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Design and study of formulation variables affecting drug loading and its release from Alginate beads

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Abstract:
The development of alginate beads as a drug carrier system is considered to be more attractive because of its biocompatibility, mucoadhesive property, and its ability to deliver drug particularly in the intestinal pH. The preparation of alginate beads by ionic gelation method avoids the usage of toxic organic solvents and considered to be relatively economical method. However its development is mainly hindered by two major limitations i.e., poor drug loading due to drug leaching during preparation and rapid release of drug from the system in the intestinal pH. This study was mainly focused on the development of alginate beads by ionic gelation method with a special emphasis taken in order to minimize the limitations of alginate beads. The concentration of sodium alginate was kept at the minimum level (2% w/v), required for the formation of beads and the effect of addition of guar gum and poly (vinyl alcohol) (0.5% w/v), respectively to the sodium alginate solution, and the addition of poly (vinyl pyrrolidone) (2%w/v) to the $CaCl_2$ solution on the drug loading and in-vitro release characteristics was studied. The results shown that the addition of guar gum, poly (vinyl alcohol) and poly(vinyl pyrrolidone) significantly improved drug loading and release characteristics, and the better drug loading and release characteristics were obtained with the formulation containing 0.5% poly(vinyl alcohol) and 2% poly(vinyl pyrrolidone).
Keywords: Alginate beads, Drug leaching, Guar gum, Poly (vinyl alcohol) (PVA), Poly (vinyl pyrrolidone) (PVP).

Introduction:

In recent years greater attention has been focused in designing the controlled drug delivery systems because of the complete understanding of its therapeutic advantages. The controlled release formulations offer numerous advantages over the conventional dosage forms which includes, reduction in dosage frequency, increase in efficiency of the drug, minimizing adverse effects of the drug by localizing it in specific target area, maintaining plasma concentration of the drug with in therapeutic range. So, it provides better patient compliance and convenience [1, 2].

Alginate beads are one of the particulate delivery systems that are developed to protect drug from the acidic environment, to improve bioavailability and to target drug at specific site, so as to improve patient compliance. Alginate is a hydrophilic polymer extracted from brown algae. It is an anionic linear polysaccharide composed of alternative blocks of 1-4 linked α-L-guluronic and β-D-mannuronic acid residues [3]. Alginate has been widely used in drug delivery because of their abundance in nature, biocompatibility [4], bio adhesiveness [5, 6, 7] and pH sensitivity [8, 9, 10](alginate shrinks at lower pH and the encapsulated drugs are not released).

The alginate beads can be prepared by ionic-gelation method under an extremely mild environment using non-toxic reagents. Alginate has the ability to form gel with divalent cations such as Ca^{2+}, Sr^{2+}, or Ba^{2+}. Alginate forms a reticulated structure on contact with calcium ions and this network can entrap the drug. Besides the simplicity and use of non-toxic reagents, this preparation procedure has a major limitation i.e., drug loss through pores of beads during its preparation [11]. Alginate normally shrinks at the acidic pH and the drug is released slowly but once it reaches the intestinal pH the drug is rapidly released because of its hydrophilicity, this is another limitation of this system.

Several research works have been carried out by the researchers to overcome the limitations of the alginate beads, like cross linking alginate with aldehydes [12], chemical modification of alginate [13], forming complexes with other polycations

(chitosan [14, 15], poly-L-lysine [16, 17], dextran [18], amino-poly oxyethylene [19]). The main objective of this present study is to prevent drug leaching during preparation and to improve the drug release time. In this study, a non-ionic polymer polyvinyl pyrrolidone is added to the crosslinking agent with a hope that increase in viscosity of cross linking solution may prevent the drug leaching. Previously no work has been carried out to the best of our knowledge using PVP in $CaCl_2$ solution to improve drug loading. The effect of PVP on drug loading and release characteristics was studied. Zidovudine, a hydrophilic, anti-retroviral drug with low oral bioavailability is used as a model drug. The effect of incorporation of Guar gum and poly (vinyl alcohol), respectively to the sodium alginate solution on drug loading and release characteristics were further analyzed.

Materials and Methods:

Materials

Sodium alginate and Guar gum powder was purchased from Himedia lab (Mumbai, India), Zidovudine and Poly(vinyl alcohol) (PVA) was obtained from Sigma Aldrich chemie (GmbH, Germany), Poly(vinyl pyrrolidone) (PVP k-30) was purchased from Sisco Research laboratory (Mumbai, India), Calcium chloride was purchased from Rankem laboratories (Mumbai, India).

Preparation of Alginate beads

The alginate beads were prepared by ionic gelation technique. Sodium alginate (2% w/v) was dissolved in 25ml of deionised water by stirring, using over head stirrer (Remi instruments, Mumbai), zidovudine was added to the sodium alginate mixture and stirred for 5-10 minutes at 1000 rpm to obtain a homogenous mixture. The mixture was kept aside until the air bubbles disappears completely and then it was extruded drop wise into 50 ml of 1% calcium chloride solution through the 26 gauge needle (Formulation A1). Similarly the drug alginate mixture was extruded into $cacl_2$ solution containing 2% w/v PVP (Formulation A2). 0.5% w/v Guar gum (Formulation A3) and 0.5% w/v PVA (Formulation A4) were added respectively to the alginate mixture and extruded drop wise into $CaCl_2$ solution with 2%w/v PVP. After 1 hour curing time calcium chloride solution was decanted and the beads were filtered and dried at 60° C for 2 hours in a hot air oven.

Fourier Tr ansform Infrared measurements (FTIR)

The drug polymer interactions were studied by infrared spectroscopy. The IR spectra were recorded in the wavelength region of 400 cm^{-1} - 4000 cm^{-1} for pure zidovudine, sodium alginate, plain alginate beads, and drug loaded alginate beads using Thermo Nicolet, Avatar 320 (USA) instrument.

Scanning Electron Microscope (SEM)

The morphology and surface structure of the beads were observed using SEM photographs taken with Jeol JSM-6360 instrument. The beads were made conductive by sputtering thin coat of platinum under vacuum using Jeol JFC-1600 auto fine coater and then the images were recorded at magnification of 80 x.

Determination of drug content of the beads

The known amount of beads was transferred into 250ml beaker containing 100ml phosphate buffer pH 7.4 and stirred using overhead stirrer for the complete swelling and bursting of the beads, then the solution was filtered through 0.45µm membrane filter and the concentration of drug in the solution was determined at 264 nm after appropriate dilution with phosphate buffer pH 7.4, using UV spectrophotometer (Perkin Elmer, Lambda EZ 201). The drug loading and entrapment efficiency was then calculated as:

$$\text{Percentage drug loading} = \frac{\text{Amount of drug in bead}}{\text{Amount of bead taken}} \times 100$$

$$\text{Percentage entrapment efficiency} = \frac{\text{Practical drug}}{\text{Theoretical drug}}$$

In- vitro drug release

The in-vitro drug release from the beads was studied in buffer pH 1.2, 6.8, and 7.4, using shaking incubator at 37° C with a shaking speed of 50 rpm/min. The known quantity of alginate beads (100 mg) from each formulation was transferred into 250 ml conical flasks containing buffer pH 1.2 placed in the shaker, the pH of the buffer was adjusted to 6.8 and 7.4, respectively at 2 hr interval. The samples of 5 ml aliquots was withdrawn at predetermined time intervals and the same volume of fresh preheated buffer medium was replaced into the conical flasks to maintain sink condition throughout the experiment. The withdrawn aliquots was filtered and analyzed for drug content using UV spectrophotometer at 264 nm after suitable dilution with respective buffer solutions.

Results and Discussion:

FTIR studies

The IR spectra of the substances used in the formulation and the prepared beads were shown in the Figure 1-4.

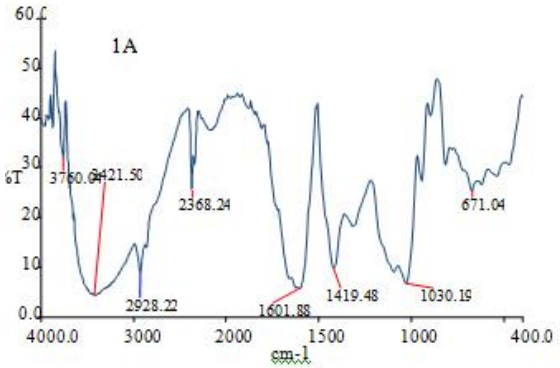

Fig.1. IR spectra of sodium alginate

The IR spectra of the prepared drug loaded beads shown the peaks at 1030 cm^{-1}, 1425 cm^{-1}, 1610 cm^{-1} corresponding to alginate, and peaks at 1090 cm^{-1}, 2365 cm^{-1}, 3411 cm^{-1} corresponding to the drug. This confirms that there is no interaction between the drug and the substances used in the formulation.

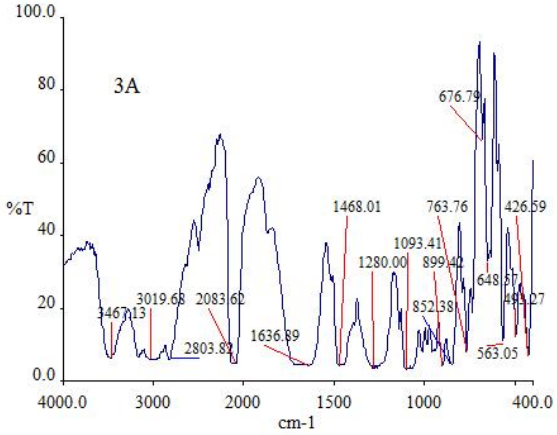

Fig.2. IR spectra of zidovudine

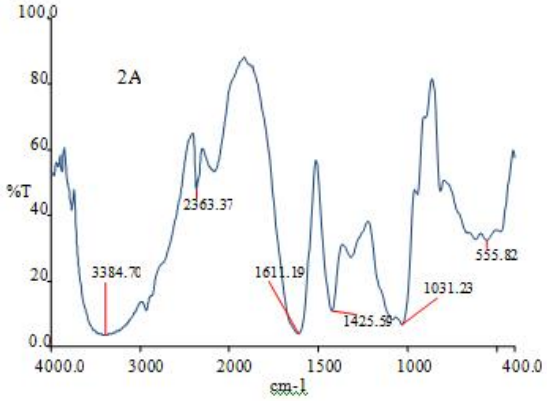

Fig.3. IR spectra of plain beads

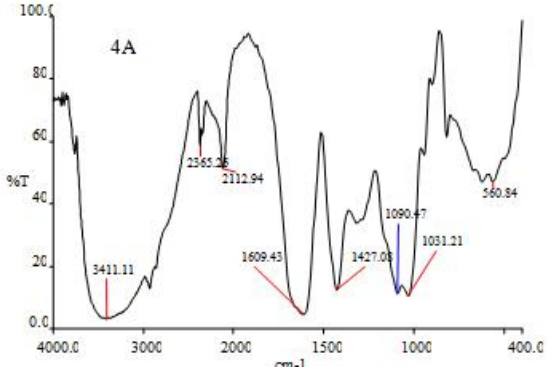

Fig.4. IR spectra of drug loaded beads

SEM analysis

SEM photograph taken at 80 x magnification was shown in Figure 5. The photograph shows that the drug loaded beads were almost spherical in shape and have a rough surface.

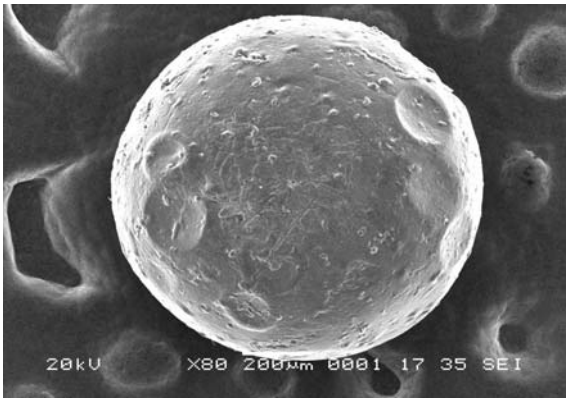

Fig.5. SEM photograph of drug loaded bead (A4) at 80 x

Drug loading and entrapment efficiency

The drug loading and entrapment efficiency of different formulations were shown in Table-1.

Table 1: Drug loading and entrapment efficiency for the formulated beads

Formulation code	% Drug loading	Entrapment efficiency (%)
A1	2.28 ± 0.26	6.84 ± 0.17
A2	3.67 ± 0.45	11.01± 0.09
A3	5.12 ± 0.34	15.36 ± 0.11
A4	5.57 ± 0.22	16.72 ± 0.12

*All values are expressed as mean ± S.E; n= 3

The formulation A4 with 0.5% w/v PVA and 2% w/v PVP shows the better drug loading efficiency compared to the other formulations.

Effect of PVA and Guar gum

The mixing of alginate with other polymers such as neutral gums, Chitosan etc… was found to solve the problem of drug leaching [20]. The results show that the drug loading was increased with the formulation containing PVA and Guar gum, respectively compared to the plain alginate beads. This may be due to increase in viscosity of the bead preparation solution on addition of these substances. So that more amount of drug is trapped by the polymer mixture and hence, the entrapment efficiency was increased. Similar result was found in the literature [21].

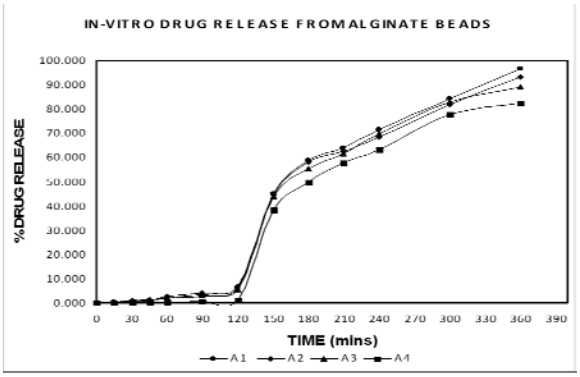

Fig.6. In – vitro drug release from the formulations

Effect of PVP

The addition of PVP to the crosslinking solution has shown significant increase in the drug loading efficiency. This may be due to the increase in viscosity of the crosslinking solution by PVP, so that it might have been blocked the pores of the alginate beads and hence, it might have been prevented the drug leaching to the crosslinking solution. The incorporation of PVP (2% W/V) and PVA (0.5% W/V) improved the loading efficiency up to 10% compared to the plain bead formulation.

In-vitro drug release

The drug release from the alginate beads were studied in buffer solutions at pH 1.2, 6.8 and 7.4 at 37^{o}C. Figure 6, shows the drug release in respective buffer solutions from different formulations. The drug release from the beads is low in acidic pH 1.2 for 2 hrs. This is because in acidic pH alginate is protonated into insoluble form of alginic acid and have less swelling rate. The release rate was found to be rapid at pH 6.8 and 7.4 [21]. The Guar gum and PVP does not have much influence on the control of release rate because of its hydrophilicity. The formulation A4 shows significant decrease in the release rate, this may be due to the effect of PVA, which has a small hydrated volume compared to alginate and forms a compact network of

macromolecular chains with alginate. Thus, the diffusion of drug from the bead is reduced compared to the plain alginate beads.

Conclusion:

The drug loading was found to be increased on extruding the alginate mixture into crosslinking solution with 2% w/v PVP, the further increase in the drug loading was achieved on incorporation of 0.5% w/v of PVA and Guar gum, respectively onto alginate mixture and extruding into PVP-$CaCl_2$ solution. The drug release rate was well controlled in the formulation with PVA. The further improvement in drug loading and release time may be achieved by increasing the concentration of PVP and PVA, respectively. Hence, PVA and PVP can be used in the formulation of alginate beads to achieve better drug loading and controlled release rate.

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