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Evaluation of the drug-polymer interaction in calcium alginate beads containing diflunisal

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Calcium alginate gel beads have been developed in recent years as a unique vehicle for oral drug delivery due to their excellent biocompatibility, biodegradability, simple method of preparation, abundant sources, low cost and minimal processing requirements. The objective of this study was to evaluate the drug-polymer interaction in calcium alginate beads containing diflunisal. Diflunisal loaded calcium alginate beads were successfully prepared by ionotropic gelation from solution of sodium alginate and diflunisal into calcium chloride solution. The weight ratio of drug to polymer was selected as 1:1. The calcium alginate beads were characterized by size, Scanning Electron Microscopy (SEM), weight uniformity and drug entrapment efficiency. The existence of a possible interaction between diflunisal and the calcium alginate was investigated by Differential Scanning Calorimetry (DSC), Powder X-Ray Diffraction (PXRD) and Fourier Transform Infra-Red (FTIR) analysis. Drug loaded beads were spherical to oval in shape with low drug entrapment efficiency. The drug was found to be present inside the beads as crystalline to semicrystalline form with no significant physical or chemical interaction between drug and excipients. The results implied that calcium alginate beads can be used as a suitable controlled release carrier for diflunisal.

1. Introduction

Diflunisal 2′,4′-difluoro-4-hydroxybiphenyl-3-carboxylic acid is a non-steroidal anti-inflammatory drug (NSAID) administered for osteoarthritis, musculoskeletal strains, pain associated with surgery and cancer (Tempero et al. 1977). In single-unit dosage forms such as a tablet, the drug is dispersed throughout a solid matrix which contains filler and/or coated with polymer films (Efentakis et al. 2000). Multiple unit dosage forms refer to pellets, beads, microparticles and minitablets where drug is uniformly dispersed inside small particles usually comprised of polymer with other additives. They are usually delivered in hard gelatin capsules or made into tablets that disintegrate instantly. Multiple-unit forms offer advantages related to more predictable gastric emptying, gastric emptying less dependent on the state of nutrition, a high degree of dispersion in the digestive tract, less absorption variability, and a lesser risk of dose dumping (Follonier et al. 1992). They are essential where drug excipients or drug-drug physicochemical interaction is possible in a single-unit formulation.

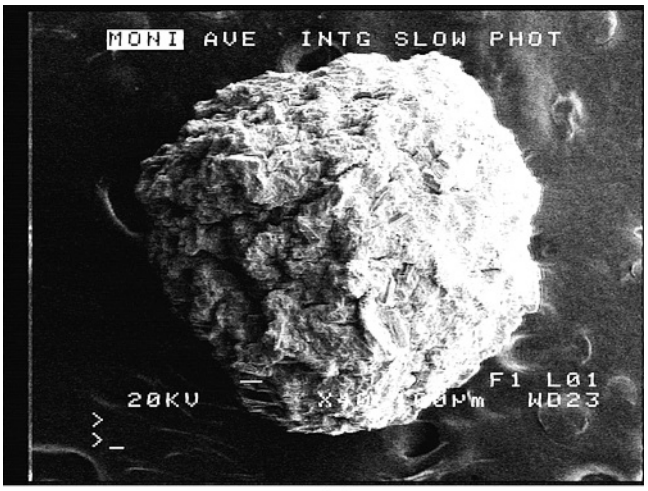
Among various multiple unit dosage forms, calcium alginate gel beads have been developed in recent years as a unique vehicle for oral drug delivery due to excellent biocompatibility, biodegradability, reproducible and simple method of preparation, abundant sources, low cost and minimal processing requirements. Sodium alginate is a sodium salt of alginic acid, a naturally occurring non-toxic polysaccharide found in marine brown algae. Chemically, it is composed of α-l-guluronic and β-d-mannuronic acids (Draget 2000). Cross-linking of the uronic acids with divalent cations, such as Ca^{2+} takes place, resulting in a three-dimensional network of calcium alginate (Grant et al. 1973). Ionotropic gelation was used to entrap non-steroidal anti-inflammatory drug molecules inside calcium alginate beads which may reduce gastric irritation. The detection of possible incompatibilities between drug and excipients is one of the basic tasks to select the best candidates for stable dosage form in preformulation laboratory (Nyqvist et al. 1986). The evaluation of drug-excipient interaction is of the utmost importance since *in vivo* drug release profile, and consequently the bioavailability of the therapeutic agent may be affected by the occurrence of interactions between drug and polymer (Carvalho et al. 2006). Currently, there is no literature available providing information on the diflunisal and calcium alginate system. Therefore, it is a timely study into possible drug-polymer interaction, which may occur inside calcium beads containing diflunisal.

The aim of this study was to evaluate any possible interactions between diflunisal and calcium alginate and also to characterize the physical state of the drug inside the calcium alginate beads. Calcium alginate beads were prepared by ionotropic gelation using sodium alginate, diflunisal and calcium chloride. FTIR, DSC and PXRD were used as analytical techniques to evaluate the drug loaded calcium alginate beads.

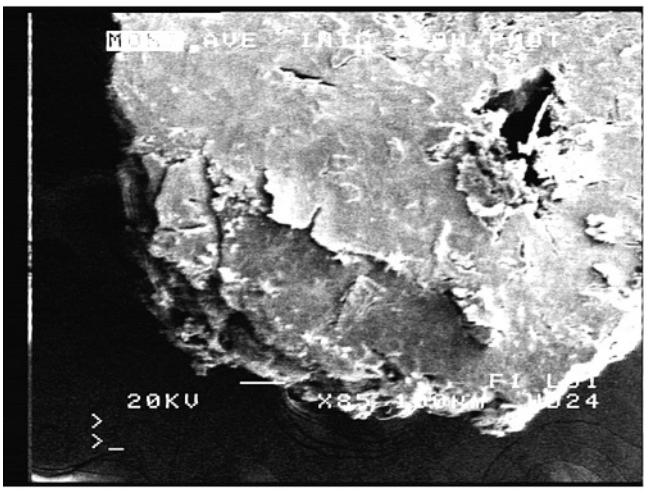
2. Investigations, results and discussion

2.1. Physicochemical characterization of beads

Diflunisal was entrapped into calcium alginate beads by the ionotropic gelation technique. The average diameter of the blank beads and drug loaded beads (assuming a spherical

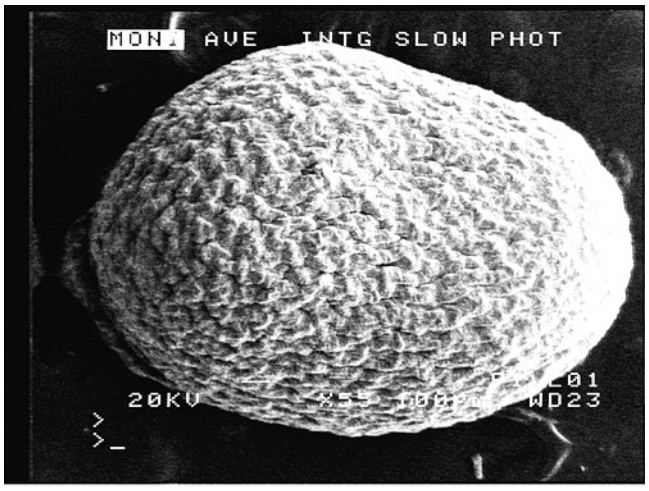


(a)

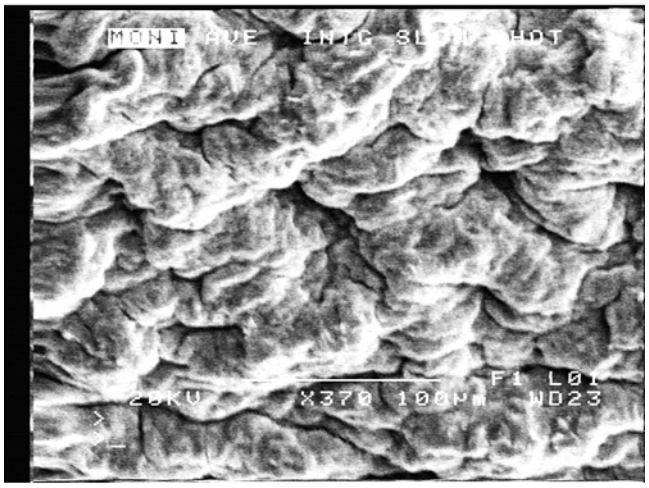


(b)

Fig. 1: (a) SEM image of the blank calcium alginate beads (without drug) (b) SEM image of the blank calcium alginate beads (cross sectional view)



(a)



(b)

Fig. 2: (a) SEM image of the diflunisal loaded calcium alginate beads (b) SEM image of the surgace morphology of the diflunisal loaded calcium alginate beads

shape) were 1.01 ± 0.02 mm and 1.53 ± 0.04 mm, respectively. Drug loaded beads showed an increased diameter over the blank beads. This is due to the fact that when drug is added to the alginate solution, the viscosity of the solution increases. As a result, droplets get bigger in size while being dropped from the syringe needle. The small value for the standard deviation indicated that the beads were uniform in size. The average weight of 100 beads was 0.2674 ± 0.0035 mg and drug content in 100 mg beads was 10.32 ± 0.35 mg. The entrapment efficiency was found to be low (about 10%) due to the partial miscibility of diflunisal in water. Diflunisal is an acidic drug (pKa of 2.9) and ionizes in water which has a pH of around 6.01 (University of Toledo water). Thus, when diflunisal comes in contact with external aqueous media, it ionizes to a great extent and escapes before its entrapment inside the polymer gel network of calcium alginate. Our ongoing parallel study revealed that the entrapment efficiency can be increased to about 80% by either incorporating a swellable, hydrophilic polymer such as hydroxypropyl methylcellulose into the beads, by changing curing time, or aqueous phase pH.

2.2. Scanning Electron Microscopy

Figs. 1A, 2A show the scanning electron microscopy (SEM) images for the blank calcium alginate beads and drug loaded calcium alginate beads, respectively. Blank calcium alginate beads were smaller in diameter compared to drug loaded calcium alginate beads. The blank beads were spherical but had a non-uniform surface while drug loaded beads showed a spherical to oval shape with a nearly smooth surface. The surface corrugations with numerous pores and channels (appeared as that of an orange peel) of beads (Figs. 1B, 2B). These were typical structures found with the calcium alginate gel system.

2.3. Differential Scanning Calorimetry

Diflunisal exhibited a sharp endotherm onset at 207.8 °C which corresponds to the melting point of the drug (Fig. 3). Sodium alginate exhibited an endothermic transition peak at around 190 °C and decomposition of the polymer took place at around 240 °C. Gelation of the alginate with calcium shifted the endothermic peak to around 180 °C. Diflunisal loaded calcium alginate beads exhibited a similar endothermic peak around 180 °C with an additional endothermic onset temperature of 207 °C, corresponding to the melting point of the drug. The thermogram showed that there is no apparent interaction of diflunisal with calcium alginate.

2.4. Powder X-Ray Diffraction analysis

PXRD analysis of diflunisal demonstrated its completely crystalline nature with characteristic sharp peaks at different 2θ values of 13.5°, 14.5°, 14.8°, 16.6°, 17.1°, 23.7° and 26.7° (seen

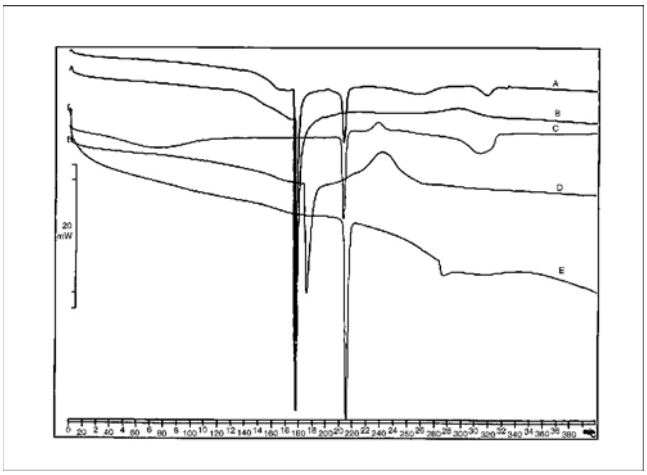


Fig. 3: DSC curves of (A) diflunisal loaded calcium alginate beads (B) calcium alginate bead (C) physical mixture of diflunisal and sodium alginate 1:1 (D) sodium alginate (E) diflunisal

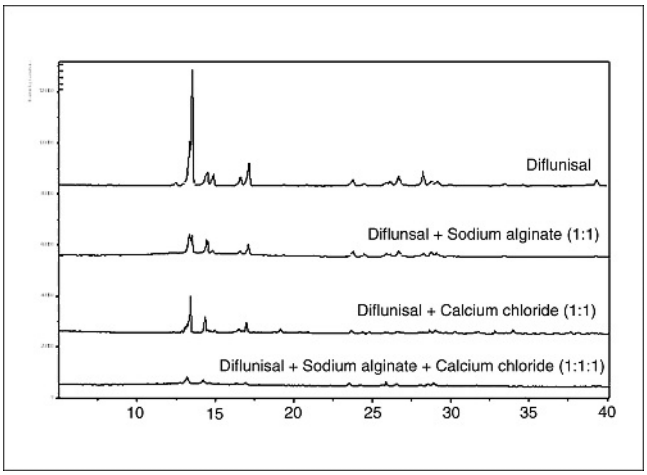


Fig. 5: PXRD spectra of diflunisal and various combinations of physical mixtures of diflunisal, sodium alginate and calcium chloride

in Fig. 4). Both sodium alginate powder and calcium alginate beads exist as the amorphous form in pure state. However, diflunisal loaded calcium alginate beads showed the exact position of the peaks as for pure diflunisal. There is a decrease in peak intensities for the diflunisal loaded calcium alginate beads. This indicates the fact that the drug may have existed inside the beads in its semicrystalline form. The amorphous polymer becomes trapped between the growing crystals of drug. As a result of the highly entangled nature of the polymer chains, the movement of the amorphous polymer becomes restricted and the semicrystalline phase formed. Another reason for a decrease in peak intensity may be due to the dilution effect. However, neither new peaks appeared nor existing peaks disappeared in diflunisal loaded calcium alginate beads. This is an indication that no drug polymer interaction occurred in the calcium alginate beads.

In the physical mixture of diflunisal and sodium alginate at a weight ratio of 1:1, the major peaks are 13.5°, 14.4°, 14.8°, 16.6° and 17.1° which are all present in the spectrum of pure difunisal (seen in Fig. 5). When diflunisal is physically mixed with calcium chloride at a weight ratio of 1:1, the few intense characteristic peaks are found at 13.4°, 14.3°, 16.5°. This signifies that when calcium chloride is present at a high concentration, no significant change in peak positions were found except as a decrease in intensity of the peaks. This phenomenon is simply due to the dilution effect of drug with calcium chloride. When diflunisal, sodium alginate and calcium chloride were present at a weight ratio of 1:1:1, we still found major peaks at 13.4° and 14.26° with reduced intensity. All other peaks had much lower intensities than the pure diflunisal. Therefore, it can be concluded that diflunisal, sodium alginate and calcium chloride are present as a physical mixture at high concentration, no significant interaction was observed.

2.5. Fourier Transform Infra-Red analysis

Molecular interaction diflunisal with alginate beads and physical mixtures were investigated by FTIR spectroscopy. The FTIR spectra for diflunisal, sodium alginate, calcium alginate blank beads, diflunisal-loaded batch are shown in Fig. 6. Diflunisal exhibited characteristic peaks at 3438.1 cm^{-1}, 3127.78 cm^{-1} and 1687.2 cm^{-1}. The FTIR spectrum for sodium alginate powder showed various distinct peaks of alginate: hydroxyl at 3,637.74 cm^{-1}, carbonyl at 1,680.25 cm^{-1} and carboxyl and carboxylate at about 1,000 to 1,400 cm^{-1} (Fig. 4). Cross-linking of alginate by calcium ion was seen by a decrease in the wave number for the carbonyl peak from 1,680.25 to 1,664.28 cm^{-1}. The hydroxyl peak for calcium alginate had a higher value for the wave number (3661.30 cm^{-1}) than that of the sodium alginate (Fig. 4). This effect may be due to the interference of calcium ions in the formation of bonds among adjacent hydroxyl groups for sodium alginate (6). With the incorporation of diflunisal, the

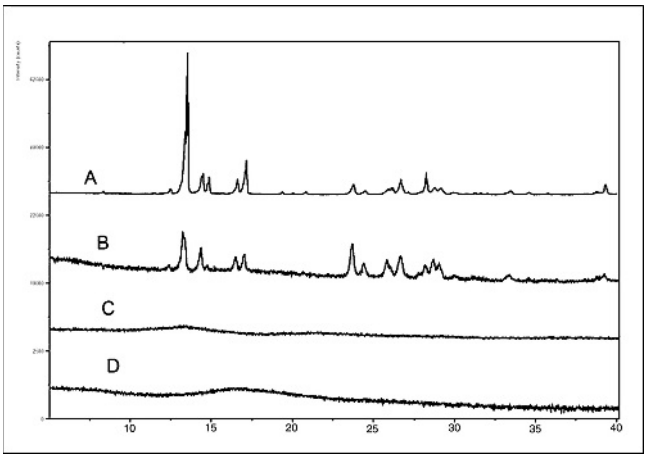


Fig. 4: PXRD spectra of (A) diflunisal (B) diflunisal loaded calcium alginate beads (C) sodium alginate (D) blank calcium alginate beads

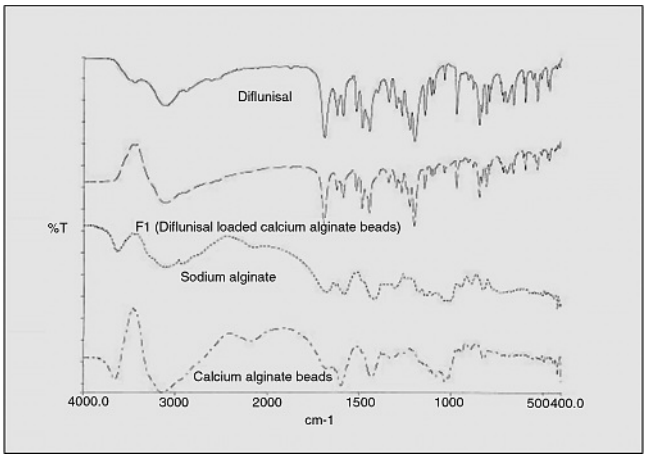


Fig. 6: FTIR spectra of diflunisal, diflunisal loaded calcium alginate beads, sodium alginate, calcium alginate beads

spectrum for the beads (Fig. 4) exhibited the peaks attributed to both diflunisal and calcium alginate. This confirms that diflunisal was entrapped inside the calcium alginate beads at the molecular level and no significant chemical interaction was observed.

2.6. Conclusions

Therefore, the following conclusions can be made on the basis of our findings. Diflunisal containing calcium alginate beads, prepared by the ionotropic gelation method using drug to polymer weight ratio of 1:1, exhibited spherical to oval shape with nearly uniform surface as examined by SEM analysis. The DSC, PXRD, FTIR analysis for the beads showed no significant physical or chemical interaction between the drug and excipients in the solid state. The drug showed compatibility with the calcium alginate system. Hence, it can be inferred that calcium alginate beads can be utilized as a suitable controlled release carrier for diflunisal.

3. Experimental

3.1. Chemicals

Diflunisal was purchased from Spectrum Chemical Mfg. Corp., Gardena, CA, USA. Sodium alginate was supplied by Rugar Chemical Co. Inc., NJ, USA. Calcium chloride anhydrous was purchased from J.T. Baker, NJ, USA.

3.2. Preparation of calcium alginate beads

Calcium alginate beads containing diflunisal were prepared by ionotropic gelation technique as described below. Diflunisal and sodium alginate (ratio 1:1) were added to water to make a 5% w/v slurry. The slurry is mechanically stirred for 5 min to form a uniform dispersion. The resulting dispersion was dropped through a 26-G syringe needle into 150 mL of 0.34 M calcium chloride solution. The beads were allowed to cure in the same solution for 30 min under slow magnetic stirring to improve their mechanical strength. The formed beads were separated, washed with distilled water and then dried in hot air oven at 50 °C for 24 h.

3.3. Physicochemical characterization

The dried beads were characterized by size, weight and content uniformity. Scanning electron microscopy (model JSM-5200, Japan) was performed to get the surface morphology of the intact beads. The instrument was operated at 20 kV acceleration voltage. The sample was shadwed in a cathodic evaporator with a gold layer of 20 nm thick.

3.4. Fourier Transform Infrared Spectroscopy (FTIR)

The FTIR was performed by using a PerkinElmer 1600 spectrophotometer with a resolution of 2 cm^{-1}, and 64 scans in the spectral region between 4000 and 600 cm^{-1} under nitrogen atmosphere. Solid powder samples were finely crushed, mixed with nujol and placed inside NaCl discs.

3.5. Powder X-Ray Diffractometry (PXRD)

Powder X-Ray Diffraction (PXRD) was performed by X'Pert-PRO multipurpose X-Ray diffractometer (PANalytical, Tokyo, Japan) using Ni-filtered, CuKα radiation, a voltage of 45 kV, and a current of 40 mA with a scintillation counter. The instrument was operated in the continuous scanning speed of 4°/min over a 2θ range of 5° to 60°.

3.6. Differential Scanning Calorimetry (DSC)

DSC (model 822, Mettler Toledo, OH, USA) was used in order to analyze the thermal behaviour of the various samples. Samples weights of 3–5 mg were accurately weighed into 100 µl aluminium pans and then sealed. The thermograms were recorded over a temperature range of 10–400 °C at a rate of 10 °C/min under nitrogen atmosphere.

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