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**Original article**

# Preparation and Evaluation of Hollow Calcium Pectinate Beads for Floating-Pulsatile Drug Delivery

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The purpose of this work was to develop hollow calcium pectinate beads for floating-pulsatile release of ofloxacin intended for chronopharmacotherapy. Floating pulsatile concept was applied to increase the gastric residence of the dosage form having lag phase followed by a burst release. A controlled release system designed to increase its residence time in the stomach without contact with the mucosa was achieved through the preparation of floating drug delivery system by rate controlled drug delivery approach. To overcome limitations of various approaches for imparting buoyancy, hollow/porous beads were prepared by simple process of acid-base reaction during ionotropic crosslinking. The floating beads provided expected two-phase release pattern with initial lag time during floating in acidic medium followed by rapid pulse release in phosphate buffer. The floating beads obtained were porous (38% porosity), hollow with bulk density <1 and had $F_{t50\%}$ of 16–22 h. This approach suggested the use of floating pulsatile dosage forms due to their potential as controlled-release drug delivery systems for treatment with chronopharmacotherapy of diseases.

**Key words:** Calcium pectinate beads, Chronotherapy, Buoyancy, Floating-pulsatile drug delivery.

## Yüzen-Pulsatil İlaç Salımı İçin İçi Boş Kalsiyum Pektinat Boncuklarının Hazırlanması ve Değerlendirilmesi

Bu çalışmanın amacı, kronofarmakoterapiye yönelik olarak ofloksasinin yüzen-pulsatil salımı için içi boş kalsiyum pektinat boncuklarını geliştirmekti. Yüzen pulsatil kavramı, ani salımı takiben ilaç şeklinin gastrik kalış süresinin artırılması için kullanıldı. Mukoza ile temas etmeden midede kalış süresini artırmak üzere tasarlanmış kontrollü salım sistemi, hız kontrollü ilaç salımı yaklaşımıyla yüzen ilaç salım sisteminin hazırlanmasıyla elde edildi. Yüzebilmesi için çeşitli yaklaşımların kısıtlamalarının üstesinden gelmek üzere, iyonotropik çapraz bağlama sırasındaki basit asit-baz reaksiyonuyla içi boş/poröz boncuklar hazırlandı. Yüzen boncuklar, beklendiği şekilde asidik ortamdaki şişme sırasında ilk gecikme süresini takiben fosfat tamponda hızlı pulse salım sağladı. Elde edilen yüzen boncuklar, poröz (%38 porozite), <1 dansite ile içi boş ve 16-22 saatlik $F_{t50\%}$ ye sahipti. Bu yaklaşım, hastalıkların kronofarmakoterapiyle tedavisi için yüzen-pulsatil ilaç şekillerinin kullanımını kontrollü salım yapan ilaç salım sistemleri olarak kullanım potansiyellerinden dolayı önerir.

**Anahtar kelimeler:** Kalsiyum pektinat boncuklar, Kronoterapi, Yüzme, Yüzen-pulsatil ilaç salımı

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## INTRODUCTION

Pulsatile drug delivery systems are usually of reservoir type, whereby a drug reservoir is surrounded by a diffusional barrier. This barrier erodes, dissolves or ruptures after a specified lag time, followed by a rapid drug release. Pulsatile drug delivery systems release active ingredient completely and rapidly after a defined lag time (1). Such systems are advantageous for (i) drugs with an extensive first pass metabolism and developed biological tolerance, (ii) the targeting of locally absorbed or acting drugs to a specific site in the intestinal tract (e.g. colon), (iii) the adaptation of the therapy to chronopharmacological needs (1-2) Natural biodegradable polysaccharides like pectin, guar gum, chitosan, carrageenans, sodium alginate and gellan gum have been used in controlled drug delivery (3-7). Multiparticulate systems obtained by ionotropic crosslinking of these polymers have been used to develop floating drug delivery. Various approaches to induce buoyancy in crosslinked beads, some of which include freeze-drying, entrapment of gas or gas forming agents, use of volatile oils or fixed oils, have been used (8-10). These approaches are complicated, as they require specific equipment and handling techniques with limited acceptance. The floating dosage forms containing sodium bicarbonate as buoyancy imparting agent are simple to produce which have been already attempted. Comparatively, oil containing beads have limitations of coalescence of oil droplets yielding beads of wider particle size distribution, volatilization or leaching of oil (11-13). Floating property of dosage forms containing sodium bicarbonate is based on the evolution of carbon dioxide when in contact with acidic environment followed by the ability of polymer gel to entrap it which decreases their density below one. On the other hand, violent gas generation, disintegration of dosage form, burst release, dose dumping and alkaline micro environment (14) are limitations of these dosage forms. Fat manur et al. (15) developed the alginate based mesalazine tablets for intestinal delivery. Sodium alginate is a biocompatible, natural polymer with pH-sensitive gel-forming ability. Srisagul et al. (16) designed multi-layer coated tablets based on gas formation consists of a drug-containing core tablet coated with a protective layer (hydroxypropyl methylcellulose), a gas forming layer (sodium bicarbonate) and a gas-entrapped membrane. Choi et al. (17) have developed porous alginate beads containing riboflavin where the carbon dioxide gas was allowed to generate during crosslinking only, followed by freeze-drying to improve porosity. Talukder and Fassihi (18) developed a floatable multiparticulate system by crosslinking low methoxylated pectin and sodium alginate. The bead so obtained by freeze-drying remained buoyant over 12 h, whereas the air-dried beads remained submerged. The study revealed the presence of air-filled hollow spaces inside the freeze-dried beads, which was responsible for the flotation property of the beads. Sriamornsak et al.(19) developed floating calcium pectinate beads by emulsion-gelation method. Such technique can be considered as alternative to overcome limitations of sodium bicarbonate containing floating drug delivery systems. The drug regime based on circadian rhythm, chronopharmacotherapy, is recently gaining much attention worldwide. Circadian phase dependent patterns have been well documented in conditions such as asthma, arthritis, epilepsy, migraine, allergic rhinitis, cardiovascular disease (myocardial infarction, angina, stroke) and peptic ulcer disease, with particular times where symptoms are more prominent and/or exacerbated (20). These diseases viz. asthma, hypertension, acidity, and arthritis show circadian variation that demands time-scheduled drug release for effective drug action, e.g., inflammations associated with morning body stiffness, asthma, and heart attack in early hours of the day (21). One must have to design the dosage form which follows above principle such that it can be given at the convenient time, e.g., bed time for the above-mentioned diseases with the drug release in the morning. This can be used for drugs which are easily decomposed in the acidic environment of the stomach e.g. peptides, or to protect the stomach from drug

side effects e.g. aspirin. Such systems are also promising for a local therapy in the lower parts of the intestine e.g. colon targeting to treat diseases like ulcerative colitis (22). Pharmacokinetics of some drugs shows circadian variation for anti-inflammatory drugs like ketoprofen, indomethacin, and ofloxacin which have greater absorption in morning as compared to evening (23), and site-specific absorption from small intestine (24-25). To develop dosage form for chronopharmacotherapy it is therefore desired that drug release should be time-specific as well as site-specific (32-44). The drug release from pulsatile release drug delivery systems should exhibit sigmoidal release pattern (A) as shown in Figure 1 rather than B & C which represents delayed release patterns.

The purpose of the present study was to produce hollow/ porous-floating beads of pectin by a process of evolution of carbon dioxide during cross-linking in acidic environment. Ofloxacin, an acid-insoluble antibacterial drug, was used as model drug. The obtained beads were evaluated for drug content, size analysis, porosity, mechanical strength, *in vitro* floating properties and *in vitro* drug release.

## MATERIALS AND METHODS

*Materials*

Low methoxy pectin was purchased from Rajesh Chemicals Mumbai. Ofloxacin was obtained as generous gift from Modern Laboretories, Indore. Other materials used in the study calcium chloride dehydrate (Sisco Research Lab. Pvt. Ltd., Mumbai, India), sodium bicarbonate (LobaChemie, Mumbai, India), acetic acid, glacial (100%) (E Merck, Mumbai, India). All chemical reagents used were of analytical grade.

*Preparation of beads*

Three hundred milligrams of pectin was dissolved in 10 mL of deionized water, 200 mg ofloxacin and various amounts of sodium bicarbonate were uniformly mixed, as shown in Table 1. The dispersion was sonicated for 30 min to remove entrapped air bubbles, if any. The resultant dispersion was dropped via a 23-gauge syringe needle (0.65 mm internal diameter) into 80 mL of 2% w/v calcium chloride ($CaCl_2$) solution containing 10% acetic acid. The content was agitated at 100 rpm using magnetic stirrer for 30 min. The beads were then strained, washed three times with distilled water and followed by oven-dried at 50°C for 6 h.

*Drug content*

20 mg beads of each batch were placed in 100 mL phosphate buffer having pH 7.4, and mechanically stirred on shaker at 200 rpm for 24 h. The resultant dispersions were filtered and analyzed at 277 nm using UV spectrophotometer (JASCO-V500, Kyoto, Japan). The encapsulation efficiency was determined by the following formula:

Encapsulation efficiency (%) = AQ/TQ x100

where AQ = actual drug content of beads and TQ = theoretical quantity of drug present in beads.

*Bead Characterization*

*Infrared spectroscopy*

The infrared spectra of ofloxacin, calcium pectinate beads (without drug, sodium bicarbonate and acetic acid) and drug-loaded porous calcium pectinate beads were recorded on FTIR (JASCO-FTIR 5300). The samples were prepared on KBr press and spectra obtained were used for preformulation studies (Figure 2).

*Size analysis*

Randomly selected 10 beads were observed under a stereomicroscope (Motic) attached with a digital camera (Watec, WAT-202, Japan). Biovis image plus software (Expert Tech Vision, India) was used to analyze the images of beads and were then expressed in terms of different parameters such as diameter, roundness and circulatory factor.

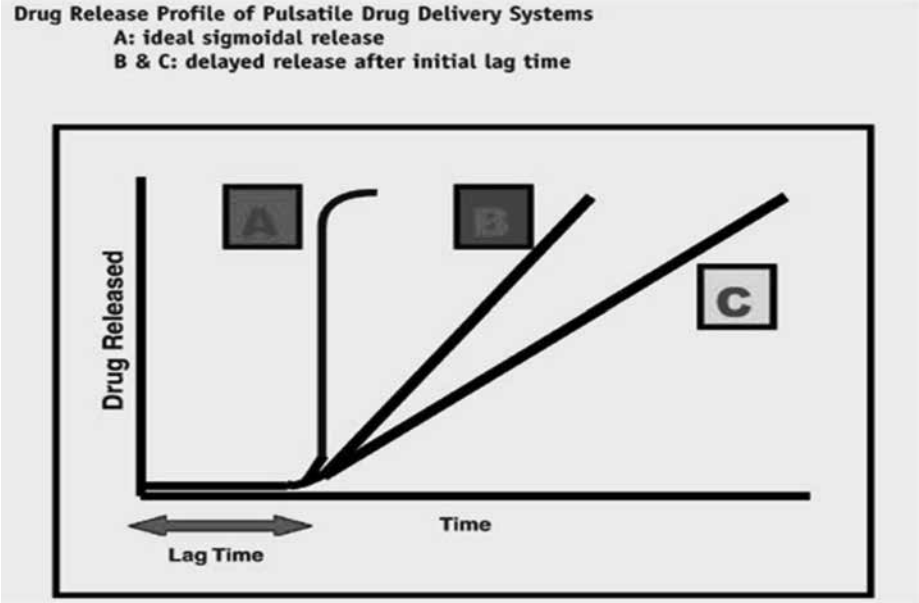



**Figure 1.** Drug release profile of pulsatile drug delivery systems (31).

*Bead porosity and bulk density*

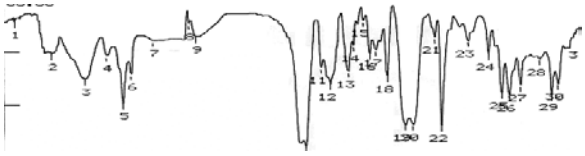
Mercury porosimetry (Autoscan 60 Porosimeter, Quantachrome software, USA) (13) was used to assess bead porosity. The mercury intrusion data were recorded and plotted against pressure. The pressure was applied from 0 to 6000 psi. Standard values for the contact angle and surface tension of mercury were used for calculations. The bulk densities of the beads were also measured using same mercury porosimeter.

**Table 1.** Composition, percent yield and encapsulation efficiency profiles of calcium pectinate beads

| **Batch No.** | **A1** | **A2** | **A3** | **A4** | **A5** |
|---|---|---|---|---|---|
| Amount of pectin (mg) | 300 | 300 | 300 | 300 | 300 |
| Amount of drug (mg) | 200 | 200 | 200 | 200 | 200 |
| SBC (mg)* | ----- | ----- | 0.075 | 0.1500 | 0.225 |
| Amount of $CaCl_2$ (g) | 1.6 | 1.6 | 1.6 | 1.6 | 1.6 |
| Acetic acid 10% (v/v) (mL) | -- | 8 | 8 | 8 | 8 |
| % Encapsulation efficiency | 63.78 ± 1.92 | 77.86 ± 2.29 | 71.48 ± 1.10 | 76.66 ± 2.66 | 80.53 ± 1.81 |
| % Yield | 92.86 ± 1.07 | 93.55 ± 1.05 | 90.03 ± 1.03 | 92.83 ± 1.40 | 88.55 ± 1.23 |

* SBC: Sodium bicarbonate

(A) Plane calcium pectinate bead



(B) Ofloxacin

(C) Batch A5

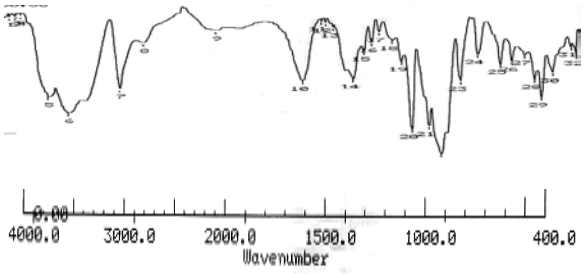



**Figure 2.** The FTIR spectra. (A) Plane calcium pectinate bead. (B) Ofloxacin. (C) Batch A5.

*Moisture content*

The total moisture content was measured using about 50 mg of beads from all the batches by Karl Fisher titration (Veegomatic-D, Mumbai, India).

*Buoyancy test*

The beads so obtained were studied for buoyancy (26) and buoyancy time using USP XXIII type 2 dissolution test apparatus (Electrolab TDT-06P, Mumbai, India). One hundred beads of each batch were placed in 900 ml of 0.1 N HCl (pH 1.2) containing 0.02% w/v Tween 80 and stirred at 100 rpm, temperature was maintained at $37^0C \pm 2$. Number of sinking beads was monitored visually. Typical profile of drug release profile of pulsatile drug delivery systems is shown in (Figure 3).

*Molar absorption coefficient and correlation coefficient (r)*

Stock solutions (1000 µg/mL) of ofloxacin was prepared by dissolving separately 100 mg of drug in minimum quantity of glacial acetic acid and finally diluted with PBS (pH 7.4) to make up the volume up to 100 mL. The maximum absorbance (λmax) of ofloxacin was obtained at 277nm. A series of standard drug solutions in concentration range of 5-30 µg/mL were prepared by diluting appropriate volumes of the standard stock solutions. The scanning for solution of ofloxacin was carried out in the range of 200-400 nm against PBS (pH 7.4) solution

as blank for obtaining spektra that was absorbance and absorptivity of series of standar d solutions were recorded at selected wavelength. The correlation coefficient (r) was found to be 0.9969.

The molar absorption coefficient equation was determined for the ofloxacin using calibration curve equations as shown below in Table 2. Further, the molar absorption coefficient was determined by using the Equation 1:

$$(\varepsilon) = E_{1cm}^{1\%} \text{ Molecular weight}/10$$

Sandell's Sensitivity = Molar Absorptivity / Molecular weight

*Dissolution studies*

The dissolution studies of the prepared beads equivalent to 50 mg of ofloxacin were performed using USP XXIII type 1 dissolution test apparatus (Electrolab TDT-06P, Mumbai, India). The drug release study was carried out in 0.1 N HCl for initial 2 or 6 h depending upon floating characteristics of beads, followed by dissolution in phosphate buffer, pH 7.4, each 900 ml, maintained at $37^0$C ± 2 and agitated at 100 rpm (n = 3). Samples were withdrawn periodically and filtered and concentration of ofloxacin was measured spectrophotometrically (UV spectrophotometer, JASCO-V500, Kyoto, Japan) at 273 and 277 nm for acidic and basic media, respectively. Analysis of data was done using 'PCP Disso v2.08' software.

## RESULTS AND DISCUSSION

Polysaccharides have been widely exploited for their use as pharmaceutical excipient owing to biocompatible, biodegradable, inexpensive and non-toxic nature. With the event of ionotropic gelation they form multi particulate system by simple ionotropic gelation, which can be formulated to provide various desired drug release profiles. Pectin, heterogeneous anionic polysaccharides with an ability to produce water-insoluble complexes with drug, has been used in oral novel drug delivery systems. In stomach pectinis not digested by gastric enzymes and has minimum swelling but undergoes rapid gel relaxation/swelling in alkaline environment (27-30).

*Preparation of beads*

In our preliminary study, 0.75:1 w/w ratio of sodium bicarbonate and sodium alginate yielded mechanically weak and irregular hollow beads. Compared to calcium alginate beads the calcium pectinate beads of same concentration showed greater mechanical strength, therefore pectin was selected to obtain hollow floating beads. The hollow/porous beads were produced during ionotropic gelling assisted by *in situ* reaction between sodium bicarbonate in wet pectin beads with acidified calcium chloride crosslinking solution. To observe the effect of acid and alkali component Batch A1 and Batch A2 were prepared as shown in Table 1. Batches A3–A6 were, respectively, prepared using increased sodium bicarbonate level to pectin in ratio of

**Table 2**. Absorbance and molar absorption coefficient of ofloxacin

| No | Concentration (µL) | Absorbance | $E^{1\%}$1cm |
|---|---|---|---|
| 1. | 5 | 0.188 | 361.80 |
| 2. | 10 | 0.235 | 336.00 |
| 3. | 15 | 0.328 | 366.00 |
| 4. | 20 | 0.475 | 308.45 |
| 5. | 25 | 0.540 | 326.70 |
| 6. | 30 | 0.622 | 360.00 |

0.25:1, 0.5:1 0.75:1 and 1:1. Batch A6 produced beads of poor mechanical strength with no spherical shape, due to the excessive liberation of gas, which made pectin matrix too weak to sustain the shape after drying.

*Drug content*

Batch A1, prepared in plain crosslinking solution, showed lowest drug encapsulation than other batches; it may be due to decreased drug solubility in acidic crosslinking solution (Table 1). Batch A2 showed high encapsulation than A3 due to the absence of sodium bicarbonate. In Batches A3–A5, encapsulation efficiency increased with the increase in amount of sodium bicarbonate (Table 1). Effect of sodium bicarbonate can be attributed to the formation of alkaline microenvironment inside the bead enhancing drug solubility combined with the effervescent action-giving rise to modifications of bead matrix in situ. In Batch A3, the less amount of sodium bicarbonate acted individually causing scattered micro channels leading to drug loss. This effect can be supported by the fact that the bulk density of this batch is more than 1 (Table 3). For batches A4 and A5 collective action exerted by the increased amount of sodium bicarbonate leads to the formation of prominent hollow structures due to entrapment of generated gas. This entrapment leads to the coalescence of gas bubbles, which pushed the internal matrix towards periphery forming thick boundaries minimizing drug leaching.

*Bead Characterization*

*Infrared spectroscopy*

The IR spectra of calcium pectinate beads showed the characteristic band C=O vibration of COOH group at 1740 $cm^{-1}$ and strong absorption band at 1617 $cm^{-1}$ belonging to the asymmetric stretching of vibration of COO. The IR spectra of ofloxacin showed the strong peak at 1600 $cm^{-1}$ in carbonyl frequency region, peak for -NH stretching of aromatic ring at 1450 $cm^{-1}$ and bending at 690 $cm^{-1}$ for meta-di-substituted chlorine on benzene. The IR spectra of drug-loaded calcium pectinate beads of Batch A5 showed all the above-mentioned peaks of calcium pectinate beads and the ofloxacin**.**

*Size analysis*

The drug-loaded calcium pectinate beads without sodium bicarbonate were comparatively spherical than other batches (Table 3). The presence of sodium bicarbonate amounts (at constant pectin concentration) might be responsible for softening of pectin beads subsequently deformed by the force of agitation. The particle size increases with the increased proportion of sodium bicarbonate in the polymer matrix. This can be attributed to the presence of entrapped gas bubbles. The increase in porosity was also observed in similar order too (Table 3).

**Table 3.** Micromeritic properties of calcium pectinate beads

| Batch No. | Diameter (mean) (mm) | Roundness | Bulk density ($g/cm^3$) | Porosity (%) |
|---|---|---|---|---|
| **A1** | 1.43 ± 0.05 | 0.77 ± 0.06 | 1.23 ± 0.01 | -- |
| **A2** | 1.47 ± 0.06 | 0.71 ± 0.08 | 1.85 ± 0.11 | -- |
| **A3** | 1.66 ± 0.06 | 0.67 ± 0.08 | 1.28 ± 0.19 | 20.41 |
| **A4** | 1.82 ± 0.09 | 0.75 ± 0.06 | 0.89 ± 0.13 | 25.61 |
| **A5** | 1.97 ± 0.10 | 0.75 ± 0.08 | 0.85 ± 0.07 | 35.70 |

*Bead porosity and bulk density*

The bulk density of hollow beads (Batches A4 and A5) was less as compared with the beads without sodium bicarbonate (Batch A2). The decrease in bulk density was observed with increase in size and porosity (Table 3).

*Buoyancy test and dissolution studies*

Floating properties of beads were studied by determining buoyancy and time required for sinking all the beads under study. The surfactant was used in medium to simulate surface tension of human gastric juice (35–50 $mN/m^2$) (21). Beads of Batches A1 and A2 were completely non-floating and sunk immediately, where as majority of beads of Batch A3 were non-floating. Batches A4 and A5 produced floating beads without buoyancy lag time (Figure 3) and remained floating for 7 and 12 h, respectively.

hollow/porous beads may be attributed to the low bulk density and the porosity of the beads; implying that the beads will have the propensity to exhibit an excellent buoyancy effect *in vivo*. The in-vitro cumulative drug release profile of Batch A5 was studied by using dissolution apparatus as shown in (Figure 4). It can be interpreted from the dissolution studied that the A5 beads gave a discrete lag of around 4 h, after that mass started to diffuse to some extent in gastric content up to the end of 5 h, until the end of study. Hence A5 beads were found to be our best formulation due to their drug release data and other results obtained throughout the study. The beads of Batch A3 were not studied for dissolution rate. The non-floating beads were assumed to remain in stomach for 2 h whereas on the basis of dissolution data floating beads were considered to be gastroretentive for 6 h,

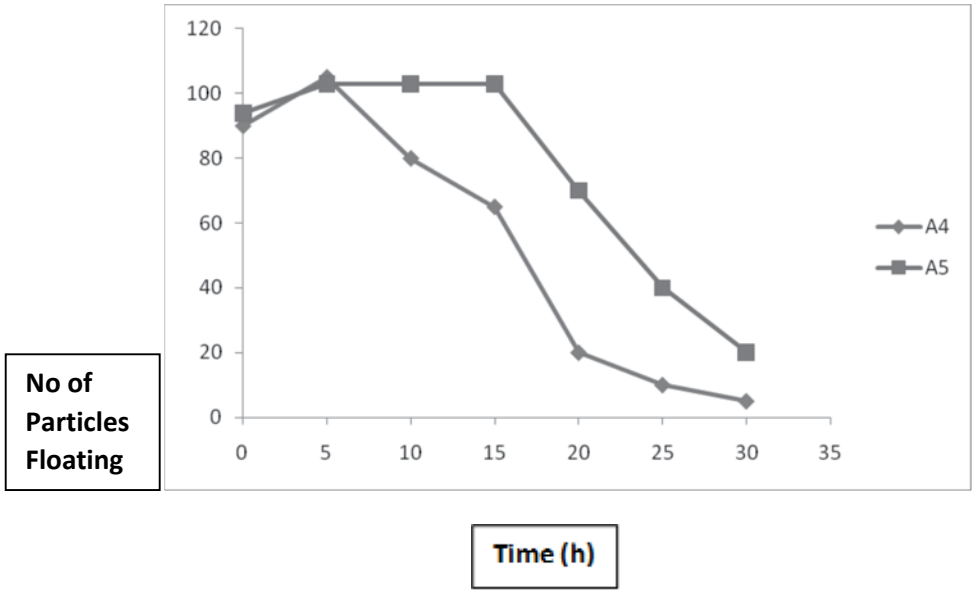



**Figure 3.** Floating profile for ofloxacin loaded calcium pectinate beads.

Ft50, the time required to sink 50% of beads assuming linear approach of sinking, was presumed to be 14 and 24 h, respectively, for Batches A4 and A5. The floating properties of

making basis for *in vitro* dissolution time in acidic medium. All the beads released 3–4% of the drug in acidic medium irrespective of time.

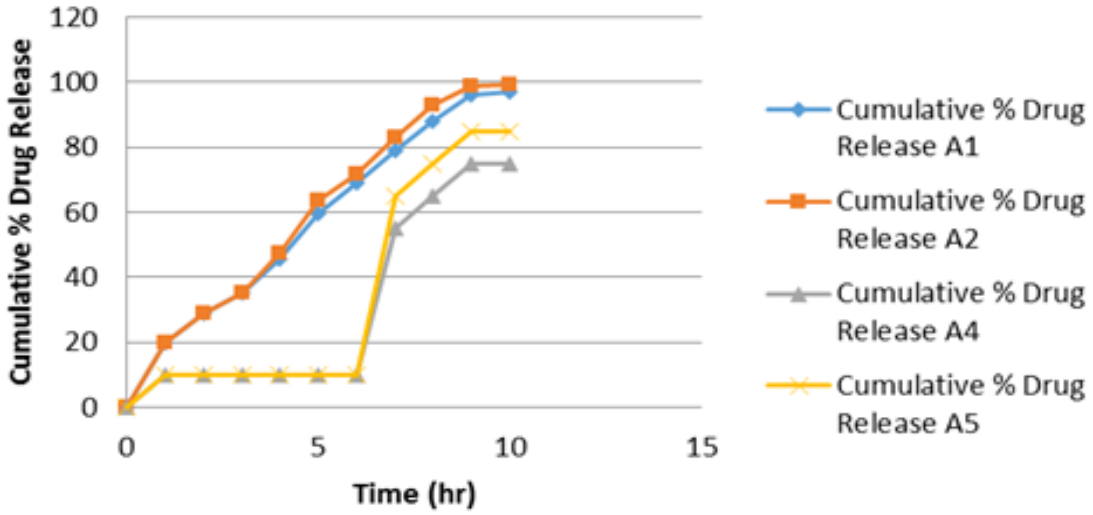



**Figure 4.** Cumulative percent drug release profile

## CONCLUSION

Novel hollow calcium pectinate beads containing ofloxacin were prepared by simple technique with *in situ* action of buoyancy imparting agents during formation. Overall, the buoyant beads provided a lag phase while showing gastro retention followed by a pulsatile drug release that would be beneficial for chronotherapy of rheumatoid arthritis and osteoarthritis. This work can be extended for time-scheduled drug release of drugs having low solubility, poor absorption or degradation in lower gastrointestinal tract.

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