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Alginate Beads Prepared by Ionotropic Gelation Technique: Formulation Design

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Abstract

The present study involves the preparation of alginate beads loaded with ranitidine hydrochloride by employing ionotropic gelation technique. The beads were prepared by varying the formulation and processing parameters such as concentration of calcium chloride solution and curing time. Effect of calcium chloride concentration and curing time on drug entrapment efficiency was investigated. It was observed that the variation in the concentrations of calcium chloride solution had no considerable effect on the encapsulation efficiency of hydrophilic drug. Moreover, it was also found that curing time influenced the leaching of hydrophilic drug.

Keywords: Alginate beads, ranitidine hydrochloride, cross linking agent, ionotropic gelation.

Introduction

Numerous encapsulation techniques based on water-insoluble polymeric materials necessitate organic solvents to solubilize the polymers. However, the safety hazards, possible toxicity, and high costs associated with organic solvents make the utilization of organic solvent-free systems desirable[1,2]. Much research endeavours have been concentrated worldwide on the development of hydrogel beads using natural polymeric carriers as they do not necessitate organic solvents, easily available, and also qualified for a number of chemical modifications. Drug loaded hydrogel beads offer an inert environment within the matrix and encapsulation is usually achieved in a medium free of organic solvents[3].

In the present study, ranitidine hydrochloride as a model drug was incorporated into alginate microparticles by utilizing the ionotropic gelation technique. Ranitidine hydrochloride is a H_2 receptor antagonist used in the treatment of gastric ulcers and Zollinger-Ellison syndrome. It has short half life and low bioavailability[4-8]. Sodium alginate is an anionic linear polysaccharide containing β-1, 4-linked D-mannuronic acid and α -1, 4-linked L-guluronic acid residues arranged randomly along the chains. It has unique property of being instantaneously gelled when contacted with multivalent cations which has been employed as a facile method to fabricate alginate based drug delivery carriers. Alginate has also attracted increasing attentions due to its excellent biocompatibility, mucoadhesive aspect, biodegradability and mild gelation conditions[9-13]. Calcium is the main cation widely utilized because it is considered as clinically safe, easily accessible and economical[14]. The objective of present investigation was to prepare alginate beads of ranitidine hydrochloride by varying the concentration of cross linking agent and curing time. Effect of calcium chloride concentration and curing time on the drug entrapment efficiency was studied.

Methodology

Preparation of calcium alginate beads: The beads were prepared by utilizing ionotropic gelation technique. Alginate solution was prepared by dissolving sodium alginate in distilled water and the solution was stirred thoroughly. Ranitidine hydrochloride was dissolved / dispersed uniformly in the alginate solution under continuous stirring. The stirring was continued after complete addition until a uniform dispersion was obtained. The resultant homogenous bubble free alginate dispersion was extruded using a 21G syringe needle into the gelation medium, which was kept under stirring to improve the mechanical strength of the beads and also to prevent aggregation of the formed beads. The gelation medium was prepared by dispersing different concentrations of calcium chloride solution (0.5%, 1.0% and 2.0%) containing acetic acid glacial.

The gel beads formed were left in the solution with gentle stirring for different time (10 min., 20 min. and 30 min.) at room temperature to be cured. Afterwards, the beads were collected, washed with distilled water twice and dried subsequently for further study[15-16].

Estimation of drug entrapment efficiency: An accurately weighed quantity of the dried beads was crushed and dissolved in simulated gastric fluid (pH 1.2) by stirring with magnetic stirrer at 37 ± 0.5°C. The drug content in the filtered supernatant was estimated spectrophotometrically following suitable

dilutions. The drug entrapment was then determined according to the following relationship[17-18].

$$\text{Drug entrapment efficiency (\%)} = \frac{\text{Actual drug content}}{\text{Theoretical drug content}} \times 100$$

Results and Discussion

Ranitidine hydrochloride alginate beads were successfully accomplished by ionotropic gelation technique. Sodium alginate was selected as a polymer for the preparation of beads owing to its excellent biocompatibility, biodegradability, non-toxicity, non-irritancy as well as compatibility with drug. The carboxylic acid groups on alginate units attribute negative charges, and thus being able to interact electrostatically with positively charged molecules to form hydrogel beads. Divalent cation (Ca^{2+}) induces gelation by binding mainly to the guluronic blocks of alginates.

Drug entrapment efficiency: Encapsulation efficiency for all calcium alginate beads was found to be low. This can be explained due to the good hydrophilic attribute of a drug. Moreover, in the absence of coating solution or any other additives which imposes a hydrophobic barrier towards the drug escaping; the developed beads with high degree of porosity resulted in the diffusion of drug during the gelation process. It is also pertinent to mention that cross-linking between the sodium alginate and calcium chloride might be insufficient in the absence of coating solution.

Keeping the alginate concentration and curing time fixed, it has been observed that the variation in the concentrations of calcium chloride solution had little effect on the encapsulation efficiency of drug as shown in table-1. Majority of the drug diffuses out during the gelation process. Low entrapment efficiency of alginate beads cross-linked with calcium ions could be attributed to the formation of porous beads ensuring the diffusion of the drug out of the beads during gelation.

Table-1
Formulation design of alginate beads prepared with varying concentrations of calcium chloride solution

Formulation	Calcium Chloride Concentration (% w/v)	Encapsulation Efficiency (%)
A1	0.5	31.48 ± 2.495
A2	1.0	30.11 ± 3.130
A3	2.0	31.23 ± 2.931

Data are presented as mean value ± SD (n=3)

Increased concentration of calcium chloride resulted in comparable encapsulation efficiency. These observations revealed that the calcium chloride concentration of 0.5% (w/v) was sufficient to form the gel network.

Table-2
Formulation design of alginate beads prepared by employing different curing time

Formulation	Curing Time (min.)	Encapsulation Efficiency (%)
B1	10	32.04 ± 3.945
B2	20	27.59 ± 2.275
B3	30	24.13 ± 3.095

Data are presented as mean value ± SD (n=3)

Effect of different curing time on the entrapment efficiency is depicted in table-2. Keeping the alginate concentration and calcium chloride concentration fixed, it has been observed that with the increase of curing time, drug entrapment efficiency decreased accordingly. This might be due to the increase in curing time leads to the increase in leaching of hydrophilic drug. The entrapment efficiency decreased with an increase in curing time owing to the increased release of drug from the matrix at longer exposures. Therefore, during ionotropic gelation method, curing time can be a key factor governing the entrapment efficiency.

Conclusion

In the present work, alginate beads of ranitidine hydrochloride were easily and successfully formulated by employing ionotropic gelation technique. It has been observed that the loose network of beads results in a major limitation of drug leakage through the pores during the gelation process. Therefore, it is anticipated that mechanical properties and permeability of calcium alginate beads can be effectively improved by the incorporation of coating solution or any other additives such as suitable polymer blends which impose a hydrophobic barrier towards the escaping of drug from the matrices.

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