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Effect of PH of $AlCl_3$ Solution on Drug Entrapment Efficiency of IPN Beads

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Abstract

Interpenetrating network (IPN) beads of sodium carboxymethyl xanthan and pectin were prepared by ionotropic gelation method using AlCl3 as a cross-linking agent. The Diltiazem Hydrochloride loaded beads were produced by the dropwise addition of the mixture of drug, sodium carboxymethyl xanthan and pectin into AlCl3 solution of different pH (2, 4, 6 and 8). Diltiazem Hydrochloride is a calcium channel blocker belonging to the benzothiazepine family. It is widely prescribed for the treatment of hypertension and angina. Bioavailability of Diltiazem Hydrochloride is 30 to 40% owing to an important first pass metabolism. Therefore, it is a suitable model candidate for sustained release formulation. The entrapment efficiency of the drug was carried out in pH 6.8 buffer solution. It was observed that the entrapment efficiency of the beads increased from 19.51% to 50.80% by increasing the pH of the AlCl3 solution from 2 to 8. Drug release studies showed that beads prepared with the drug in buffer solution provided some sustained release characteristics.

Keywords: Diltiazem HCl, IPN Beads, Drug Entrapment, Swelling Ratio, Drug Release

Contents

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1. Introduction

IPN consists of two polymers, each in network form, which can be cross-linked in the presence of each other to give a three dimensional network structure and hence, combine the properties of two cross-linked polymers in a network form. IPNs are thus emerging as a rapidly developing branch of polymer blended technology and are finding applications in artificial implants, dialysis, membranes, and drug delivery systems and in agricultural field[1]. Pectin (PEC), a natural polysaccharide, It's applications in the field of sustained release formulations can be used. Pectin is a heterogeneous anionic polysaccharide present in the cell wall of most plants.

It is non-toxic, almost totally degraded by colonic bacteria and is not digested by gastric or intestinal enzymes. Pectin forms water-insoluble complexes with several drugs and may be useful additive for sustained-release preparations. Although xanthan gum, a polysaccharide obtained from Xanthomonas campestris, can not form gel

beads, its Na-salt of carboxymethyl derivative is able to form gel beads through ionotropic gelation with Al3+ ions. Sodium carboxymethyl xanthan (SCMX) beads have been found capable of encapsulating albumin and diltiazem hydrochloride. Diltiazem hydrochloride is a benzothiazepine calcium channel blocker. It is widely used in the treatment of angina pectoris and hypertension, especially in children and elderly patients[2]. The drug has a relatively short half-life (3–5 h) and is usually administered 3–4 times daily in the form of an immediate release formulation. Based upon these properties, there is a great need for the introduction of a new controlled release formulation of DTZ. A sustained release formulation may be necessary to reduce the frequency of the drug administration and thus improve patient compliance.

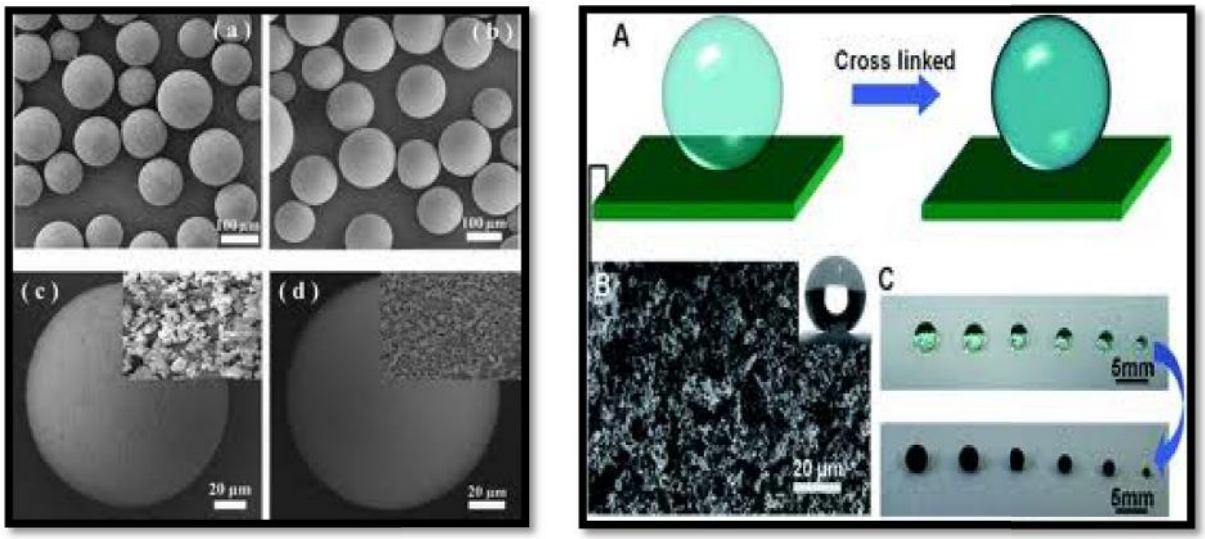

Figure 1. **SEM micrographs IPN BEADS beads**

2. Materials and Methods

Materials

Diltiazem HCl was obtained as gift samples from the, SLMIOP Amgaon., , India. Pectin (mole. Wt. 30,000 – 1,00, 000) was obtained from Trade N Trade Tumsar (Glaxo), Xanthan gum (mole. Wt. 6 Million), Monochloroacetic acid, Sodium hydroxide was obtained from SLMIOP Amgaon. Sodium carboxymethyl Xanthan Gum (SCMX) from Xanthan Gum was synthesized in laboratory.

Preparation of Sodium Carboxymethyl Xanthan (SCMX)

Required amount of xanthan gum was dispersed in ice cold solution of 45% w/v sodium hydroxide. The dispersion was kept at 5-8°C with continuous stirring for 1h. Monochloroacetic acid solution (75% w/v) was added with stirring in the reaction mixture and the temperature was raised slowly to 15-18°C. After 30 min, the temperature was raised to 75°C and maintained for additional 30 min. Followed by the reaction mixture was, then cooled to room temperature, cut into small pieces and dried at 60°C. The dried product was milled, washed with 90% v/v methanol and again dried.

Determination of degree of substitution

About 500 mg of synthesized gum was dispersed in 5 ml of 80% methanol. Then add 2-3 drops of conc. HCl was added. It was then stirred for 2-4 hours. After that pure methanol was added and filtered through it. The residual mixture was washed with 80% methanol until washing showed neutrality to litmus paper and dried[3]. Then about 200 mg accurately weighed dried sample was taken in a conical flask and to that 1.5 ml 70% methanol was added. It was then allowed to stand for few minutes. Then 20ml water was added and 5 ml 0.5 N sodium hydroxide was added. The mixture was shaken until the sample was dissolved. The solution obtained thus was back titrated with 0.4N HCl, using phenopthalein as indicator. The degree of substitution was calculated as:

$$DS = 0.162A/1 - 0.058A$$

Where A= (mEq/L) Mili equivalents of sodium hydroxide required per gram of sample**.**

Preparation of Interpenetrating Network (IPN) Bead

Required amount of diltiazem hydrochloride (DTZ) was homogenously dispersed in an aqueous solution of SCMX and PEC. The resulting dispersion was extruded through 21 G flat-tip hypodermic needle into AlCl3 solution[4]. The AlCl3 solution was prepared in different pH solution (pH 2,4,6 and 8). Gelation of the beads was carried out for 30 minutes of time. The beads were, then collected by filtration,

Table 1. Composition of sodium carboxymethyl xanthan (SCMX) and pectin (PEC) IPN beads

Formulation	SCMX% : PEC%	Drug load (% w/w of total polymer)	Gelation time (hr.)	Concentration of AlCl3 (% w/v)
F1(pH 2.0)	1 : 1	40	0.5	4
F2 (pH 4.0)	1 : 1	40	0.5	4
F3 (pH 6.0)	1 : 1	40	0.5	4
F4 (pH 8.0)	1 : 1	40	0.5	4

3. Evaluation Parameters

Drug Entrapment Efficiency

IPN beads were accurately weighed in phosphate buffer (PB) solution (pH 6.8), and shaken for 2h on a mechanical shaker[5]. The beads were crushed and add further 10 ml PB solution and shaken for 1h. The solution was filtered and an aliquot following suitable dilution was analyzed at 236 nm in a UV-Visible spectrophotometer and the content of the beads was determined using a calibration curve constructed using PB solution of pH 6.8.

$$\text{DEE (\%)} = (\text{Determined drug content}/\text{Theoretical drug content}) \times 100$$

Swelling Study

The swelling study of IPN beads was studied in different pH solution (PH 1.2 and pH 6.8). The beads were removed at different times by filtration and blotted carefully to remove excess surface water. The swollen beads were weighed. The swelling ratio of the beads was determined using the following formula:

$$\text{Swelling ratio} = (\text{Weight of swollen beads-weight of dry beads})/\text{weight of dry beads}$$

Drug release study

In-vitro drug release study was carried out in 500ml acidic solution (pH 1.2) and in PB solution (pH 6.8) dissolution rate test apparatus (model Electrolab) at 37^0C. Undiluted or suitably diluted withdrawn samples were analyzed spectrophotometrically at **236 nm** for acidic solution and **236 nm** for PB solution[6].

4. Results and Discussion

Drug Entrapment Efficiency

IPN beads having 40% w/v of diltiazem HCl were prepared using concentration of polymers (1:1) and gelling for 0.5 h in 4% w/v AlCl3 solution. In cross-linking solution of pH 2 to pH 8, the drug entrapment was found to 19.51%, 33.30%, 44.93%, 50.80%[7]. In these, the drug loading and DEE was increased by increasing the pH in solution of AlCl3. The solubility of diltiazem HCl in acidic solution is more, gelation medium may cause decreases DEE in acidic pH but increases in basic pH[8].

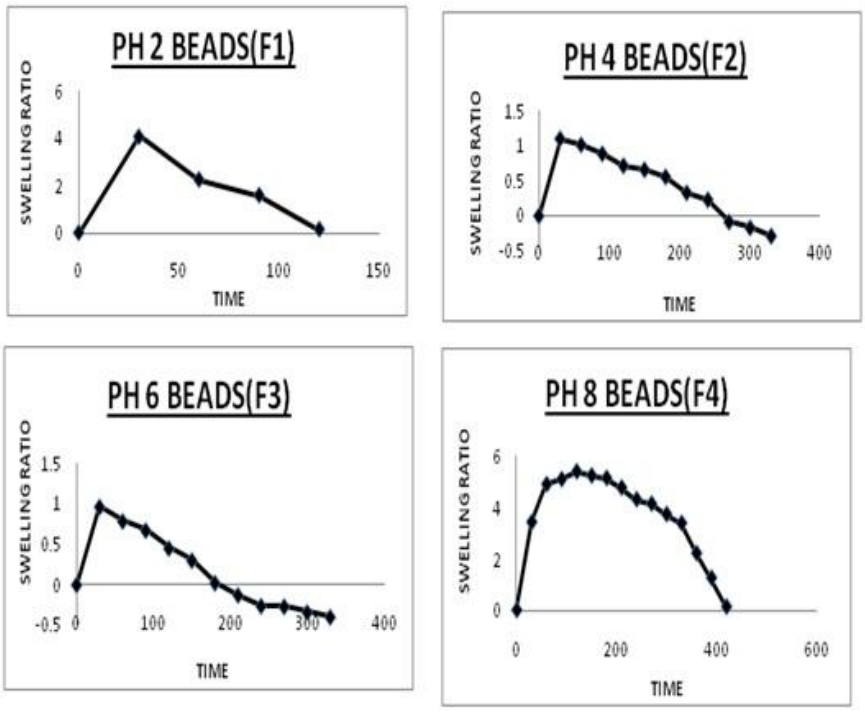

Figure.2

Table.2

Formulation	Drug loading (%)	DEE (%)
F1(pH 2.0)	3.272	19.51
F2 (pH 4.0)	5.568	33.30
F3 (pH 6.0)	7.454	44.93
F4 (pH 8.0)	8.545	50.80

Swelling Study

In these study, the swelling ratio of IPN beads in acidic solution (pH 1.2) and PB solution (pH 6.8) of pH 8 beads was more as compared to pH 2,4 and 6. The swelling ratio of these four formulations (F1 to F4) in PB solution (pH 6.8) was more as acidic solution (pH 1.2).

5. Conclusion

SCMX-PEC interpenetrating network beads were prepared by ionotropic gelation method using Al3+ ions as cross-linking agent for both the polymers. The DEE was found to 19.51%, 33.30%, 44.93%, 50.80%. *The results of the study indicate that high drug-loaded IPN beads can be prepared using SCMX and PEC by ionotropic gelation process in which DEE of F4 is reasonably high as compared to F1, F2 and F3.* Finally, it could be concluded that the proper selection of formulation conditions are very important to achieve high entrapment efficiency and to control the release of DTZ from SCMX-PEC beads.

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