange resin beads, J. Contr. Rel., 1996, 42, 25-28.

6) Choi B.Y, Park H.J, Hwang S.J, Park J.B., Preparation of alginate beads for floating drug delivery system: effects of C0(2) gas-forming agents, Int. J. Pharm., 2002, 239, 81-91.

7) Joseph N.J, Lakshmi S, Jayakrishnan A., A floating-type oral dosage form for piroxicam based on hollow polycarbonate microspheres: in vitro and in vivo evaluation in rabbits, J. Contr. Rel., 2002, 79, 71-79.

8) Kawashima Y, Niwa T, Takeuchi H, Hino T, Itoh Y., Hollow microspheres for use as a floating controlled drug delivery system in the stomach, J. Pharma. Sci., 1992, 81, 135- 140.

9) Lannuccelli V, Coppi G, Sansone R, Ferolla G., Air compartment multiple unit system for prolonged gastric residence, Part 2 In vivo evaluation, Int. J. Pharm., 1998, 174, 55-62.

10) Murthy S.N., Preparation and evaluation of floating microspheres by core solubilization technique, Indian Drugs., 1997, 34, 674-675.

11) Nath B.S, Reddy C.S., Ibuprofen embedded wax/fat micro spherules for floating drug delivery systems for controlled delivery, Eastern Pharmacist., 1995, 38, 169-172.

12) Soppimath K.S, Kulkarni A.R, Rudzinski W.E, Aminabhavi T.M., Microspheres as floating drug-delivery systems to increase gastric retention of drugs, Drug Metab. Rev., 2001, 33, 149-60.

13) Umamaheswari R.B, Jain S.K, Tripathi P.K, Agrawal G.P, Jain N.K., Floating-bioadhesive microspheres containing acetohydroxamic acid for clearance of Helicobacter pylori, Drug delivery., 2002, 9, 223-31.

14) Sriamornsak P, Nunthanid J., Calcium pectinate gel beads for controlled release drug delivery, I. Preparation and in-vitro release studies, Int. J. Pharm., 1998, 160, 207-212.

15) Hao Z, Xuetao J, Lingshan K, Shen G., Design and Evaluation of a Dry Coated Drug Delivery System With Floating-Pulsatile Release, Journal of pharmaceutical sciences., 2008, 97, 263-273.

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