

Research Journal of Pharmaceutical, Biological and Chemical Sciences

Effect of Various CO₂ Gas-Forming Agents on Floating Pulsatile Calcium Pectinate Beads.

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ABSTRACT

Pulsatile drug delivery systems (PDDS) are gaining importance nowadays that delivers the drug at specific time as per the pathophysiological need of the disease resulting in improved patient therapeutic efficacy and compliance. In this PDDS, floating pulsatile concept is specifically applied to increase the gastric resistance of the dosage form having lag phase in stomach followed by a burst release in the distal small intestine which minimize the inter and intra-subject variability due to difference in gastric emptying rates with predictable gastro intestinal transit time and maximum drug absorption at maximum absorption site and ensure greater product safety. Various approaches to bring this floating pulsatile concept, some of which includes various buoyancy imparting agents of gas forming agents, oils and freeze drying, have been used. These floating pulsatile beads were formulated by using different gas forming agents as sodium bi carbonate, sodium carbonate, potassium bi carbonate, potassium carbonate and calcium carbonate with acetic acid by acid base reaction during ionotropic cross-linking. The formulated beads were evaluated for its bulk density, porosity, particle size and shape with buoyancy test. The results of these studies indicate that sodium bi carbonate is superior to others in the gas forming agent with polymer ratio of 0.5: 1.0 in calcium pectinate beads preparation.

Keywords: Floating pulsatile Drug Delivery, pectinate beads.

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INTRODUCTION

Floating pulsatile concept was applied to increase the gastric residence of the dosage form having lag phase followed by a burst release, which shows a two phase release pattern with initial lag phase during floating in an acidic medium of stomach followed by rapid pulse release in basic medium of intestine [1]. This system is superior to the traditional drug delivery of getting a simple chemical absorbed predictably from the gut or from the site of injection and also suitable for drugs which follow chronopharmacokinetic phenomena. Nowadays, chronopharmaceutical drug delivery system (ChDDS) has emerged, treat certain diseases which require different amounts of drug at predictably different times within the circadian cycle which will maximize desired and minimize undesired drug effects. This new ChDDS is the best choice in the management of Rheumatoid Arthritis which needs to take medicine at bed time to design a release only in the early hours of morning symptoms such as stiffness and pain due to the inhibition of inflammatory cytokines [2-7].

Over the last three decades, various approaches have been pursued to induce the buoyancy of cross-linked beads by use of volatile oils, freeze drying and entrapment of gas or gas forming agents. In this, beads formed by incorporating gas forming agents are simple to produce, which have been reported. Sodium bi carbonate has frequently been employed as gas forming agent in FPDDS. But by the review, there is no more research to check the effects of various CO₂ gas forming agents on floating pulsatile drug delivery system [8-14]. During the formation of floating pulsatile beads by using this gas forming agents, carbonate salts are reacted with acetic acid to produce carbon di oxide. The evolving gas permeates through the pectinate leaving gas bubbles or pores. The Low methoxy pectin, with the degree of esterification less than 50% can form rigid gels by the action of calcium ions or multivalent cations, which crosslink the galacturonic acid chain of pectin to yield hydrogels that are stable at low pH [15].

The aim of the present study is to produce floating pulsatile calcium pectinate beads of indomethacin by a process of acid base reaction during ionotropic cross-linking with the various CO₂ gas forming agents such as sodium bi carbonate, sodium carbonate, potassium carbonate, potassium bi carbonate and calcium carbonate to check the effects of these agents on floating nature of the beads, density, porosity, particle size and shape. Indomethacin was chosen as a model drug because of its chronopharmacokinetic nature which made greater absorption in morning as compared to evening. Also indomethacin is acidic drug that diffuse rapidly across the epithelium and are therefore quickly and completely absorbed from small intestine after oral administration [16].

MATERIALS AND METHODS

Materials

Indomethacin was purchased from Yarrow Chemicals, Mumbai and Low methoxy pectin (LMP) was obtained as gift sample from Krishna Pectins Pvt. Ltd, Jalgoan. The other materials and solvents used in the present investigation were AR/LR grade.

Experimental Methods

Formulation of floating pulsatile calcium pectinate beads

The floating pulsatile beads of indomethacin were prepared using ionotropic gelation technique, by dissolving the specified amount of 500 mg LMP and specified amount of 100mg indomethacin in 10 ml of deionised water and specified amount of various gas forming agents(0.5: 1 ratio of gas forming agent to polymer) uniformly mixed. The dispersion was sonicated for 30 min to remove any air bubbles. The resultant dispersion was dropped via a 23-gauge syringe needle (0.65 mm internal diameter) into 100 ml of 2% w/v calcium chloride solution containing 10% acetic acid. The content was stirred at 100 rpm using a magnetic stirrer for 15 min. The beads were filtered and washed three times with distilled water and subsequently oven dried at 50°C for 4 h. The prepared beads were collected and weighed. As the same method dummy beads without gas forming agents were prepared and stored [12].

Characterization of prepared beads

The bulk density and tapped density were determined with the help of a measuring cylinder by using the following formulas.

$$\text{Bulk density} = \text{Weight of beads taken} / \text{Bulk volume}$$
$$\text{Tapped density} = \text{Weight of beads taken} / \text{Tapped volume}$$

Size analysis

The particle size of prepared beads was measured with an optical microscope fitted with a calibrated eyepiece. The mean of 100 beads was noted as particle size.

Scanning Electron Microscopy

Morphological analysis or surface topography of beads was carried out using Scanning Electron Microscope (Field Instruments, Japan). Beads and their cross sections were coated with a thin gold palladium layer by a sputter-coater unit operated at an acceleration voltage of 10 kV

In-vitro Floating Time of the Beads

The time required for beads to raise to surface of dissolution medium and duration of time the beads constantly float on dissolution medium were noted. The test was performed by using a USP XXIII type II dissolution test apparatus. One hundred beads of each batch were placed in 900 ml 0.1 N hydrochloric acid (pH 1.2) containing 0.02% w/v tween 80. The media was maintained at 37°C ± 0.5 and stirred at 100 rpm. At hourly intervals, stirring was stopped for 2 minutes and the number of settled beads was counted visually [13].

RESULTS AND DISCUSSION

The Effect of CO_2 gas-forming agents on formulation of beads

The floating pulsatile beads of indomethacin were prepared using ionotropic gelation technique. This process was achieved by cross linking of indomethacin-low methoxy pectin dispersion with calcium ions to induce the spontaneous formation of calcium pectinate containing indomethacin beads. As comparing all NaHCO_3 containing formulation (0.5: 1 gas forming agent to polymer) produce sufficient viscous solution which can pass through the syringe easily and form good beads than KHCO_3 and K_2CO_3 . While comparing KHCO_3 and K_2CO_3 , K_2CO_3 produce more viscous, but it was pass through syringe form beads. While comparing remaining carbonates, Na_2CO_3 produced more viscous forming liquid and CaCO_3 also not possible to syringe because of insolubility of CaCO_3 in water. So trail formulations were formed to produce beads with reduced viscosity, but formed irregular beads (Fig 2: d, e).

The Effect of CO_2 gas-forming agents on density

The bulk densities of all porous beads were less than one (Table 1). This may be due to insitu action of carbonates in acidic cross-linking solution led to liberation of CO_2 as gas bubbles and this was entrapped by thick boundaries of polymer resulted inside hollow floating beads. This may attributed to decrease in bulk density and made the beads to float on stomach pH. As comparing all, NaHCO_3 containing beads had very low bulk density, which results excellent floating nature and more effective gas forming agents than remaining.

Table 1: Density and Particle Size Of Prepared Beads

| Formulation code | Density (gm/ml) | | Particle Size in mm |
|---|-----------------|--------------|---------------------|
| | Bulk | Tapped | |
| F ₁ (NaHCO_3) | 0.657 ± 0.12 | 0.721 ± 0.05 | 0.772 ± 0.02 |
| F ₂ (KHCO_3) | 0.775 ± 0.09 | 0.890 ± 0.08 | 0.757 ± 0.05 |
| F ₃ (K_2CO_3) | 0.790 ± 0.14 | 0.996 ± 0.09 | 0.692 ± 0.07 |
| F ₄ (Na_2CO_3) | - | - | - |
| F ₅ (CaCO_3) | - | - | - |

The Effects on particle size of beads

The particle size of beads were analyzed by optical microscopy and reported in Table 1. The mean particle size of the beads formulated by NaHCO_3 is high as comparing remaining, it may be due to the reason of entrapped more amount of gas inside the beads leads to larger particle size.

The effects on shape, surface and cross-sectional morphology

The shape, surface and cross-sectional morphology of floating pulsatile beads were analyzed by digital camera and SEM and which was compared with the gas-forming agent free dummy beads (Fig.1-a) has not shown internal air space but with the gas forming agent dummy beads has a centrally air entrapped structure which was closely noted in the ordinary digital camera photo (Fig 1-b) and also digital camera photos of all formulation

shown in fig 2. The SEM photographs (Fig 3.a-c) indicate that NaHCO_3 entrapped beads were good in spherical shape and more size than others. The cross-sectional morphology of gas entrapped beads was also examined with photomicroscope (Fig. 3-d), which results low bulk density and made it to float.

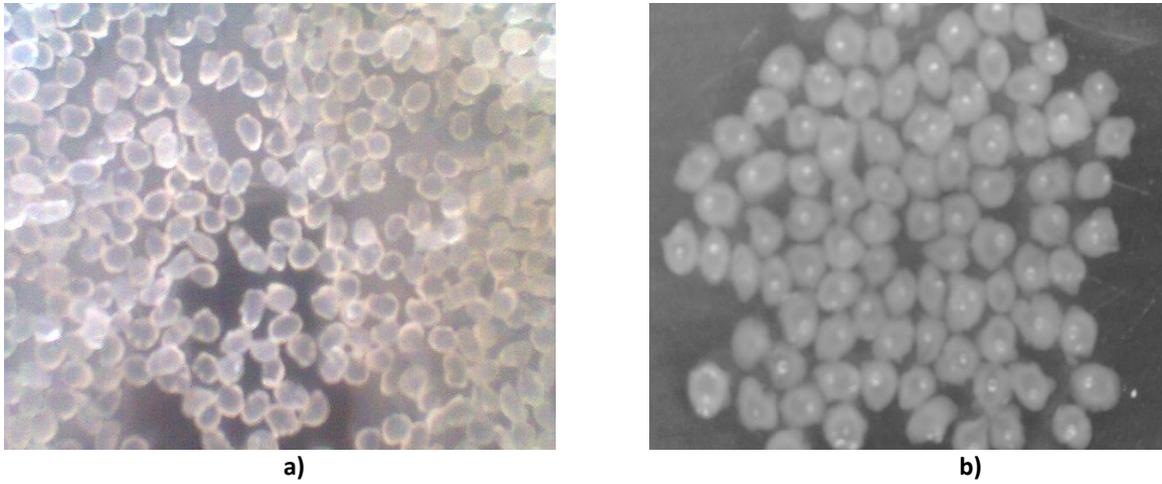
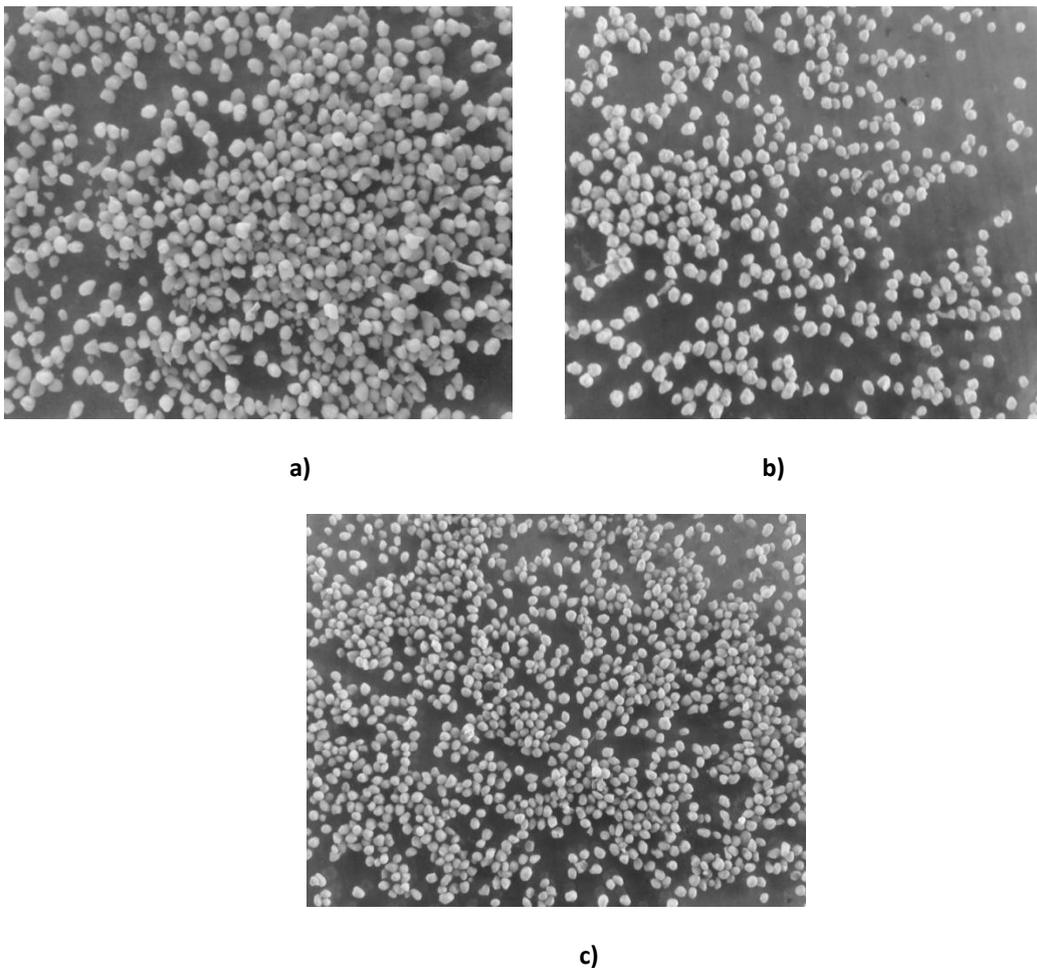
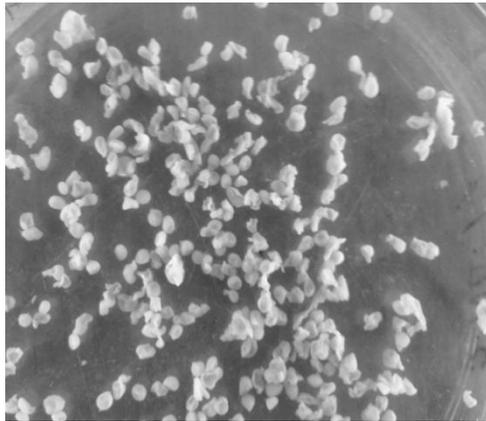
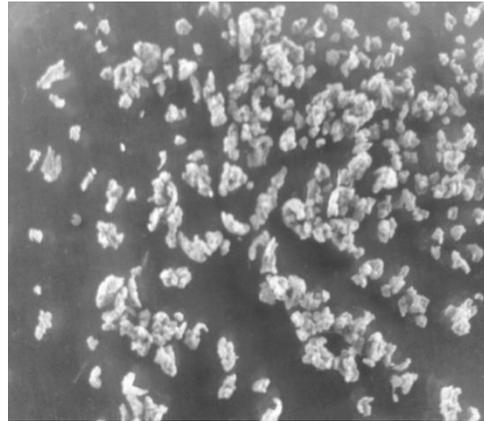


Figure 1: Digital camera Photos of formulation
a) Dummy beads without gas forming agent
b) Dummy beads with gas forming agent shown centrally air entrapment



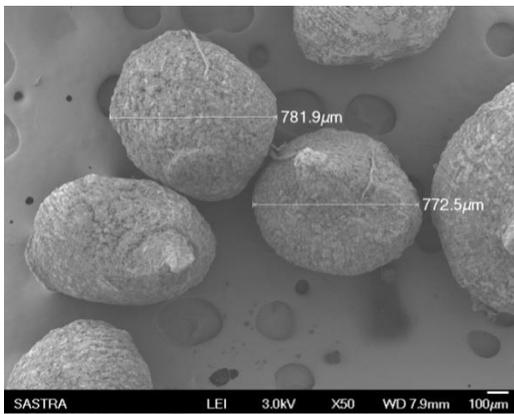


d)

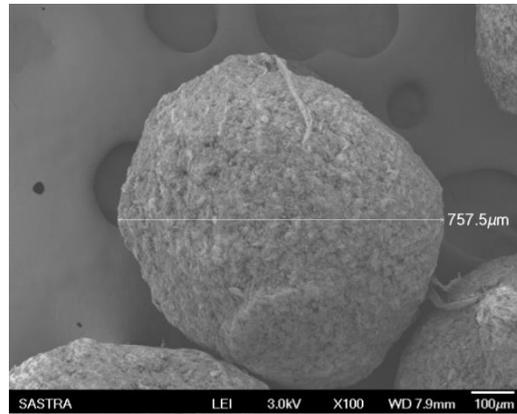


e)

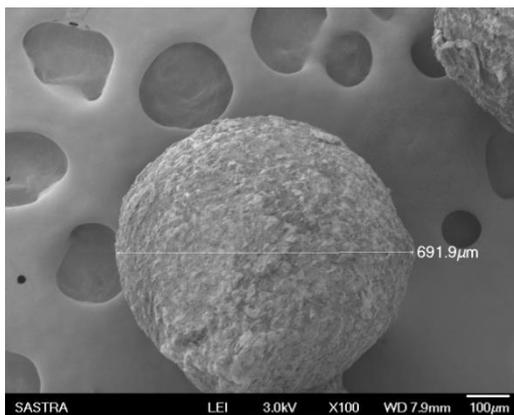
Figure 2: Digital camera Photos of various gas forming agents containing beads
 a) F₁ (NaHCO₃) b) F₂ (KHCO₃) c) F₃ (K₂CO₃) d) F₄ (Na₂CO₃) and F₅ (CaCO₃)



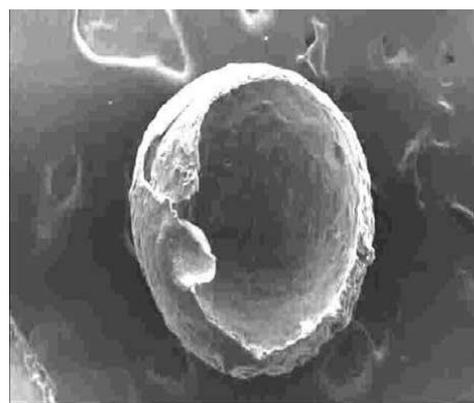
a)



b)



c)



d)

Figure 3: SEM images of formulation a) F₁ b) F₂ c) F₃ d) cross section

The Effects on floating time of the beads

The floating ability of prepared beads was evaluated in stomach pH. While gas forming agent free beads sink uniformly, but the beads containing gas forming agents were float. While comparing KHCO_3 and K_2CO_3 , KHCO_3 produced 50% beads to float but K_2CO_3 produced very few beads only float. Comparing all NaHCO_3 containing beads have shown excellent floating nature and increase the time of floating up to 6 hours because of very low bulk density than others (Table.2).

Table 2: In-Vitro Bouyancy Study of Prepared Beads

| Formulation code | Floating nature | Floating time (hrs) |
|---|-----------------|---------------------|
| F ₁ (NaHCO_3) | +++ | 6 |
| F ₂ (KHCO_3) | ++ | 3 |
| F ₃ (K_2CO_3) | + | 3 |
| F ₄ (Na_2CO_3) | - | - |
| F ₅ (CaCO_3) | - | - |

Note: +++ completely float, ++ partially float, + fair float, - not forming beads

The in-vitro release of NaHCO_3 containing beads with various drug (indomethacin) to polymer(LMP) ratio was performed and reported in our previous article [17] that its release was conformed as pulsatile manner after lag time of least release in stomach pH and complete release in intestinal pH which suggest that This floating pulsatile beads is the best choice in the management of Rheumatoid Arthritis which need to take medicine at bed time to design a release only in the early hours of morning symptoms which made maximum drug absorption at maximum absorption site of small intestine and ensure greater product safety with more patient compliance.

CONCLUSION

Overall, it was demonstrated that NaHCO_3 is more effective gas forming agent than other gas forming agents such as sodium carbonate, potassium bi carbonate, potassium carbonate and calcium carbonate. It produced superior calcium pectinate beads with decreased bulk density results excellent floating nature and increase the time of floating up to 6 hours than others. It was concluded that the enhanced buoyancy of NaHCO_3 containing beads of indomethacin made them an excellent candidate for floating pulsatile drug delivery system.

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