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Research Article

Sodium Alginate with PEG/PEO Blends as a Floating Drug Delivery Carrier – In vitro Evaluation

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Abstract

Purpose: Floating drug delivery system reduces the quantity of drug intake and the risk of overloading the organs with excess drug.

Methods: In the present study, we prepared the blends of sodium alginate with polyethylene glycol (PEG) and polyethylene oxide (PEO) as a matrix, sodium hydrogen carbonate as a pore forming agent, methyl cellulose as a binder and barium chloride containing 10% acetic acid as a hardening agent. Different ratios of pore forming agent to the polymer blend was used to prepare the floating beads with different porosity and morphology. Ciprofloxacin hydrochloride was used as a model drug for the release kinetics studies.

Results: The beads were characterized by optical and FESEM microscopy to study the morphology and pore dimensions. The results obtained shows decrease in beads size with increase in the concentration of the pore forming agent. The swelling properties of the beads were found to be in the range of 80% to 125%. The release kinetics of the ciprofloxacin from the beads was measured by UV-Visible spectroscopy at λmax of 278nm and the results shows for highly porous beads.

Conclusion: By varying the amount of alginate and pore forming agent the release kinetics is found to get altered. As a result, ciprofloxacin hydrochloride release is found to be sustained from the blended beads.

Introduction

The primary aim of the controlled drug delivery system is to deliver the drug for longer period of time to achieve better bioavailability. But this is difficult due to number of physiological problems such as fluctuation in the gastric emptying process, narrow absorption window and stability problem in the intestine.[1-3] To overcome this problem, different approaches like bio adhesive systems, floating drug delivery systems, swelling and expanding systems and delayed gastric emptying systems have been proposed to retain the dosage form for a longer duration in stomach.[4,5] Floating dosage forms have a bulk density lower than that of gastric fluids and therefore remain buoyant on the stomach contents to prolong the gastric retention time.[6,7]

The floating drug delivery system offers a simple and practical approach to achieve increased gastric residence time for the dosage form which results in the sustained drug release.[8] Among the water-soluble polymers, PEG and PEO were used as a matrix, since they are available in a wide range of desired molecular weights and possessing a well-defined macromolecular structure.[9,10] Sako et al demonstrated the blend of PEG and PEO can be used as an oral controlled absorption system (OCAS). PEG a hydrophilic agent which promotes water uptake into the tablets, so that it undergoes complete gelation within few hours. As a result, oral controlled absorption system enables the sustained release of drug throughout GI tract, including colon where the availability of water is limited.[11-13] PEO and PEG denote essentially identical polymers and the only difference between the respective notations is the methoxy group of PEO is replaced with the terminal hydroxyl group of PEG.[14] Due to their low toxicity and high solubility in water, they have been conjugated to an array of pharmaceuticals to overcome the limitations of low solubility, short circulating lifetime and immunogenicity.[10] Because of the good biological activities of PEG and PEO, a combination of PEG and PEO may have beneficial effects on the biological characteristics of complex membranes.[15-17]

PEO has been proposed as an alternate to the cellulose and ethylene glycol derivatives in the production of controlled release drug delivery system.[16-26] Further it also has mucoadhesive properties which may assist in prolonging the gastric residence time. They are characterized with flocculent, thickening, sustained-release, lubrication, dispersing and a water-retention property which extends its application to various drug delivery systems.[6] It is often blended or compounded with other polymer and utilized in the field of controlled drug delivery system. Several reports are available, in

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which alginate is used in combination with polyethylene glycol and polyethylene oxide for various biomedical applications.[25-28]

The rate of drug release from hydrophilic matrix depends on various factors such as nature of polymers, solubility of drug, polymer content, particle size of drug and types of filler used in the formulation.[14] The adjustment of polymer concentration, viscosity grade and addition of different types and levels of excipients to the polymer matrix can modify the kinetics of drug release.[18] Also the release kinetics is significantly affected by the polymer molecular weight characteristics, polymer swelling and dissolution rate, and drug diffusivity in the polymer gel surrounding the tablet.

The floating drug delivery systems can be prepared by means of the reaction between carbonate salts present in alginate matrix and acetic acid which produces carbon dioxide gas. The carbon dioxide evolved permeates through the alginate leaving gas bubbles or pores. The most commonly used pore forming agents are $NaHCO_3$ and $CaCO_3$.[2,8,23,27]

In the present study we prepared the floating beads containing sodium alginate/PEG or PEO loaded with ciprofloxacin hydrochloride. In order to investigate the release kinetics of the drug from the blended beads, the ratio of the polymers and amount pore forming agent were varied. Moreover, physiochemical properties of the blended beads such as drug uptake, entrapment efficiency, diffusion properties, swelling properties, and drug release in the dissolution media were also investigated.

Materials and Methods

High viscosity sodium alginate salt (Mw 10,000-600,000) was obtained from AR Sigma Aldrich 99%, Polyethylene glycol 4000LR with an average molecular weight of 3500-4500 was purchased from Sisco research laboratory, Polyethylene oxide (*Mw* ca.200,000 inhibited by 200-500ppm) was obtained from Sigma Aldrich were used as received. Barium Chloride (99%, Qualigens, India), NaCl (99.9%, AR, SDFCL, India) and KH_2PO_4 (99.5%, AR, Thomas Baker, India), $CaCl_2$ (90.0%, LR, SDFCL, India), KCl (99.5%, AR, SDFCL, India), are commercially available were used without further purifications.

Preparation of the Beads

Two different polymer blends was prepared by taking different ratios of polymer concentration. The blend with equal weight of sodium alginate and PEG was termed as SAPEG and the blend with more sodium alginate and less PEG was termed as SA Enriched PEG. The stock solution of the drug carrier was prepared by mixing different ratios of sodium alginate to PEG. To the mixture 0.1 g of methyl cellulose was added as a binder and the resultant solution was made up to 100 ml by adding distilled water. The various ratios of pore forming agent to alginate solution was prepared by adding different quantity of pore forming agent to the fixed ratio of alginate/PEG blend and the resultant mixture was degassed by using sonicator. The viscous alginate/PEG blend with pore forming agent was added drop wise by using a syringe into the 1% $BaCl_2$ solution containing 10% acetic acid. The beads formed were stirred with a magnetic stirrer for 10 min to improve the mechanical strength of the beads. The hardened beads were filtered and kept in a hot air oven at 60 $^{\circ}$C for drying. The dried beads were stored for further analysis. The same procedure was followed for the preparation of sodium alginate/PEO blend. But in case of PEO, the beads of 50% and 33% were not stable and collapsed to form a semi solid mass hence the formulations were shifted to the lower percentage of 17% and 14%. The formulation compositions of PEG and PEO are tabulated below as Table 1.

Table 1. Formulation compositions of the PEG & PEO beads

Sodium alginate/PEG& PEO (g)	PFA (g) in PEG	PFA (g) in PEO	Methyl cellulose (g) in PEG & PEO	% of PFA in the blend	% of PFA in the blend
0.75	0.25	0.75	0.025	25%	50%
0.75	0.187	0.375	0.025	20%	33%
0.75	0.15	0.25	0.025	17%	25%
0.75	0.125	0.187	0.025	14%	20%

Preparation of Gastric Juice

In 1000 ml of deionized water, analytical grade of 3.5 g of glucose, 2.05 g of NaCl, 0.60 g of KH_2PO_4, 0.11 g of $CaCl_2$ and 0.37 g 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 liter.[23]

Loading Ciprofloxacin Hydrochloride in Floating Beads

30 dried beads of uniform size were suspended in a test tube containing 10 mg of ciprofloxacin hydrochloride dissolved in 10 ml of distilled water. After two hours, the beads were taken out of the drug solution and the swollen beads were kept for drying at 60 °C in a hot air oven. 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 size of swollen beads and dried beads were measured by using screw gauge to study the swelling property.

Procedure for the Measurement of Release Kinetics

Drug release kinetics studies were carried out in USP dissolution apparatus containing 900 ml of gastric juice,

at temperature of 37 °C with a stirring speed of 100 rpm. At regular time intervals, 2 ml of the sample was collected and replaced with 2ml of fresh gastric juice. Release kinetics was measured at λ_{max} of 278 nm by using UV-visible spectrometer.

Characterization

The beads were characterized under an optical microscope (Carl zeiss, Imager a 1 M) to study the effect of concentration of the pore forming agent on the pore size and morphology of the beads. A size-weight analysis of the beads was also carried out using screw gauge and digital balance to understand the effect of pore forming agent ratio in the blend in the size and weight of the beads. The surface morphology of the beads was studied under a Field Emission Scanning Electron Microscope (JSM-6700 F, JEOL Ltd). The drug release kinetics was studied by using UV-Visible Spectrometer (Hitachi, U- 2800 Spectrophotometer, Japan). Molecular interaction of PEO and PEG in sodium alginate beads was investigated by using FT-IR spectrophotometer (Hitachi, U- 2800 Spectrophotometer, Japan).

Determination of Buoyancy of Beads

The buoyancy of the beads was determined by visual observation.The floating duration of the beads on gastric juice at 37.5 °C was analyzed by measuring the duration of floating by using stop watch.

Results and Discussion

FT-IR spectral analysis

Alginate with PEG/PEO was chosen as a matrix to carry the drug as it is a biodegradable and biocompatible polymer. PEG/PEO forms a bio-adhesive and stable gel with alginate. Sodium bicarbonate is used as a pore forming agent as the mechanism of the reaction with acetic acid is as follows:

$$NaHCO_3 + CH_3COOH \longrightarrow CH_3COONa + H_2O + CO_2$$

The molecular interaction of sodium alginate with PEG/PEO loaded ciprofloxacin beads was studied by using FT-IR spectrophotometer (Figure 1) (JSM-6700 F, JEOL Ltd). The FT-IR spectroscopy of the blends was carried out in order to detect the peak shift that could be attributed to the interactions between the two polymers alginate with PEG/PEO, such as hydrogen bonding or complexation. Each sample was gently triturated with KBr powder in a weight ratio of 1:10 and then pressed by using a hydrostatic press at a pressure of 1tones for 5 mins. The disc was placed in the sample holder and scanned from 4000 cm^{-1} to 500 cm^{-1}. The FTIR spectra of sodium alginate showed peaks around 1622, 1423, and 1080 cm^{-1} indicating the stretching of COO^- (symmetric), COO^-(asymmetric) and C-O-C respectively.

The spectra of the drug loaded alginate bead shows peak around 3404 cm^{-1} indicating the presence of O-H, N-H stretching and aliphatic C-H stretching respectively. The characteristic band of PEO and PEG was observed at 817 cm^{-1} and 954 cm^{-1} due to C-O-C bending. The characteristic C-O stretching and C-N stretching was at 1080 cm^{-1} and 1089 cm^{-1}. For SAPEG and SAPEO blend, a significant difference in the region of C-O-C asymmetric stretch was observed. The interaction between sodium alginate with PEG and PEO can be seen at 3404 cm^{-1} due to the hydrogen bonding between the hydroxyl groups of sodium alginate and the ether oxygen groups. The peak at 608 cm^{-1} and 609 cm^{-1} was attributed to C-H out of plane bending. The intense band at 2922 cm^{-1} is due to hydroxyl (-OH) and alkyl chain.

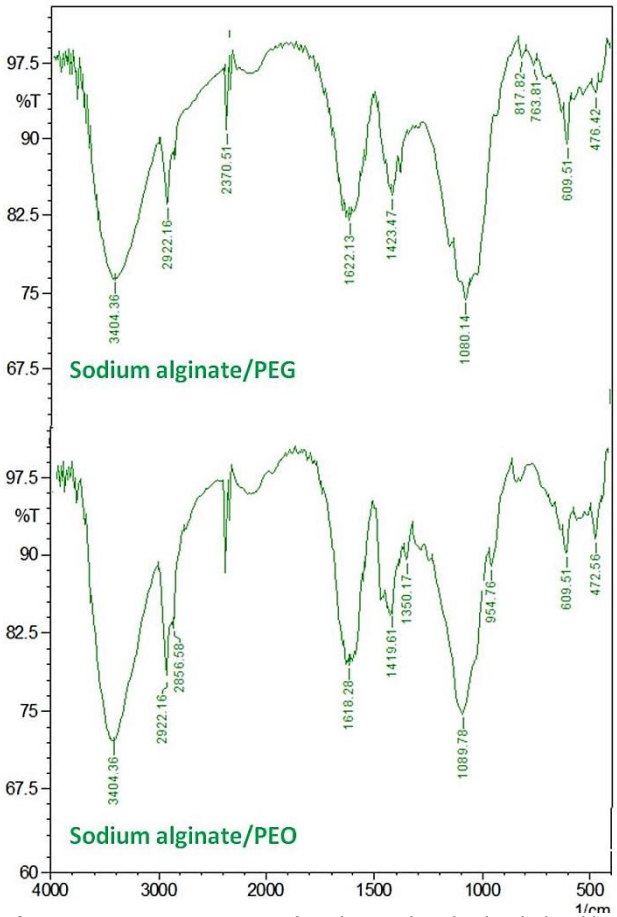

Figure 1. FT-IR spectra of polymer beads loaded with ciprofloxacin hydrochloride

Optical microscopic analysis

The optical microscopic images of drug loaded alginate beads showed bigger pores for the beads with higher pore forming agent concentration. With the decrease in the concentration of pore forming agent the pore size is found to be smaller. The bigger size of the pores may be due to combination of smaller pores together to form a bigger size pores. In SAPEG beads, the pore size is found to be approximately 400 µ and the pore size of SAPEO beads is found to be in the range of 500 to 600 microns and pore morphology is irregular in shape.

FESEM analysis of beads

The morphological features of the drug loaded beads of SAPEG and SAPEO have been studied by FESEM (Figure 2). In order to gain a clear sight into the surface topography of the polymer beads, the images were recorded at three different magnifications. The image of SAPEG beads shows a bigger pore size in the range of 80 µ and a smooth surface at lower magnification. However at higher magnification, the surface of the beads appear to possess irregular morphology and one of the polymer forms a branch like structure on the surface of the another polymer. The nature of the surface becomes clearer at larger magnification in SAPEG beads. The SAPEO beads, surface contain other polymer and the bead shows a flower-like morphology and the pore dimension is found to be in the range of 600 microns.

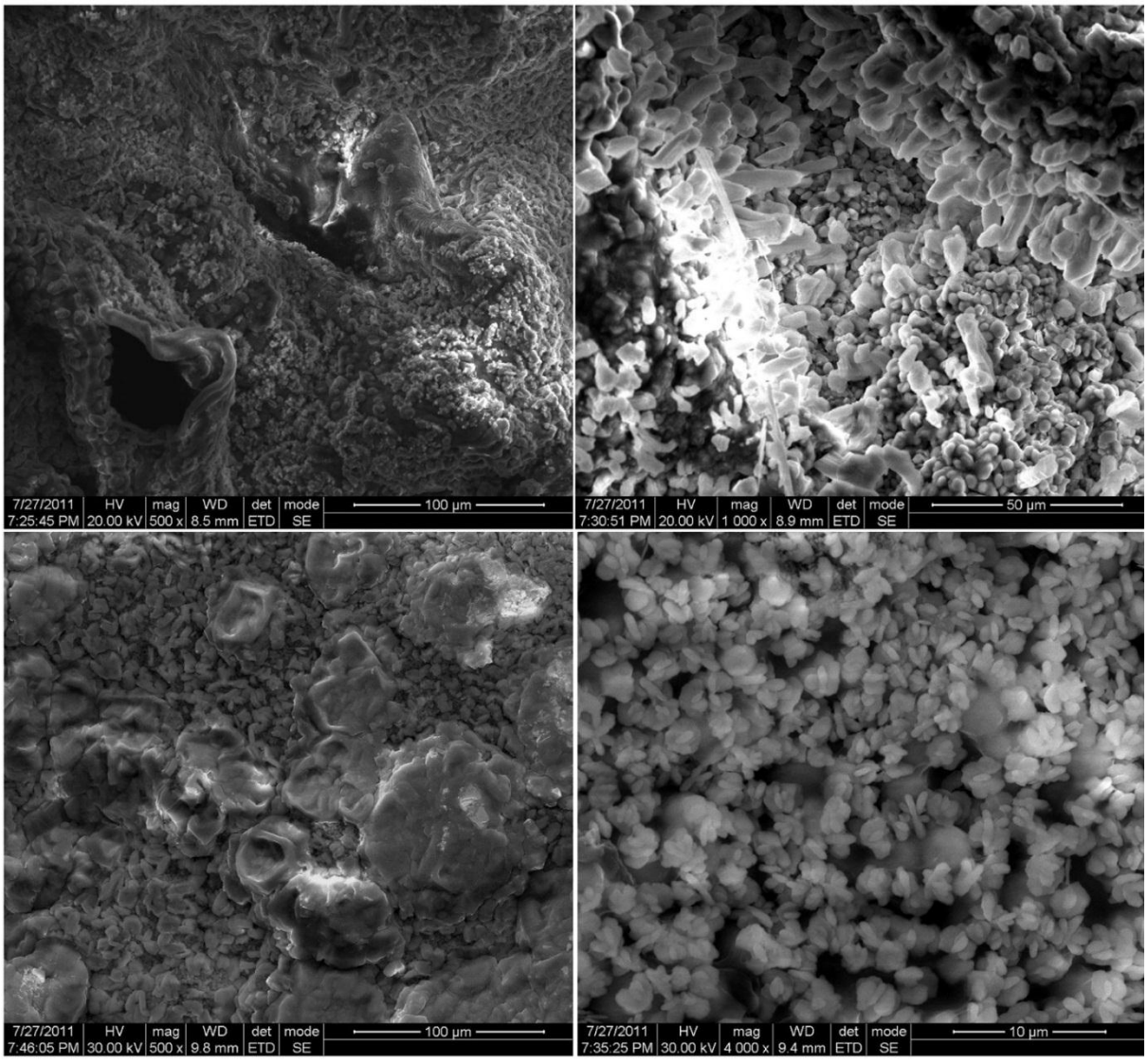

Figure 2. FESEM images of SAPEG beads at different magnifications

The beads with more pore forming agent shows a uniform surface whereas the beads with less pore forming agent shows agglomerated surface with irregular morphology. This clearly indicates the effect of PFA on the morphology of the beads which is expected to influence the release kinetics of the drug from beads.

Drug loading characteristics of beads

From Table 2, it is observed that the beads with lesser PFA shows poor absorption rate of drug solution than the beads with more PFA in the stipulated time. This may be due to the high porosity of the beads containing high pore forming agent. Hence through the pores the drug molecules can penetrate into the beads whereas the low pore forming agent containing beads, the drug molecules has to diffuse which reduces the absorption of the drug.

Table 2. Percentage of drug loaded in the SAPEG, SAPEO and SA Enriched beads

% of PFA to the Blends		Drug loaded % of SAPEG blends (mg)	Drug loaded % of SAPEO blends (mg)	Drug loaded % of SA Enriched PEG blends (mg)	Drug loaded % of SA Enriched PEO blends (mg)
PEG	PEO				
50%	25%	8.6	7.2	8.7	8.3
33%	20%	8.5	7.0	8.6	8.4
25%	17%	7.3	6.8	8.2	7.8
20%	14%	7.1	6.5	8.0	7.5

Swelling behavior of SAPEG and SAPEO beads

In order to test the suitability of the polymeric beads for the floating drug delivery, their swelling behavior was tested in the drug solution at the physiological temperature of 37 °C. The beads of SAPEG and SAPEO with uniform size was weighed and immersed in the drug solution over a period of 2 hours. Prior to weighing, the swollen beads were dried gently at room temperature. The drug absorption analysis is listed in Table 3 and in Table 4. The average size of the beads before and after drying was measured by using micrometer screw guage. The effect of concentration of sodium alginate in the blend on swelling property of the beads was studied.

Table 3. Swelling property of PEG &PEO beads

% of PFA in the blends		Dried beads(mm)		Swollen beads (mm)	
PEG	PEO	SAPEG	SAPEO	SAPEG	SAPEO
50	25	0.33 to 0.40	0.30 to 0.40	0.75 to 0.74	0.70 to 0.74
33	20	0.35 to 0.45	0.35 to 0.45	0.85 to 0.87	0.80 to 0.85
25	17	0.48 to 0.50	0.45 to 0.55	0.92 to 0.95	0.90 to 0.93
20	14	0.54 to 0.56	0.50 to 0.63	1.15 to 1.17	1.10 to 1.12

Table 4. Swelling property of SA Enriched PEG &PEO beads

% of PFA in the blends		Dried beads(mm)		Swollen beads (mm)	
PEG	PEO	SA Enriched (PEG)	SA Enriched (PEO)	SA Enriched (PEG)	SA Enriched (PEO)
50	25	0.30 to 0.34	0.25 to 0.30	0.72 to 0.75	0.65 to 0.63
33	20	0.35 to 0.38	0.30 to 0.33	0.80 to 0.83	0.75 to 0.76
25	17	0.40 to 0.44	0.35 to 0.37	0.85 to 0.87	0.80 to 0.84
20	14	0.45 to 0.47	0.40 to 0.43	0.90 to 0.93	0.85 to 0.87

From the results it is observed that the beads with 20% PFA shows maximum swelling property when compared to the rest of the formulations. This may be due to high porosity of the beads as more quantity of PFA will induce large number of pores in the beads.The increase in alginate concentration in the blend did n't affect the bead size immaterial of the concentration of the pore forming agent present in the blend. The bead size is found to be similar to that of the formulations containing PEG/alginate. This is due to the similar chemical structure which makes the interaction between the polymers also similar hence the physical properties of the blend didn't vary. Also 50% and 33% PFA loaded alginate/PEG blends were stable but the same percentage of alginate/PEO blends were not stable as it collapses to form a semi solid mass. This may be attributed due to the change in the molecular weight of PEG and PEO even though they have identical chemical structure.

To evaluate the extent of shrinkage upon drying, the diameter of SAPEG beads was measured before and after drying. When compared with SAPEG beads the size of SA enriched beads were found to be small for all ratios. When compared to the previous set of formulations containing PEO the size of dry SA enriched beads were found to decrease in the range of 10% to 30% and the swelling property is also found to decrease in the range of 10% to 30%. When compared to both sets of polymer blends the alginate rich blend shows decrease in the swelling property. The reason for the loss in the swelling property is attributed to the fact that at much higher content of alginate the insoluble polymer fraction becomes greater in the blend and therefore, the penetrating water molecules have to travel a longer path to cause swelling of the beads and

consequently the swelling ratio decreases. If alginate concentration is less than the water soluble portion of blend is more hence a slight dissolution with the uptake of water will takes place.

Weight of dry and wet beads of alginate blends

The average weight of the wet and dried beads is depicted in Figure 3. The weight of the wet beads is found to be higher than the weight of dried beads. The 50% PFA loaded SAPEG beads shows a lesser weight whereas 20% shows a higher weight. The change in weight may be either due to the bigger pore size or more number of pores present in the beads which varies the density of beads.

Even though PEO and PEG have the same chemical structure they are distinguished by their molecular weight. The effect of molecular weight is clearly seen in the results as the beads formed are highly homogeneous in the PEO blends when compared to PEG blends. Figure 3 shows a sharp and steady increase in the weight when compared with PEG blends. But when the weight of similar ratios of PFA to blend is compared the weight of the beads remains constant which indicates the change in molecular weight didn't influence on its physical properties.

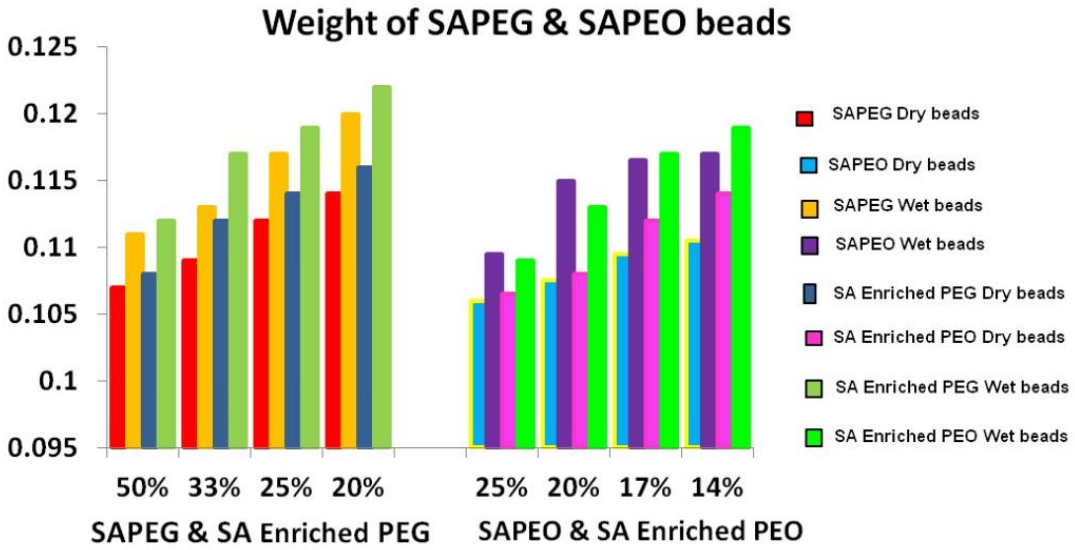

Figure 3. Weight analyses of dry and wet beads

Figure 3 indicates that, the wet beads of SA Enriched PEG shows higher weight than the SA Enriched PEO beads. In both the cases higher weight percentage was observed in PEG whereas lesser weight percentage was observed in PEO.

Release kinetics of SAPEG and SAPEO blends

The release pattern depends upon the type of polymers, amount of polymers and percentage of pore forming agent used. A great deal of research has dealt with the mechanism of drug release form the PEG and PEO matrices. A complete clarification of drug release mechanism for the different polymers under study is beyond our scope. In fact, for each polymer we aimed at verifying the percentage of drug release within the transit time of 2 hours as the transit time in stomach is close to this duration. From the release kinetics graph (Figure 4) it is seen that, beads with 50% pore forming agent shows a maximum release of ciprofloxacin hydrochloride at the 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. The formulations with low pore forming agent (SAPEO) shows the least release of the drug, is due to 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.

SAPEO blends (Figure 4) shows less release of the drug for all formulations. The beads with, 17% shows a least release of the drug (5%) because of the presence of less amount of pore forming agent. But all other formulation shows a maximum release of 10% of the drug in the stipulated time.

Release kinetics of SAEnriched PEO and SA Enriched PEG blends

The release of drug depends not only on the nature of the matrix, but also upon the polymers concentration which is evident from Figure 5.

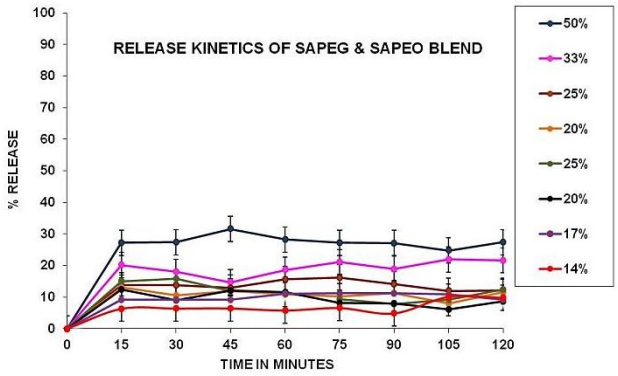

Figure 4. Release kinetics of SAPEG & SAPEO blends

From the Figure the release kinetics of the drug from SA Enriched blends was found to be in the range of 10%-40% within the transit time. The drug release is found to be a rapid release in first 15 minutes and then the release is found to be sustained due to the diffusion of the drug from the core of the beads. 25% PFA loaded SA Enriched PEO blend shows 40% drug release whereas the same quantity of PFA loaded SA Enriched PEG blend shows only 20% release of the drug. The results shows that it may be due to the structural reorganization of the hydrophilic polymers, sodium alginate with PEO and PEG. It is already reported that by increasing the alginate concentration, the release kinetics of the drug gets increased (sarojini et al). With this formulation minimum release of 17% and maximum release of 70% can be achieved within the transit time.

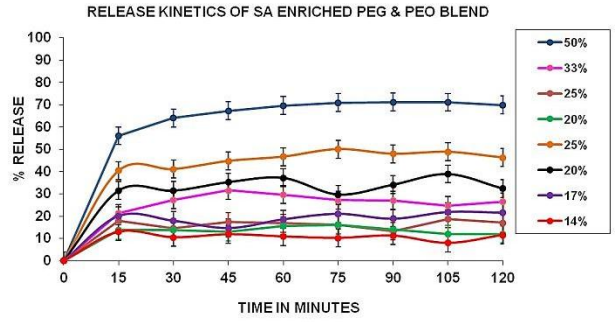

Figure 5. Release kinetics of SA Enriched PEG & SA Enriched PEO blends

When compared to the release kinetics of the polymer blends the maximum release of ciprofloxacin hydrochloride is observed for PEG blend and the lowest release is observed for PEO blend when equal amount of blend and PFA is taken. The reason may be that the hydrophilic PEG might have facilitated the release of the drug. The crystalline PEO with high molecular weight shows less release of the drug whereas the liquid PEG with low molecular weight releases maximum drug in a rapid rate. From the results it is concluded that by decreasing the concentration of PFA the effect of crystallinity will get diminished.

Conclusion

It is concluded that ciprofloxacin hydrochloride release from the floating drug delivery system was sustained and the system were completely depleted the drug within 2hrs. Sodium alginate, when incorporated as a part, modulated the drug release significantly. The result indicates that by changing the percentage of polymers and amount of pore forming agent plays a vital role in the release kinetics of the drug. In this way, the 50% of both SAPEG and SAEnriched PEG are sufficiently strong and also uptake appreciable amount of the drug, whereas the 14% of both SAPEO and SA Enriched PEO beads shows lower drug uptake, higher stability and lower the release kinetics. During digestion, the drug loaded polymers will be digested and absorbed by the body and at that time the drug left out in the matrix will be released and some portion of it will be absorbed.

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Ethical Issues

Not applicable.

Conflict of Interest

The Authors report no declaration of interest.

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