Sodium Alginate/Starch Blends Loaded with Ciprofloxacin Hydrochloride as a Floating Drug Delivery System - In Vitro Evaluation

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ABSTRACT: *In the present study, Floating Drug Delivery Beads (FDDS) were prepared with sodium alginate/ starch blend as a matrix, sodium hydrogen carbonate as a pore forming agent, methyl cellulose as a binder and barium chloride solution as a hardening agent. In order to prepare the beads with different porosity and morphology the ratio between pore forming agent to polymer blend and ratio of the constituents of the blend were varied. Ciprofloxacin hydrochloride was used as a model drug for in-vitro studies. The swelling property of the dry beads is found to be in the range of 80% to 125% from its original dimension. The amount of drug released from the beads was measured by UV-Visible spectrometer at* λ_{max} *of 278. The drug release from the floating beads can be varied from 7% to 67% by varying the ratios of composition of the blend and pore forming agents to the polymer blend. From the results it is proved that this system can be used as an oral delivery system with an ability of controlled release of drug in a sustained manner.*

KEY WORDS: *Floating drug delivery system, Sodium alginate, Starch, Controlled release, Sustained release.*

INTRODUCTION

Blending of polymers is an interesting route for producing new materials, basically due to economical aspects [1]. Several approaches are currently utilizing in the prolongation of the Gastric Residence Time (GRT); including Floating Drug Delivery Systems (FDDS), swelling and expanding systems, polymeric bio-adhesive systems, modified-shape systems, high-density systems and other delayed gastric emptying systems [2]. The current study addresses about the FDDS that is one of the leading methodology in gastro retentive drug formlations.

Floating drug delivery system is also called as the Hydro Dynamically Balanced System (HBS) [12]. FDDS have a bulk density which is less than the gastric contents and hence remains buoyant in the stomach for a prolonged period of time without affecting the gastric emptying rate [9]. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After the release of drug, the residual system is emptied from the stomach. This results in the increase of GRT and a better control of the fluctuations

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1021-9986/15/2/25 7/$/2.70

in plasma drug concentration [4]. The floating dosage form by virtue of its floating ability is reserved in stomach and maintains the high concentration of the drug at stomach [5].

Starch products differ in digestibility. The rate and extent of digestion is reflected in the magnitude and period of the glycemic response [8]. Starch is the only qualitatively essential digestible polysaccharide and has been regarded as nutritionally greater to low molecular weight carbohydrate or sugars [11]. Starch containing alginate beads were reported as a Drug Delivery System (DDS) and found to posses some advantages, including greater degree of swelling in water, which would be useful for its application in DDS [17]. To achieve a controlled or sustained DDS based on the SA beads, an alginate-coating strategy was developed. Thus the efficient control of the initial latent time and the release rate was successfully demonstrated with the model peptide drug L-phenylalanine.

Starch may not be suitable in some controlled drug delivery systems, as many drugs are released too fast from systems based on native starch [10]. This is due to a substantial swelling and rapid enzymatic degradation of native starch in biological systems. It is often compounded with other polymers or used alone in the fields of drug controlled release [13]. Recently different starch polymer blends have been suggested to have potential use in distinct biomedical applications. These include the use of starch based biomaterials as scaffolds for the tissue engineering of bone and cartilage [3] this is because of its suitable biocompatibility and non-toxicity [13].

Starch is the oldest and probably the most widely used disintegrant in the pharmaceutical industry and have been extensively employed for microencapsulation of bioactive materials and as a carrier in drug delivery systems [6]. Regular corn starch has certain limitation and has been replaced to some extent by modified starches with specialized characteristics to serve specific functions. The mode of action of starch is that the disintegrate forms pathways throughout the tablet matrix that enable water to draw into the structure by capillary action, thus leading to the disruption of the tablet.

Ciprofloxacin water solubility is strongly dependent on the acidic PH and mainly absorbed in the GI tract and bioavailability of the drug is about 70% in 2 hours and the elimination half-life is 4 hours. Therefore, sustained release formulations liberating the drug content results in an incomplete release of the drug from the drug delivery system, leading to diminished efficacy of the administered dose. Therefore, an effective floating delivery system of this drug may offer pharmacokinetics and pharmacodynamic advantages.

In this study, we developed a completely new approach to attain sustained release of drugs within the alginate based beads. This study intended to prepare the different ratios of polymer blends such as equal ratio of polymer1 & polymer2 and polymer1 enriched beads with lesser content of polymer2. To this blends various amounts of pore forming agent is added to form FDDS with different buoyancy and porosity. The resultant beads are expected to show different buoyancy and drug release kinetics.

EXPERIMENTAL SECTION

Barium Chloride (99%, Qualigens, India), NaCl (99.9%, AR, SDFCL, India), KH_2PO_4 (99.5%, AR, Thomas Baker, India), $CaCl_2$ (90.0%, LR, SDFCL, India), KCl (99.5%, AR, SDFCL, India), Sodium alginate (High viscosity, HiMedia Chemicals, India), Starch (SISCO, India), HCl (36.5%, SDFCL, India) were purchased and used as received.

Preparation of the beads

Two different formulations of polymer blends were prepared by taking the polymer concentrations in equal ratios (Sodium Alginate = Starch) which is termed as SAST and polymers in different ratios (Sodium Alginate > Starch) which is termed as SA Enriched. The stock solution of the drug carrier was prepared by mixing the different ratios of sodium alginate and starch. To the mixture 0.1g of methyl cellulose was added as a binder and the resultant solution is made up to 100ml by adding distilled water. The various ratios of pore forming agent to alginate solution was prepared by adding up differen quantity of pore forming agent to the fixed ratio of alginate and starch blend. The pore forming agent to alginate / starch blend ratios prepared were 1:1, 1:2, 1:3, 1:4 and the resultant mixture was degassed using sonicator. To the 1% $BaCl_2$ solution containing 10% acetic acid solution the viscous alginate and starch mixture was added drop wise by using a syringe. The beads formed were stirred with a magnetic stirrer for

Table 1: Swelling property of the beads (SAST).

PFA to Alginate/ Starch blend ratios	Dry beads of SAST blends (cm)	Swollen beads of SAST blends (cm)
1:1	0.35 to 0.37	0.85 to 0.87
1:2	0.40 to 0.43	0.90 to 0.93
1:3	0.45 to 0.48	0.95 to 0.98
1:4	0.52 to 0.54	1.15 to 1.17

Table 2: Swelling property of the beads (SA Enriched).

PFA to Alginate/ Starch blend ratios	Dry beads of SA Enriched blends (cm)	Swollen beads of SA Enriched blends (cm)
1:1	0.32 to 0.34	0.80 to 0.83
1:2	0.37 to 0.39	0.85 to 0.87
1:3	0.43 to 0.45	0.95 to 0.97
1:4	0.50 to 0.52	1.10 to 1.13

10 min to improve the mechanical strength of the beads. The hardened beads were filtered and kept in a hot air oven at 60°C for drying. The dried beads were stored for further analysis.

Preparation of gastric juice

In 1000ml of deionized water, analytical grade of 3.5g of Glucose, 2.05g of NaCl, 0.60g of KH_2PO_4, 0.11g of $CaCl_2$ and 0.37g of KCl were dissolved in the same order. The solution was sterilized and pH was brought down to 2.0 by adding 1M HCl and then the volume of the solution was made up to one litre.

Procedure for the measurements for the release kinetics

Totally 30 number of drug loaded beads were taken for analysis. Drug release kinetics studied was carried out in USP dissolution apparatus containing 900ml of gastric juice with the beads placed at a temperature of 37ºC with a stirring speed of 100rpm. At regular intervals, 2mL of the solution was collected and replaced with 2ml of fresh gastric juice. Release kinetics was measured by using UV-Visible spectrometer at λ_{max} of 278nm.

Characterization of the beads

The beads thus prepared were characterized under an optical microscope (Carl Zeiss, Imager a 1 M) to study the effect of the varying concentrations of the pore forming agents on the pore size of the beads. The beads were also characterised by FT-IR spectroscopy (Shimadzu). A size-weight analysis of the beads was also done by Screw Guage and Electronic balance to understand how the amount of pore forming agent affect the average size and weight of the beads. The surface morphology of the beads was studied under the Scanning Electron Microscope. The amount of drug released was estimated using UV-visible spectrometer (Hitachi, U- 2800 Spectrophotometer, Japan).

RESULTS AND DISCUSSION

The average size of the beads before and after drying was measured by using micrometer screw gauge.

From the Tables 1 and 2, it is observed that 1:4 ratio beads show a maximum swelling property than other three ratios. Also it is proved that the ratio of pore forming agent to polymer blend affects the size of the beads. For higher ratios the beads observed were small in size and for lower ratios the beads observed were comparatively bigger in size. When compared to the SA Enriched beads, the SAST beads is showing more swelling property. The swelling property of the dry beads was measured by using screw gauge and the swelling of beads is found to be in the range of 80% to 125% from its original dimension.

Weight of the 30 numbers of wet beads and dry beads was carried out in electronic balance which is represented in the Figs. 1 and 2. The density of wet beads is more than the density of dry beads which is due to the absorption of water. The change in the density of beads with different ratios of blends to pore forming agent may be either due to the bigger pore size or more number of pores present in the beads.

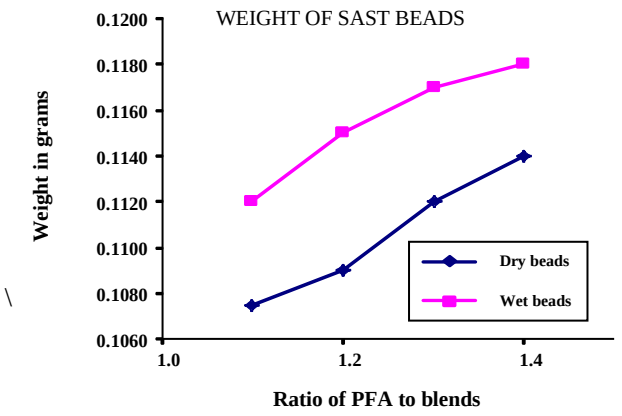

Fig. 1: Weight of dry and wet beads of SAST blends.

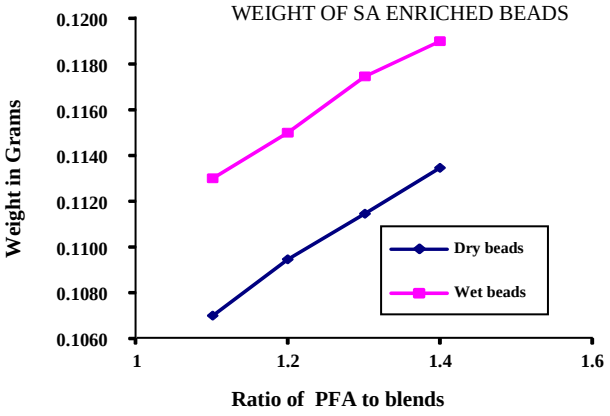

Fig. 2: Weight of dry and wet beads of SA Enriched blends.

The number of pores per bead depends on the reaction between the pore forming agent and the acetic acid solution which releases CO_2. As the concentration of $NaHCO_3$ decreases, the amount of CO_2 produced will be lesser and the beads formed will be less porous with increase in weight.

This is proved from the experimental results as the 1:1 ratio beads are lesser in weight whereas 1:4 ratio beads are more in weight. The number of pores and pore size depends on the nature of polymer present in the blends. Change in porosity will affect the drug release kinetics as the bigger pores will have fast kinetics as the mechanism predominates is dissolution whereas the smaller pores involves dissolution and proceed with diffusion further. If the pores are smaller and lesser in number then the drug has to diffuse through the matrix and get released from the beads. This is influenced by the nature of the polymer present in the blends and the nature of porosity induced by the polymer. If the constituent is having good swelling properties then the release kinetics will be sustained as the drug has to diffuse through large distance.

Optical microscopic image (Figs. 3 and 4) of Alginate/Starch shows shrinkage in the beads. This shrinkage is due to the drying of the beads at 60°C. The optical microscopic image shows that the pores formed by $NaHCO_3$ are bigger, in which a bigger pore is due to the combination of smaller pores formed. The pore morphology is highly irregular and the size of the pore is 800microns which is found to be bigger.

The size and surface morphology of the dried beads were visualized in FESEM. Fig. 5 shows the FESEM images of the beads with 1:3 ratio of SAST blend to PFA. At higher magnification the surface of the beads is found to have two different morphologies of flakes and rods.

The FT-IR spectra of ciprofloxacin loaded alginate/starch beads are shown in Fig. 6, which clearly confirm the presence of alginate/starch and ciprofloxacin in the loaded beads. The pure alginate characteristic absorption bands were observed at $1612cm^{-1}$ and $1413cm^{-1}$ shows –C=O stretching and CH_2 bending. The FT-IR spectra of alginate/starch showed the peaks around $3397cm^{-1}$ and $2924cm^{-1}$ indicating the presence of O–H, N–H stretching and aliphatic CH stretching respectively. The characteristic C–O stretching and C–N stretching were at $1082cm^{-1}$ and $1028cm^{-1}$. The peak at $611cm^{-1}$ was attributed to C–H out of plane bending.

Loading of ciprofloxacin hydrochloride in alginate/starch blends

30 dried beads of uniform size were added to the test tube containing 10mg of ciprofloxacin hydrochloride dissolved in 10 mL of distilled water. Beads were allowed to absorb the drug solution for two hours and the swollen beads were taken out and kept for drying. The test tube is washed and analyzed for the amount of drug left out in order to calculate the quality of the drug loaded in the beads. The amount of drug loaded is calculated by the formula:

Drug loaded = Total drug taken- Drug left out after absorption

The results were tabulated in Table 3.

It was observed from the Table.3 that the beads with lesser PFA showed poor absorption rate of drug solution than the beads with more PFA in the stipulated period of two hours. This may be due to the high porosity of 1:1 beads than the other beads.

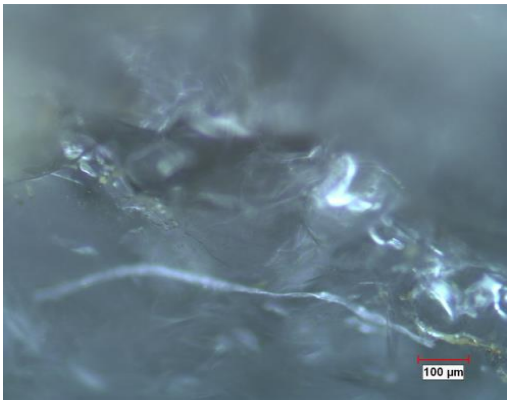

Fig. 3: Optical microscopic image of 1:1 ratio alginate/starch blends to PFA beads.

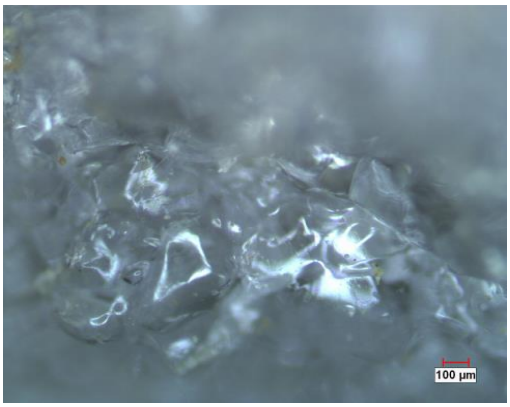

Fig. 4: Optical microscopic image of 1:1 ratio alginate/starch blends to PFA beads.

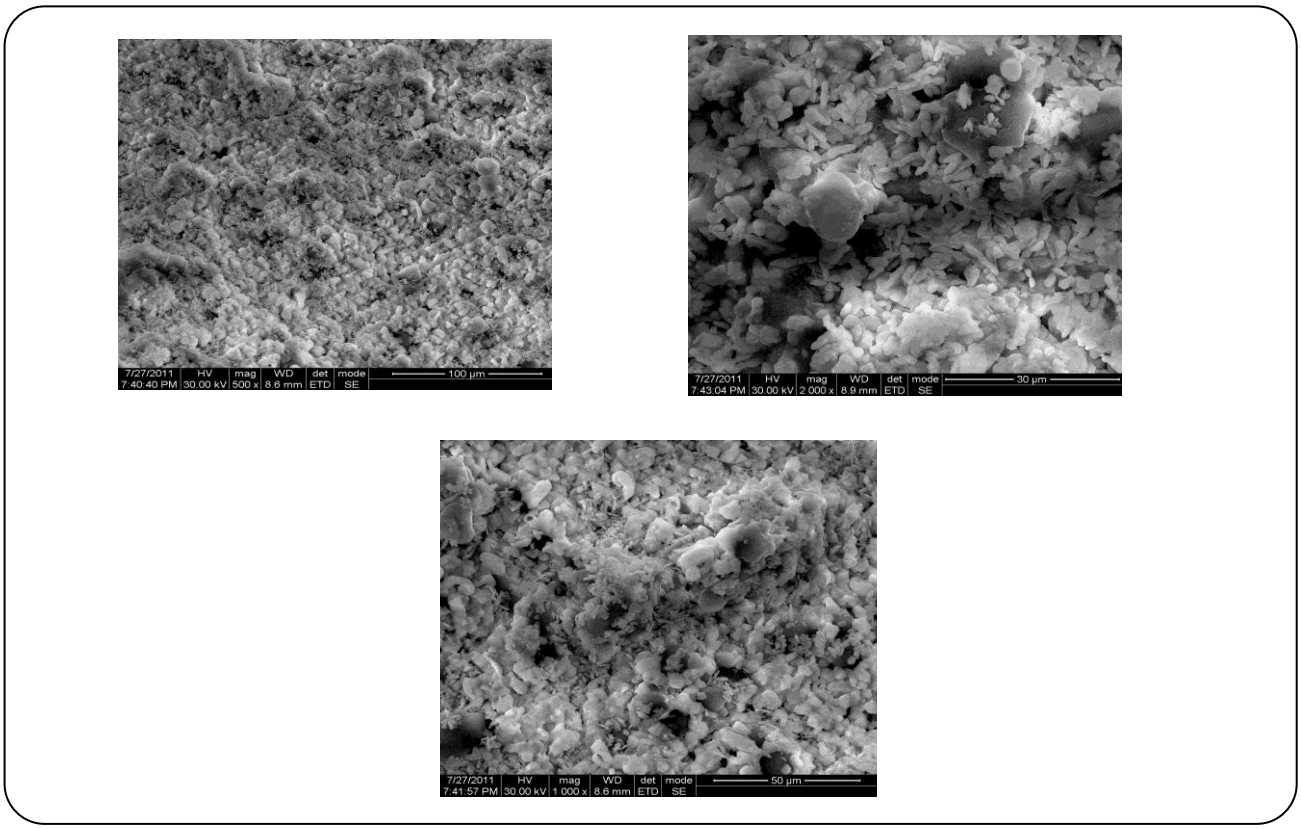

Fig. 5: FESEM image of 1:3 ratio of Alginate/starch blends to PFA beads.

From the release kinetics graphs (Figs.7 and 8), it is evident that 1:1 ratio beads show a maximum release of ciprofloxacin over duration of two hours. Large amount of pore forming agent present in the formulation leads to more CO_2 evaluation which induces more number of pores in the beads.

Due to the large number of pores, when the beads were placed in the gastric juice dissolution of the drugs from the surface of the pores predominates the diffusion of the drugs from the matrix, hence the maximum release of the drug is observed in the stipulated time. 1:4 ratios shows the least release of the drug which is due to

Table 3: Percentage of drug loaded in the Sodium alginate/ Starch blends.

Ratios of the PFA to the blends	Drug loading % of SAST blends	Drug loading % of SA Enriched blends
1:1	8.9	9.4
1:2	8.6	9.3
1:3	7.9	9.2
1:4	7.8	8.7

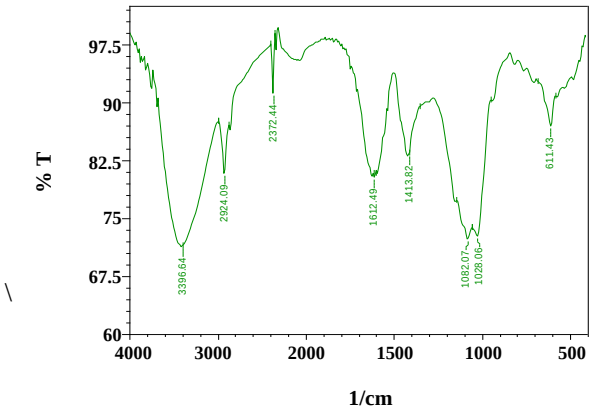

Fig. 6: The FT-IR spectra of ciprofloxacin loaded alginate/ starch beads.

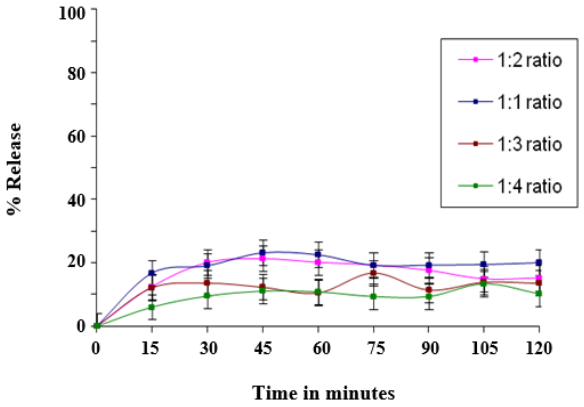

Fig. 7: Release kinetics of ciprofloxacin from SAST blends.

the decrease in the concentration of pore forming agent which leads to lesser CO_2 production and correspondingly lesser pores. Due to lesser number of pores the diffusion mechanism predominate dissolution hence the release is found to be slow and sustained. With increase in alginate ratio in the blend the release kinetics is found to got altered and it is comparatively higher for all the ratios of the blend to pore forming agent. With lowest PFA the starch blend shows a minimum release when compared with other systems which is found to be less than 10%.

CONCLUSIONS

The beads containing sodium alginate with starch blends were successfully prepared and the release kinetics of antibiotics from the polymer matrix was studied and has proved to be suitable for the use as a sustained-release form of ciprofloxacin hydrochloride. Among all the ratios of PFA to the starch blend, 1:1 ratio shows a rapid release of ciprofloxacin over the duration of two hours. This may be due to the larger size of pores which results in more dissolution in first few minutes than diffusion, whereas for other ratios due to high density the diffusion predominates dissolution hence the release is sustained. From the results, it was found that the blending of sodium alginate with starch shows a greater swelling property. The increase in swelling ratio could be attributed to the fact that due to the presence of more amount of alginate. The observed finding may be explained by the fact that due to the hydrophilic nature of starch, which imparts increasing hydrophilicity to the blend and brings about an increase in swelling ratio. Amount of drug absorbed by the beads is enhanced to 9.4% with the increase in the percentage of sodium alginate in the blend. The beads containing equal ratio of sodium alginate and starch shows 20% drug release in 2h whereas sodium alginate enriched beads shows up to 65% of drug release.

Acknowledgement

The authors would like to thank Technology Business Incubator, VIT University for FTIR and UV-Visible measurements. The authors are also thanking Prof. Geetha Manivasagam, School of Mechanical and Building Sciences, VIT University for optical microscopic measurements.

Received : Feb. 3, 2014 ; Accepted : Feb. 2, 2015

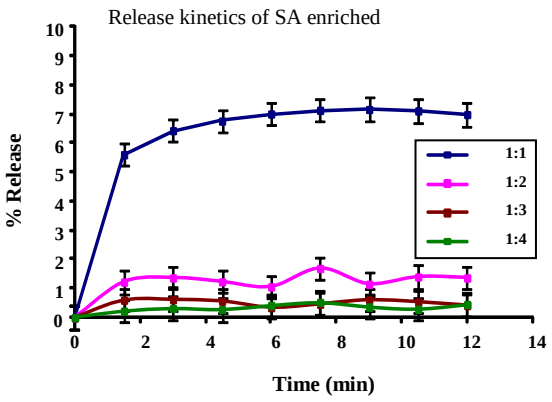

Fig. 8: Release kinetics of ciprofloxacin from SA Enriched blends.

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