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Development and *In- Vitro* Evaluation of Gastroretantive Floating Beads of Ofloxacin

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ABSTRACT

The present study deals with the formulation of multiple type floating beads of Ofloxacin to prolong gastric residence time (upto 24 hours) for slow and complete release in stomach and to provide sustained release action. Since, its solubility and absorption is better in the upper part of GI tract, so it was proposed to prepare floating beads of Ofloxacin to localize the drug at its maximum absorption site. Floating beads were prepared by drop wise addition of 3%, 4%, or 5% w/v Sodium Alginate solution containing drug and different gas forming agents or oils, into Calcium chloride solution 1% w/v in glacial acetic acid (10%) using 21 G needle. The solution containing suspended beads were stirred with magnetic stirrer for 10 minutes to improve the mechanical strength of beads and allowed to complete the reaction to produce gas. The fully formed beads were collected, washed with ethanol and distilled water and subsequently dried. Different oils such as Peppermint oil and Light liquid paraffin were used in the ratio of 3:5, 3:10, 3:15, and 3:20 respectively. The beads were evaluated for average diameter of beads, lag time, duration of floating drug entrapment efficiency, percent drug loading, floating time and in-vitro drug release in fasted and fed state. As we increased the concentration of polymer and oils, the diameter of beads increases taking all the parameters such as drug ratio, curing agent, curing time, needle nozzle size, dropping rate and height of needle from calcium chloride solution to be constant. The gastric retention of sodium alginate floating beads was best found to be using 20% light liquid paraffin. Also the lag time at this concentration was found to be zero thus leading to float into stomach for upto 24 hours. The drug release profile was best observed in using 4% of sodium alginate polymer and it was 92.719% in 20 hours.

Keywords-floating beads, ionotropic gelation, beads size, effervescent system, sodium alginate

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INTRODUCTION

Gastro retentive system can remain in the stomach in the gastric region for several hours. Such retention are important for the drugs that are degraded in intestine or for drug like antacids or certain antibiotic, enzymes that should act locally in the stomach. If the drugs are poorly soluble in the intestine due to the alkaline p^H and then it retention in the gastric region may increase the solubility before they are emptied, resulting increase bioavailability, reduce the drug waste. Such systems are more advantageous in improving G.I. absorption of drug with narrow absorption window as well as for controlling release of drugs having the site absorption limitation. Retention of drug delivery system in the stomach prolonged over G.I. transit time, there by resulting in improved bioavailability of some drugs. Gastro retention helps to provide better availability of new product with new therapeutics possibilities and substantial benefits for patients.[1, 2, 3]

Extended release dosage form with prolonged residence time in stomach are highly desirable for drug:

- That drugs which are useful for the localized treatment of gastric acidity and gastrointestinal disorder such as duodenal ulcer, peptic ulcer, and chronic gastritis. e.g. cimetidine, ranitidine , metronidazole , tinidazole, tetracycline etc.
- That have absorption window in stomach or in upper small intestine relative to lower gastrointestinal tract. e. g. acyclovir, captopril etc.
- That are unstable in intestinal or colonic environment
- The drugs which have poor solubility such that an increased retention time in the stomach allows for greater quantity of the drug to be delivered from the dosage form than would otherwise cure.

Following approaches can be utilized for prolonging gastric residence:

Swelling system[4]

There are the dosage forms which after swallowing, swells to an extent that prevent their exit from the pylorus. This system may be named as plug type system.

Bio/mucoadhesive system[5]

That systems are those in which dosage form bind to the gastric epithelial cell surface or mucin and serve as a potential mean of extending the retention time of drug delivery system in the stomach by increasing the duration of contact of drug with biological membrane.

FACTORS AFFECTING GASTRIC RETENTION [6-14]

Gastric residence time of an oral dosage form is affected by several factors. To pass through the pyloric valve into the small intestine the particle size should be in the range of 1 to 2 mm. The pH of the stomach in fasting state is ~1.5 to 2.0 and in fed state is 2.0 to 6.0. A large volume of water administered with an oral dosage form raises the pH of stomach contents to 6.0 to 9.0. Stomach doesn't get time to produce sufficient acid when the liquid empties the stomach; hence generally basic drugs have a better chance of dissolving in fed state than in a fasting state. The rate of gastric emptying depends mainly on viscosity, volume, and caloric content of meals. Nutritive density of meals helps determine gastric emptying time.

TYPES OF GASTRORETENTIVE DOSAGE FORMS

A. Floating drug delivery systems

Floating drug delivery systems (FDDS) have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach. This results in an increased GRT and a better control of the fluctuations in plasma drug concentration.

FDDS can be divided into non-effervescent and gas-generating (effervescent) system:

Non-effervescent systems

This type of system, after swallowing, swells unrestrained via imbibitions of gastric fluid to an extent that it prevents their exit from the stomach.

This system can be further divided into four sub-types:

(i) Colloidal gel barrier system

Sheth and Tossounian first designated this 'hydro dynamically balanced system[15]. Such a system contains drug with gel-forming hydrocolloids meant to remain buoyant on the stomach content.

(ii) Micro porous compartment system

This technology is based on the encapsulation of a drug reservoir inside a micro porous compartment with pores along its top and bottom walls[16].

(iii) Alginate beads

Multi-unit floating dosage forms have been developed from freeze-dried calcium alginate[17]. Spherical beads of approximately 2.5 mm in diameter can be prepared by dropping sodium alginate solution into aqueous solution of calcium chloride, causing the precipitation of calcium alginate. The beads are then separated, snap-frozen in liquid nitrogen, and freeze-dried at -40ºC for 24 hours, leading to the formation of a porous system, which can maintain a floating force for over 12 hours. These floating beads gave a prolonged residence time of more than 5.5 hours.

(iv) Hollow microspheres / Microballons

Hollow microspheres loaded with drug in their outer polymer shelf were prepared by a novel emulsion solvent diffusion method[18].

Floating Tablets

These systems are retained in the stomach and are useful for drugs that are poorly soluble or unstable in intestinal fluids. The underlying principle is very simple. One attempts to make the dosage form less dense than the gastric fluids so that it can float on them. The density of the system can be reduced by incorporating a number of low density fillers into the systems such as hydroxyl cellulose, lactates or microcrystalline cellulose.

Gas-generating (Effervescent) systems

These buoyant systems utilize matrices prepared with swellable polymers such as methocel, polysaccharides (e.g., chitosan), effervescent components (e.g., sodium bicarbonate, citric acid or tartaric acid)[19].

Expandable systems

Expandable gastroretentive dosage forms (GRDFs) have been designed over the past 3 decades. They were originally created for possible veterinary use but later the design was modified for enhanced drug therapy in humans. These GRDFs are easily swallowed and reach a significantly larger size in the stomach due to swelling or unfolding processes that prolong their GRT. After drug release, their dimensions are minimized with subsequent evacuation from the stomach[20].

Bio/Muco-adhesive systems

Bioadhesive drug delivery systems (BDDS) are used as a delivery device within the lumen to enhance drug absorption in a site- specific manner. This approach involves the use of bioadhesive polymers, which can adhere to the epithelial surface in the stomach[21].

High-density systems

Sedimentation has been employed as are tention mechanism for pellets that are small enough to be retained in the rugae or folds of the stomach body near the pyloric region, which is the part of the organ with the lowest position in an upright posture. Dense pellets (approximately $3g/cm^{-3}$) trapped in rugae also tend to withstand the peristaltic movements of the stomach wall. With pellets, the GI transit time can be extended from an average of 5.8–25 hours, depending more on density than on the diameter of the pellets[22]. Commonly used excipients are barium sulphate, zinc oxide, titanium dioxide and iron powder, etc. These materials increase density by up to 1.5–$2.4g/cm^{-3}$.

Approaches to Design Floating Dosage Forms

The following approaches have been used for the design of floating dosage forms of single- and multiple-unit systems.[23]

Single-Unit Dosage Forms

In Low-density approach4 the globular shells apparently having lower density than that of gastric fluid can be used as a carrier for drug for its controlled release. A buoyant dosage form can also be obtained by using a fluid-filled system that floats in the stomach. In coated shells[24] popcorn, pop rice, and polystyrol have been exploited as drug carriers. Sugar polymeric materials such as methacrylic polymer and cellulose acetate phthalate have been used to undercoat these shells. These are further coated with a drug-polymer mixture.

Multiple-Unit Dosage Forms

The purpose of designing multiple-unit dosage form is to develop a reliable formulation that has all the advantages of a single-unit form and also is devoid of any of the above mentioned disadvantages of single-unit formulations. Spherical polymeric microsponges, also referred to as "microballoons," have been prepared. Microspheres have a characteristic internal hollow structure and show an excellent in vitro floatability.[25]

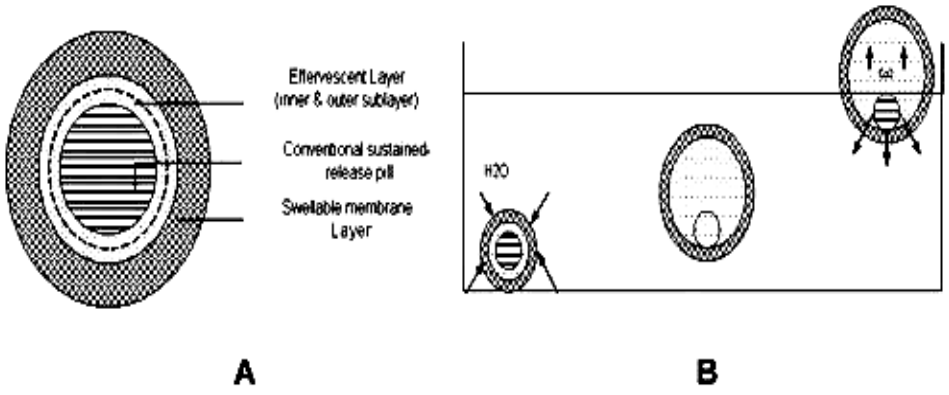

Figure1. (A) Multiple-unit oral floating drug delivery system. (B) Working principle of effervescent floating drug delivery system

Floating drug delivery system [26,-35]

- Effervescent floating dosage form (single & multiple unit system)
- Non effervescent floating dosage form (single & multiple unit system)

1) **Effervescent floating dosage form (single & multiple unit system)**

This buoyant system utilize matrices prepared with swellable polymer such as methocel or polysaccharides,eg., chitosan,alginate,pectin, CMC, and effervescent components, eg., sodium bicarbonate and citric or tartaric acid or matrices containing chamber of liquid that gasify at body temperature. They are formulated in such a way that when in contact with the acidic gastric

contents, CO_2 is libretedand gets entrapped in swellowen hydrocolloiods, which provides buoyancy to the dosage forms. A decrease in specific gravity causes the dosage form to float on the chyme.

It was concluded that calcium carbonate formed smaller but stronger beads than sodium carbonate. Calcium carbonate was shown to be less effective gas forming agent than sodium carbonate but it produced superior floating beads with enhance control of drug release rates.

(2) **Non effervescent FDDS (single &multiple unit system)**

- Colloidal barrier system
- Microporous compartment system
- Alginate beads
- Microballones

Beads are produced by drop wise addition of alginate or pectin in to calcium chloride solution, followed by removal of gel bead and freeze-drying. It also produced by addition of low density oil such as

Mineral oil (relative density =0.84)

Peppermint oil (relative density =0.90)

Olive oil (relative density =0.91)

Rice oil (relative density =0.91)

Sesame oil (relative density =0.91)

Sun flower oil (relative density=0.94)

It provide to the system to low density (<1), by which system float in stomach fluid.

TECHNIQUES USED IN PREPARATION OF FLOATING BEADS

1. Preparation of floating beads using ionotropic gelation technique.
2. Preparation of floating beads using emulsion geletion technique.
3. Preparation of floating beads using gas forming agents.
4. Preparation of floating beads using emulsification extraction method.

Advantages of Gastroretentive Floating Drug Delivery Systems[36, 3, 38]

i. Enhanced bioavailability
ii. Sustained drug delivery/reduced frequency of dosing
iii. Targeted therapy for local ailments in the upper GIT
iv. Reduced fluctuations of drug concentration
v. Reduced counter-activity of the body
vi. Extended time over critical (effective) concentration

vii. Minimized adverse activity at the colon

viii. Site specific drug delivery

MATERIALS AND METHOD

Ofloxacin is a broad spectrum, fluorinated quinolone antibacterial drug, and Ofloxacin is official in BP, USP and IP (2007). Ofloxacin, sodium alginate (Algin) and all other laboratory conditions necessary for the formulation, optimization and evaluation of drug as well as dosage form was provided by Raj Kumar Goel Institute of Technology Ghaziabad (UP).

Alginate (hydrophilic polymer) [39,40,41]

Alginate is a linear, naturally occurring polysaccharide extracted from brown sea algae. It contain D-mannuronic (M) &L-guluronic acid (G) which are arranged in homopolymeric MM or GG blocks separated by blocks with an alternative sequence, MG block. While alginic acid insoluble in water, Alginic acid salts with monovalent cations and magnesium do dissolve in water. In the presence of various divalent (Ca^{2+} but also Ba^{2+} & Zn^{2+}) or trivalent ions (Al^{3+}) an elastic gel is form due to ionic interaction between the ion and carboxyl groups of mainly guluronic blocks.

Others excipient that can be used in formulation of beads

- Calcium chloride ($CaCl_2$)
- Peppermint oil
- Light liquid paraffin

Method

The ionotropic gelation method will be used for preparation of beads.

Ionotropic Gelation Method [42,43,38]

In this methodology prepare polymeric solution , drug is added in polymeric solution , stirrer it on magnetic solution , proper solution or dispersion is formed , then this solution is added in calcium chloride solution drop wise via a needle, spherical beads form upon contact with calcium chloride solution. Dry it in freeze or tray drier.

PREPARATION OF FLOATING ALGINATE BEADS [40,41,42]

Floating beads were prepared by drop wise addition of 3 %, 4%, or 5% w/v Sodium Alginate solution containing drug and different gas forming agents or oils, into Calcium chloride solution 1 % w/v in glacial acetic acid (10 %) using 21 G needle. The solution containing suspended beads are stirred with magnetic stirrer for 10 min to improve the mechanical strength of beads and allowed to complete the reaction to produce gas. The fully formed beads were collected,

washed with ethanol and distilled water and subsequently dried.

Different oils such as:

- Peppermint oil
- Light liquid paraffin

Were used in the ratio of 3:5, 3:10, 3:15 and 3:20 respectively

Table 1: Different batches and batch code

Sl. No.	Drug : polymer (%)	Oils (% v/v) Peppermint oil	Light liquid paraffin	Batch code
1	3 : 3	5		A1
2	3 : 3	10		A2
3	3 : 3	15		A3
4	3 : 3	20		A4
5	3 : 3		5	B1
6	3 : 3		10	B2
7	3 : 3		15	B3
8	3 : 3		20	B4
9	3 : 4		5	C1
10	3 : 4		10	C2
11	3 : 4		15	C3
12	3 : 4		20	C4
13	3 : 5		5	D1
14	3 : 5		10	D2
15	3 : 5		15	D3
16	3 : 5		20	D4

RESULTS AND DISCUSSION

Average Diameter of Beads

As the ratio of sodium alginate and oil increases in each batch, the diameter of floating beads increases taking all the parameters to be constant. From batch A1 to A4, B1 to B4, C1 to C4 and D1 to D4 the diameter increases from 1.23 to 1.50, 1.23 to 1.53, 1.27 to 2.01, 1.30 to 2.09 respectively.

Lag Time

The lag time of beads decreases as the concentration of light liquid paraffin oil increases. In batches A1 to A4 the use of peppermint oil in increasing concentration of 5%,10%,15% and 20% they do not float showing lag time of upto 24 hours. But after using light liquid paraffin in batches B1 to B4, C1 to C4 and D1 to D4, there is decrease in lag time as the concentration of oil increases from 5% to 20% and batches having 20% oil (B4,C4 and D4) do not have lag time. They float just after putting into 0.1 N HCl.

Table 2: Evaluation of different parameters of beads

Sl. No	Batch code	Average Diameter D(mm)±0.03	Lag time (min)	Duration of buoyancy (hours)	Drug content (% w/v)	Swelling study after 20 hours (ratio)
1	A1	1.23	-	Not floating	37.01	-
2	A2	1.35	-	Not floating	36.83	-
3	A3	1.48	-	Not floating	36.58	-
4	A4	1.50	-	Not floating	36.20	-
5	B1	1.23	15	8	50.15	1.548
6	B2	1.46	10	12	50.02	1.550
7	B3	1.49	3	15	49.39	1.552
8	B4	1.53	No	19	49.12	1.555
9	C1	1.27	20	7	39.95	1.559
10	C2	1.35	12	11	39.10	1.561
11	C3	1.65	4	17	38.88	1.564
12	C4	2.01	No	23	38.51	1.568
13	D1	1.30	23	7	37.45	1.569
14	D2	1.43	14	14	37.32	1.571
15	D3	1.89	7	19	36.91	1.573
16	D4	2.09	No	24	36.31	1.574

Table 3: Ratio of beads (drug : polymer) and floating agents

Sl. No.	Drug :polymer (%)	Floating agents(%)		Floating property	Duration of floating (hours)
		Peppermint oil	Light liquid paraffin		
1	3:3	5		-	-
2	3:3	10		+	2
3	3:3	15		+	5
4	3:3	20		++	10
5	3:3		5	+	6
6	3:3		10	++	10
7	3:3		15	++	16
8	3:3		20	++	24
9	3:4		5	+	7
10	3:4		10	++	11
11	3:4		15	++	17
12	3:4		20	++	24
13	3:5		5	++	6
14	3:5		10		10
15	3:5		15	++	17
16	3:5		20	++	24

Duration of Floating

Peppermint oil in the concentration of 5%, 10%, 15% and 20% do not show floating behavior. But light liquid paraffin in the increasing concentration of 5%, 10%, 15% and 20% leads to enhancing the floating behavior of the beads as shown in table-3. Beads (drug : polymer) : 20% light liquid paraffin oil as floating agents is considered as best ratio on the basis of floating

property.

Drug Content

Taking all the parameters constant such as Needle size, height of dropping and dropping rate of emulsion, there is very slight change in the content of drug as we increase the ratio of oil and sodium alginate polymer. The drug content decreases as the ratio of polymer and oil increases taking drug to be constant.

Swelling Study

The beads formed from peppermint oil do not swell but the beads formed from light liquid paraffin show remarkable swelling behavior. Swelling behavior increases as we move from batches B1 to B4, C1 to C4 and D1 to D4.

DRUG RELEASE STUDY

USP method:

The in-vitro release study of the beads was carried out in USP type II apparatus using 900 ml of 0.1 N HCl as the dissolution medium at 50 rpm and 37 ± 1.0 ^{0}C. 5 ml of the samples were withdrawn at every 30 minutes time intervals for up to 8 hours and 5 ml of dissolution medium was replaced after every withdrawal and the last sample was withdrawn after 24 hours. The samples were analyzed spectrophotometrically at maximum wavelength 294 nm. Batch B4 shows fast and highest drug release than batch C4 and D4. The optimum drug release with sustained action was shown by batch C4. .

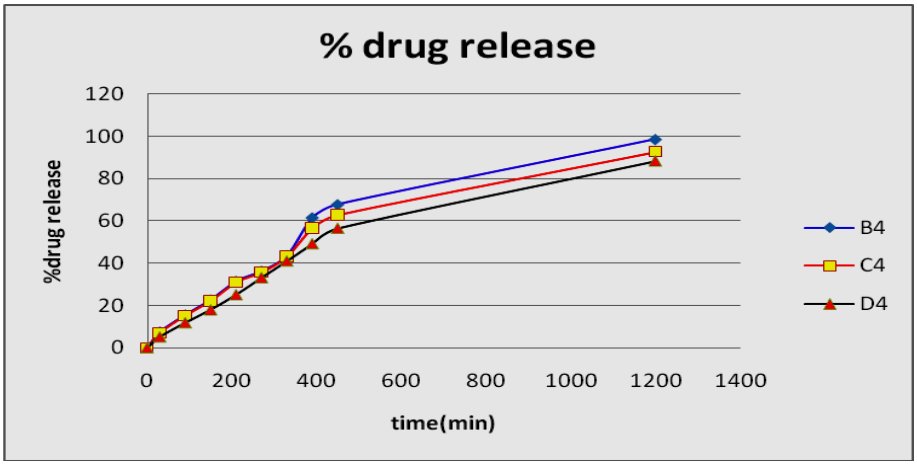

Figure-2 Drug Release profile

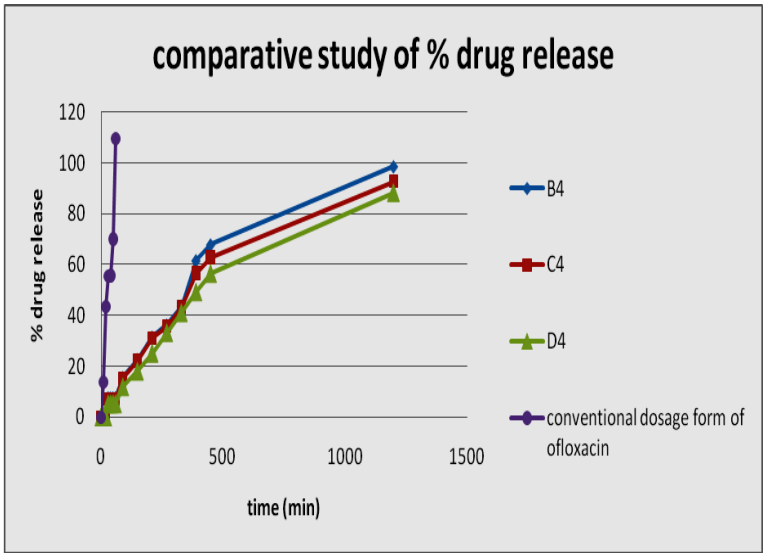

Figure-3 Comparison graph of marketed product and floating beads of Ofloxacin

CONCLUSION:

The gastroretentive floating beads of Ofloxacin formed from taking different ratio of polymer sodium alginate, calcium chloride as curing agent and mineral oil as floating material by ionotropic gellation method. The different mineral oils are used such as peppermint oil and light liquid paraffin but the best floating behavior was obtained in light liquid paraffin. As the ratio of oil increases the floating time increases and the lag time of floating decreases prolonging the gastric retention of Ofloxacin i.e. in acidic pH of stomach As we increase the ratio of sodium alginate polymer the drug content and drug release decreases but prolongs the sustained action of the beads into gastric media. There is no marked change in the swelling index of the beads because sodium alginate does not show much swelling behavior. As we increases the concentration of polymer and oils, the diameter of beads increases taking all the parameters such as drug ratio, curing agent, curing time, needle nozzle size, dropping rate and height of needle from calcium chloride solution to be constant. The gastric retention of sodium alginate floating beads was best found to be using 20% light liquid paraffin also the lag time at this concentration was found to be zero thus leading to float into stomach up to 24 hours. The drug release profile was best observed in using 4% of sodium alginate polymer and it was 92.719% in 20 hours. The drug release of conversional preparation of Ofloxacin was compared with the sustained release gastroretentive floating beads and was found that conventional dosage form releases all the drug within 60 min while beads releases drug for more than 20 hours and thus gives sustained action.

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