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Effect of Polymer and Cross Linking Agent on *In Vitro* Release of Quercetin from Microbeads

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ABSTRACT

This investigation describes the effect of polymers and cross linking agent on in vitro release of quercetin from sodium alginate beads. The formulations were prepared by utilizing 2^3 factorial designs. Hydrophilic polymer hydroxy propyl methyl cellulose (15- 24 cps) was used for its gel forming and release controlling properties. The effect of different concentrations of cross linking agent (calcium chloride) on entrapment efficiency and drug release profile were investigated. The beads were prepared by changing the experimental variables such as concentration of polymer and cross linking agent in order to optimize independent variables. The bead formulations were prepared by Ionotropic gelation method. Quercetin was used as model drug. The prepared beads were evaluated for its particle size, drug entrapment efficiency and in vitro release. The entrapment efficiency and particle size was between the range of 16.62% to 72.47% and 0.726 ± 0.0088 mm to 1.179 ± 0.0547 mm respectively. Results reveal that on increasing polymer concentration and cross linking agent, entrapment efficiency of drug increases with decrease in its release rate. The result indicates the possibility of getting controlled release system by varying the concentration of polymer and cross linking agent.

KEYWORDS: *Sodium Alginate, Calcium Chloride, Ionic Cross linking technique, Quercetin, Factorial Design, Beads*

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INTRODUCTION

Alginates are naturally occurring substances obtained from brown seaweed and algae. It is used as a vehicle for controlled drug delivery. Alginates can be considered as block polymer which is made up of mannuronic acid, glucuronic acid and mannuronic – glucuronic blocks. [1, 2] Addition of divalent ions (Ca^{2+}) and polyvalent ions to alginate solution cause gel formation due to cross linking. Alginate has several unique properties that enable it to use as matrix for controlled release study. [3] These includes: comparatively inert aqueous environment within matrix, high gel porosity which allows high diffusion rates, dissolution and biodegradation of system under normal physiological condition. [4, 5] Beads are the microparticles that are spherical in shape and entrap drug within it. The active substance of this investigation is quercetin, which is flavanoid glycoside and is used for a variety of indications like inflammation, cancer and as a gastroprotective agent. [6] Oral bioavailability of quercetin is 2% due to first pass metabolism. Its $t_{1/2}$ being 0.1-6 hours [7] it is used as model drug for the present investigation.

The main objective of present study was to evaluate the effect of various concentrations of polymer and cross linking agent on *in vitro* release from beads by using factorial design.

MATERIAL AND METHODS

Materials: Sodium alginate, Calcium chloride ($CaCl_2$) and Hydoxy propyl methyl cellulose (HPMC) were obtained from S.D. Fine chem. Ltd. Quercetin

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was purchased from S.D. Fine chem. Ltd. All other chemicals are of analytical grade.

Methods:

Factorial design: Alginate beads were prepared based on 2^3 factorial designs [1, 2]. The independent variables are sodium alginate concentration (X_1) and calcium chloride concentration (X_2). Drug entrapment efficiency (Y_1) and *in vitro* drug release (Y_2) are response parameters as dependent variables. (Table 1)

Preparation of alginate gel beads: Alginate gel beads were prepared by dissolving sodium alginate in distilled water with agitation to have different concentration (1%, 2%, 3% w/v). 2% HPMC was also added in sodium alginate solution. Quercetin was dissolved in methanol and then methanolic solution of quercetin was added to alginate solution. Quercetin-alginate solution was added drop wise using 22G hypodermic needle fitted with syringe into different concentration of $CaCl_2$ solution (2.5%, 5%, and 10%) at room temperature with continuous magnetic stirring. After 5min of contact time, the beads were filtered and air dried. [2]

EVALUATION OF BEADS

Particle size determination: Particle sizes of 30 beads were measured using micrometer for each formulation and mean particle size was determined. [8]

Determination of entrapment efficiency: The volume obtained after filtering the calcium chloride solution was subjected to UV spectrophotometer and concentration was obtained at 375.5 nm. The drug entrapped is calculated by using formula. [9]

$$\text{Entrapment efficiency} = \frac{\text{Total dose} - \text{Non entrapped dose}}{\text{Total dose}} \times 100$$

***In vitro* drug release**: The release of quercetin was studied in 900 ml phosphate buffer saline (pH 7.4) as dissolution media using USP II (paddle type) dissolution apparatus. [10, 11] The samples were withdrawn at an interval of 15, 30, 45, 60, 120, 240, 300 min and replaced simultaneously with fresh buffer. The collected samples were assayed with the help of UV spectrophotometer at 375.5 nm. All measurements were carried out in triplicate and average values plotted as shown in Figure 1.

RESULTS AND DISCUSSION

Particle size: The formed beads were almost spherical as shown in Figure 2. The mean particle size of nine formulations was between 0.726 ± 0.0088 mm to 1.179 ± 0.0547 mm (mean ± standard deviation). It was found that the mean particle size was different among formulations and no significant variation in particle size of beads prepared by using different cross linking agents was observed.

Effect of sodium alginate concentration:

As concentration of sodium alginate increases, it results in increased entrapment of drug from 45.23% to 70.23%. This is due to more polymer concentration which will entrap more amount of drug. As concentration of sodium alginate increases, release of drug decreases from 87 to 64.36%. This may be attributed to more polymer concentration due to which slow release is observed in 6 hours. This is clearly illustrated in Figure 3.

Effect of different calcium chloride concentration:

The entrapment efficiency was found to be more in high calcium chloride concentration from 48.67% to 66.7%. This may be attributed to more cross linking, which will entrap high amount of drug. As concentration of calcium chloride increases, the *in-vitro* release was found to be decreases from 83.03% to 74.03%. More cross linking will sustain the release of drug and more amount of drug will be entrapped as shown in Figure 4.

CONCLUSION

The effect of polymer and cross linking agent on *in vitro* release of sodium alginate beads was well

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investigated. The results show that as the concentration of polymer and cross linking agent increases, entrapment efficiency increases and release rate decrease. Thus, it can be concluded that this technique could be used for development of sustained release dosage forms.

Table 1: Formulation Table

Factors	Low(-1)	Medium (0)	High (+1)
Sodium alginate	1%	2%	3%
Calcium chloride	2.5%	5%	10%

Table 2: 2^3 Factorial design table

Batches	Sodium alginate concentration (X_1)	Calcium chloride concentration (X_2)	Entrapment Efficiency (Y_I) (%)	*In vitro* drug release (Y_2) (%)
F1	-1 (1%)	-1 (2.5%)	16.62	89
F2	-1 (1%)	0 (5%)	57.89	87
F3	-1 (1%)	+1 (10%)	61.18	85
F4	0 (2%)	-1 (2.5%)	64.26	84
F5	0 (2%)	0 (5%)	65	82
F6	0 (2%)	+1 (10%)	66.312	81
F7	+1 (3%)	-1 (2.5%)	68.18	76.109
F8	+1 (3%)	0 (5%)	69.89	60.89
F9	+1 (3%)	+1 (10%)	72.62	56.109

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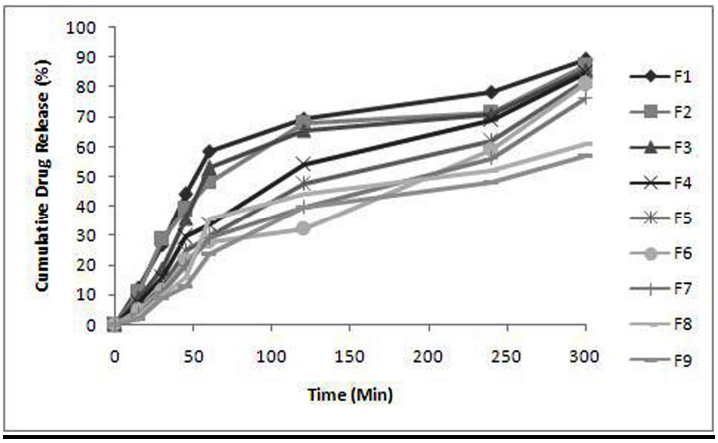

Figure 1: *In vitro* drug release profiles of nine formulations of sodium alginate beads

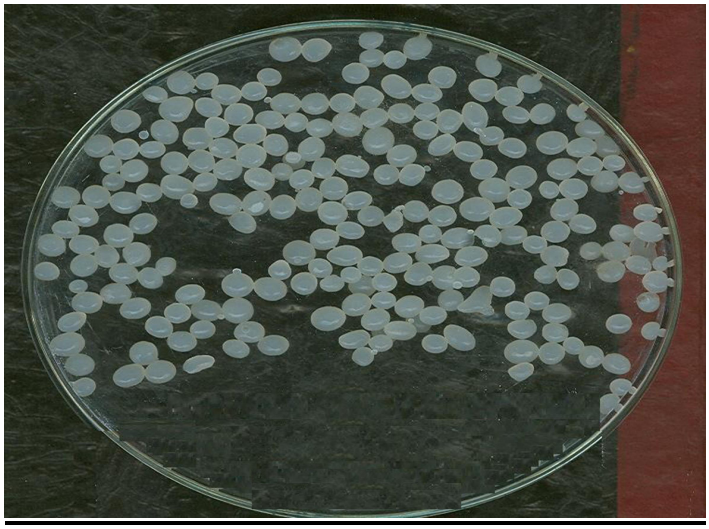

Figure 2: Photograph of Sodium alginate beads

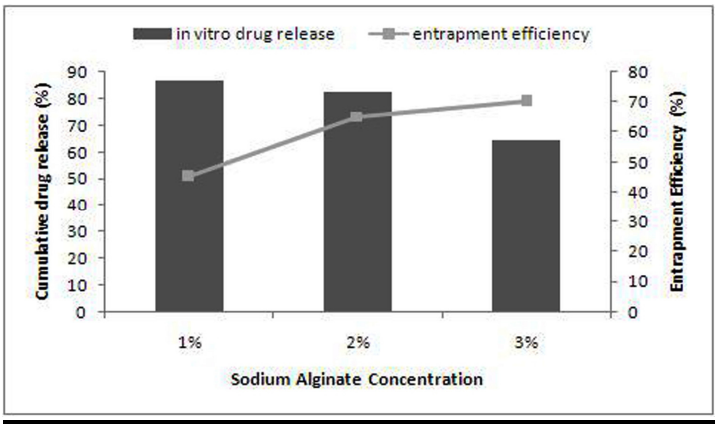

Figure 3: Effect of polymer concentration on drug release and entrapment efficiency

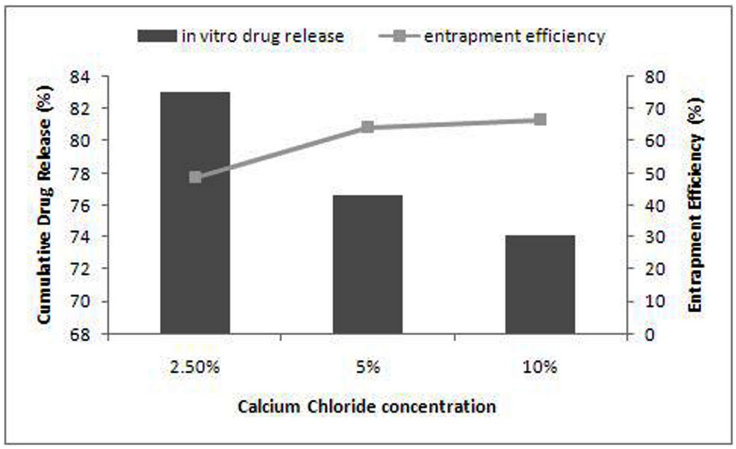

Figure 4: Effect of cross-linking agent concentration on drug release and entrapment efficiency

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