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Original Article

Formulation of Ibuprofen Beads by Ionotropic Gelation

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Abstract

Microencapsulation has become a common technique in the production of controlled release dosage forms. Many results have been reported, concerning the use of alginate beads as controlled release drug formulations. Alginate has a unique gel-forming property in the presence of multivalent cations, in an aqueous medium. Ibuprofen is an excellent analgesic and antipyretic, non-steroidal anti-inflammatory agent with a high therapeutic index. Formulation of ibuprofen in beads could reduce its gastric ulcerogenicity. Hence, in this study the formation of Ca-alginate ibuprofen beads, through ionotropic gelation has been investigated.

For this purpose, different cross- linking agents including: Ca^{2+}, Ba^{2+}, Mn^{2+}, Co^{2+}, Sn^{2+} and Pb^{2+}, were used for bead preparation. Next, characterization of the beads, size distribution, encapsulation efficiency of ibuprofen within the beads, the bead swelling and the drug release kinetic were investigated.

Results showed that only Ca ion is suitable for the formation of ibuprofen beads. A good swelling profile for beads in phosphate buffer (pH=7.4) and the lack of swelling in hydrochloric acid (pH= 1.2), show the suitable nature of the beads. In addition, formulation of Na-alginate (2%) and Ca-chloride (2%) beads,resulted in an encapsulation efficacy of around 90%. The drug release studies showed a rapid and complete ibuprofen release from the beads, specially those prepared from Na-alginate (2%) and Ca-chloride (2%), in phosphate buffer medium. However, no detectable drug release was observed within the acidic medium.

In conclusion, ibuprofen is capable of being n be microencapsulated as a bead formulation, with suitable properties and release profile.

Keywords: Ibuprofen; Microencapsulation; Ionotropic gelation; Bead formulatin; Drug release; Na-alginate.

Introduction

Microencapsulation has become a common technique in the production of controlled release dosage forms (1). One approach for controlled release formulation of different therapeutic agents is the production of polymeric gel beads. The beads are discrete spherical microcapsules that serve as the solid substrate on which the drug is coated or encapsulated in the core of the beads (2). Beads can provide sustained release properties and amore uniform distribution of drugs include, within the gastrointestinal tract (2, 3). Furthermore, bioavailability of drugs formulated in beads has been enhanced (2). Numerous studies have been reported, concerning the use of alginate beads as a controlled release carier. Alginate, is a linear unbranched polysaccharide composed of varying proportion of 1, 4 -linked β-D-mannuronic acid (M) and α-L-guluronic acid (G) residues (4).

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Alginate has a unique gel-forming property in the presence of multivalent cations, such as calcium ions in an aqueous medium, which takes place mainly at junctions in the G-G sequence rich chain region know as "egg box junctions"(3). When divalent metal ions such as calcium, barium and stannous diffuse into an alginate solution (5), the rapid ion binding and formation of a polymeric network produces an inwardly moving gelling zone (5). In fact, alginate moves from the gel core towards this gelling zone, leading to the deletion of alginate within the core (5). The polymer gradient is essentially governed by the relative diffusion rate between the soluble alginate molecules and the gel forming ions (5). Therefore, alginate is used as an immobilization matrix for cells and enzymes as well as a pharmaceutical and food adjuvant (3, 5, 6). In various studies, alginate beads have been used as excellent vehicles. Rabbit articular chondrocytes immobilized in alginate beads maintained normal morphology and metabolic activity for more than two weeks. In this study, calcium, barium, and strontium were used for the gel formation (7). In an investigation carried out to study the effect of *Streptomyces marinensis,* NUV-5 cells were immobilized in calcium alginate for the production of neomycin. The effect of various parameters, including the effect of alginate concentration, type of cation used ($CaCl_2$, $BaCl_2$, and $SrCl_2$), concentration of cation and the curing times, on neomycin production and bead stability were studied (8).The interactions between alginate and polycations have been studied, using different labeling techniques (9). In this study, $Ca^{2+}$and Sr^{2+} were used as cations. Another advantageous property is their re-swelling ability. This property is sensitive to the environment pH. Hence acid-sensitive drugs incorporated within the beads would be protected from the gastric juice (3). Many protein and peptide drugs cannot be administered through the oral route, due to their degradation by digestive enzymes of the stomach and small intestine (3). Also, gastric ulcerogenic drugs, such as most of the NSAIDs, need to be covered to prevent them from direct contact with the gastric mucosa. Ibuprofen is an excellent analgesic and antipyretic, non-steroidal anti-inflammatory agent with a high therapeutic index (10). Formulation of ibuprofen beads could help to reduce its gastric ulcerogenicity. Hence, in this study the formation of Ca-alginate ibuprofen beads, through ionotropic gelation, was investigated using several cations. Different characteristics of the prepared beads, including their drug release kinetics and encapsulation efficiency were determined.

Experimental

Materials

Ibuprofen was a kind gift from Loghman Pharmaceutical Co.,Tehran, Iran. Na-alginate (850 cP, 2% solution), Magnesium chloride ($MgCl_2 .2H_2O$), Lead nitrate ($Pb(NO_3)_2$), Cobalt chloride ($CoCl_2.6H_2O$), Stannous chloride ($SnCl_2.2H_2O$) and Barium chloride ($BaCl_2.2H_2O$), were all obtained from the Merck Chemicals, Gmbh-Germany. All other chemicals were of analytical grade and used without further purification.

Methods

Preparation of the beads

Two percent (W/V) solutions of various metal ions (listed above) as well as three different concentrations of Na alginate (1%, 2% and 3%) were prepared in deionized water.

Ibuprofen was added (2%) and suspended in the polymer solutions. Then, each of these drug suspensions was dropped (10 ml/min) through a syringe nozzle (21G) into each of the ion solutions. Different procedure for the preparation of beads, ibuprofen (2%) was dispersed with in a Ca chloride solution, by magnet stirring, and the polymeric solution was added dropwise through a needle syringe into this dispersion. Furthermore, in order to select the best procedure, the bead formation was examined using ibuprofen and Na-alginate solution in phosphate buffer, as well as Ca chloride solution in phosphate buffer All these procedures took place at room temperature. In both bead production methods, different concentrations of Na-alginate (1%, 2% and 3%), and Ca chloride (2, 3%) as well as varying curing times (15, 30 and 45 min) were examined.

The obtained beads were filtered using Wattman paper filters, washed twice by deionized water and dried at 37 °C for 24 h.

Characterization of the beads

Determination of the particle size and wall strength of the beads

The particle size of the beads was determined by reading the size of 100 particles, using an optical microscope (CETI), assembled with an eyepiece micrometer.

The wall strength of the beads was evaluated using a petry dish. An accurately weighed amount of the beads was placed in the larger section of the petry dish.The smaller section of the dish was placed inversely on the beads and a fifty gram balance weight was put down on it. In case of not observing any fracture in almost all the beads, a "++" sign was designated. In case of observing fracture in half the beads, a "+" sign was designred. Complete fractur in all the beads was shown by a "-"sign.

Encapsulation efficiency of Ibuprofen

One hundred mg of dried beads were levigated with 15ml ethanol to break the wall and dissolve ibuprofen. Then the mixture was filtered through a regular paper filter and a Millipore® membrane filter (0.45 µ), respectively. The filtered solution was diluted with ethanol. The amount of ibuprofen extracted was measured spectrophotometrically at 220 nm.The drug encapsulation efficiency was calculated using the following equation (equation 1):

$$\%\text{Encapsulation Efficiency}=[\text{Ibuprofen}]_{\text{in beads}} \times 100 / [\text{Ibuprofen}]_{\text{initial amount}} \quad \text{(Equation 1)}$$

Bead swelling measurement

The swelling behavior of the beads was studied by measuring the weight of the beads after exposure to phosphate buffer, pH 7.4. Beads (0.1g) were placed into a glass vial, followed by the addition of 20 ml of buffer and stirring using a magnet set at 200rpm at 37 °C. At specific time intervals beads were removed and dried by filter papers. The weights determined were used for plotting the swelling profile. The swelling kinetic was evaluated using the $M_t/M_\infty = Kt^n$ equation (19), in which M_t is the bead weight at time intervals (t), M_∞ is the final weight of the beads at steady state and n is the swelling parameter.

Drug release kinetic studies

The drug release studies were performed on the beads, using a conventional USP type I dissolution apparatus (basket method). A weighed amount of individual bead formulations were added to the dissolution vessel, which contains 200 ml of phosphate buffer (pH 7.4) or HCl buffer (pH 1.2) at 37 °C. At set times, samples were collected, filtered and the amount of drug released was assayed spectrophotometrically.

Results

As shown in Table 1, the appearance of beads is influenced by the ion used. The particle average size of Ca-alginate beads was 5.1±0.2 mm. The beads prepared from Ca, Ba, and Pb ions were found tobe more appropriate in terms of shape, wall strength and aggregation. We had to use Pb and Ba ions for screening. However, due to the toxicity of Pb and Ba, these cations were not used in the following steps. The shape of the calcium alginate beads can be seen in Figure 1. Beads prepared by the use of ibuprofen and Na-alginate solution (in phosphate buffer) were ununiformly shaped, with a low wall strength (Figure 2). Addition of Ca chloride solution to the phosphate buffer resulted in a very turbid solution with some undissolved particles. In addition, beads which formed by dispersion of ibuprofen in the Ca chloride solution had a very low encapsulation efficiency and were omitted from this study. Finally, dispersion of ibuprofen in Na-alginate solution (i.e water) gave the best characteristics. Hence, this method was selected. Using this method, different formulations were prepared. These formulations composed of different amounts of Na-alginate (1, 2, and 3%) and Ca chloride (2, 3%) as well as varying curring times (15, 30 and 45 min). The encapsulation efficacies of individual formulations were determined. Results obtained are shown in Table 2. These results show that the greatest amount of drug entrapment was within the Na alginate (2%) and Ca chloride

Table 1. Characteristics of different bead formulations.

Ion salt	Na alginate	Bead formation	Bead shape	Wall strength
$CaCl_2$	1%	+	Ununiform	++
	2%	+	Spherical	++
	3%	+	Spherical	++
$BaCl_2$	1%	+	Ununiform	++
	2%	+	Spherical	++
	3%	+	Spherical	++
$MnCl_2$	1%	_	_	_
	2%	+	Ununiform	_
	3%	+	Platy	_
$CoCl_2$	1%	+	Platy	+
	2%	+	Platy	+
	3%	+	Globular	++
$SnCl_2$	1%	+	Ununiform	_
	2%	+	Platy	_
	3%	+	Platy	_
$Pb(NO_3)_2$	1%	+	Ununiform	++
	2%	+	Spherical	++
	3%	+	Spherical	++

++ = No fracture was seen in almost all the beads
+ = Fracture was seen in about half the beads
_ = Fracture was seen in all the beads

(2%) formulation, after a 15 min curring time. The lowest amount of drug entrapment was seen with Na-alginate (1%) and Ca chloride (3%), following a 30 min curing time. In the swelling studies, a rapid swelling was observed in ca-alginate beads (Figure 3). The release studies showed a rapid and complete drug release from the beads, especially the Na-alginate (2%) and

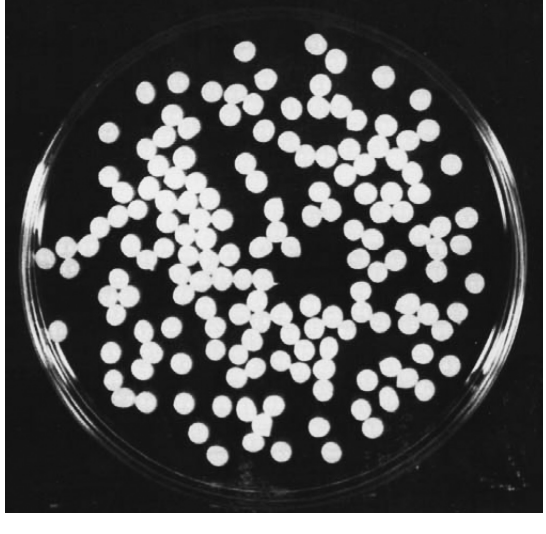

Figure 1. The Spherical shape of the calcium alginate beads.

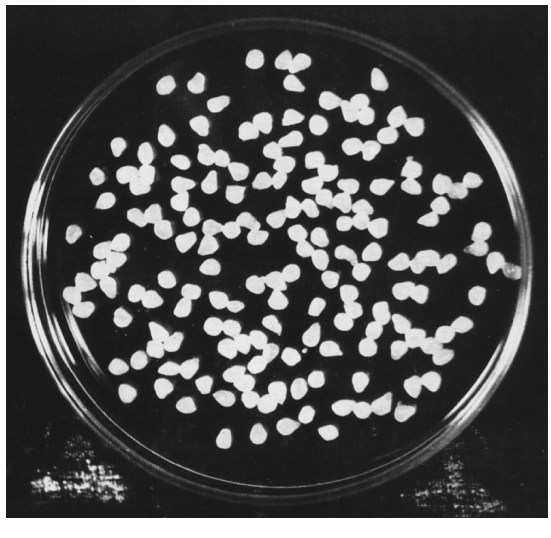

Figure 2. An example of ununiform beads.

Table 2. Encapsulation efficacy (%) of ibuprofen in different Ca-alginate beads.

Bead formulation	Encapsulation efficacy(%)			Mean ± SD
	1	2	3	
Alg1%-Ca2% CT: 30 Min	83.94	84.89	84.81	84.54±0.53
Alg1%-Ca3% CT: 30 Min	82.27	84.93	84.83	84.01±1.51
Alg2%-Ca2% CT: 30 Min	88.04	86.12	88.39	87.52±1.22
Alg2%-Ca3% CT: 30 Min	87.32	87.79	86.88	87.33±0.455
Alg 3%-Ca 2% CT: 30 Min	87.88	87.44	86.35	87.22±0.787
Alg3%-Ca3% CT: 30 Min	87.74	88.38	85.38	87.16±1.58
Alg2%-Ca2% CT: 15 Min	89.72	88.38	87.49	88.53±1.12
Alg2%-Ca2% CT: 45 Min	85.34	87.02	89.72	87.36±2.20

Alg ≡ Na-alginate, Ca≡$CaCl_2$, CT≡Curing time, n=3

Ca-chloride (2%) beads in the phosphate buffer medium (Figure 4).There was no detectable drug release in the acidic medium.

Discussion

Several ions had been used as cross-linking agents for Na-alginate gelation.The best one is Ca^{2+} (11). Due to the size and ability of Ca^{2+}ion to form continuous Ca-alginate film, it has been used as a release control barrier for several drugs (12, 13). Due to the suitable swelling kinetic of Ca-alginate beads (14), lack of toxicity and its influence on the release of non-steroidal anti-inflammatory agents such as diclofenac (15) and indomethacin (11), we tried to use this ion for ibuprofen, too. Falamarzian and Varshosaz (16) showed

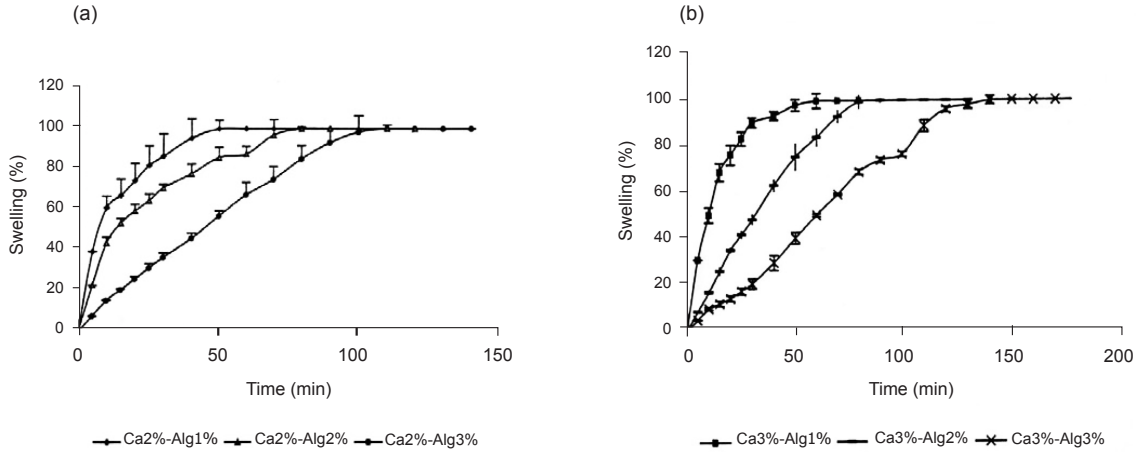

Figure 3. The swelling profile in different Ca-alginate beads, using (a) 2% Ca and (b) 3% Ca solutions (n=3, mean±SD).

Table 3. The swelling parameter in different Ca-alginate beads.

Bead formulation	Swelling Constant parameter (n)			Mean±SD
	1	2	3	
Alg1%-Ca2% CT: 30 Min	1.0341	1.0238	1.0219	1.0266±0.0065
Alg1%-Ca3% CT: 30 Min	1.0272	1.0208	1.0306	1.0262±0.0049
Alg2%-Ca2% CT: 30 Min	1.0134	1.0169	1.0190	1.0164±0.0028
Alg2%-Ca3% CT: 30 Min	1.0234	1.0217	1.0256	1.0236±0.0019
Alg3%-Ca2% CT: 30 Min	1.0218	1.0190	1.0169	1.0192±0.0025
Alg3%-Ca3% CT: 30 Min	1.0094	1.0129	1.0176	1.0133±0.0041

Alg ≡ Na-alginate, Ca ≡ $CaCl_2$, CT ≡ Curing time, n=3, ($p<0.001$)

that Ca-alginate beads had a better swelling kinetic and wall strength. This study, the most desirable beads were also obtained by Ca^{2+}ion. These beads had a more unique size and shape. Statistical analysis showed that there was no significant difference ($p<0.01$) between the extent of drug entrapment in beads made from different concentrations (1, 2 and 3%) of Na-alginate. This is in agreement to the findings of Badwan *et al.* (17). They showed that the concentration of Na-alginate had no significant effect on sulfamethoxazole loading. Based on this study, it can be concluded that an increase in the percentage of Na-alginate could led to a greater viscosity of the solution, and hence a larger drop needs to be dripped out of the needle. As a result, larger beads were formed and diffusivity was decreased. Different concentrations (2 and 3%) of Ca chloride had no significant influence on drug loading ($p<0.001$). Aslani and Kennedy (14) found that the minimum concentration of Ca chloride needed to form Ca-alginate beads is 1% W/V, and higher concentrations had no effect on the

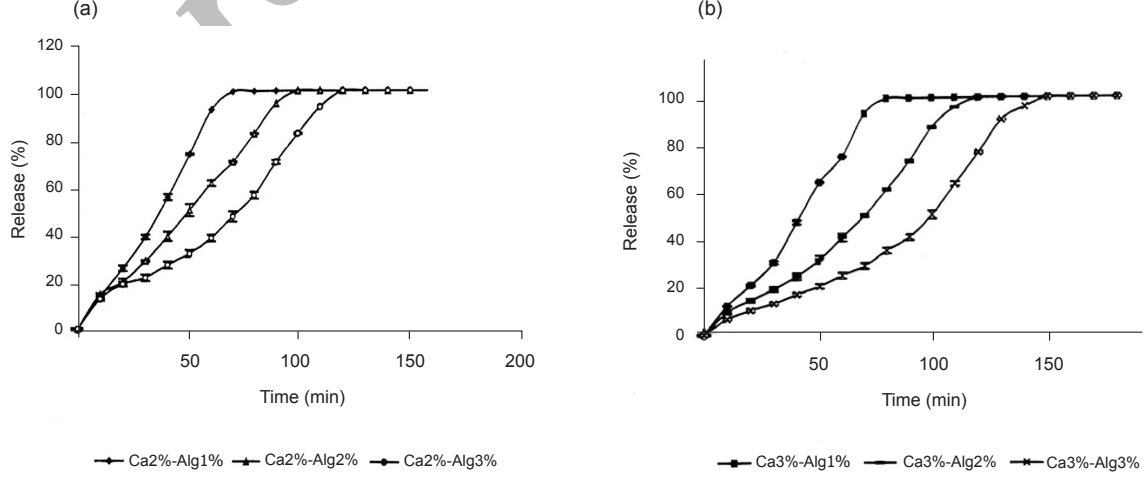

Figure 4. The ibuprofen release profile from different Ca-alginate bead formulations, using (a) 2% Ca and (b) 3% Ca solutions (n=3,mean±SD).

Table 4. The diffusion model and release constant (k) in different Ca-alginate beads.

Bead formulation	Diffusion model	k
Alg1%-Ca2% CT:30 Min	Zero order	1.5856
Alg1%-Ca3% CT: 30 Min	Zero order	1.3856
Alg2%-Ca2% CT: 30 Min	Zero order	1.0246
Alg2%-Ca3% CT: 30 Min	Hixon Crowell	0.0175
Alg3%-Ca2% CT: 30 Min	Hixon Crowell	0.0145
Alg3%-Ca3% CT: 30 Min	Hixon Crowell	0.0138

n=3, **($p<0.001$)**

acetaminophen loading. Our data show that, by increasing the concentration of Ca chloride, the resulting beads acquire a stromger wall strength. This maybe a result of further cross-linking between the polymer and the ion (18). The swelling kinetic was evaluated by the use of $M_t/M_\infty=Kt^n$ equation (19). The results (Table 3) shows that swelling kinetic obeys the super case II transport kinetic ($n>1$) (14, 19) and the change in formulation procedures had no effect on its kinetic ($p<0.001$). In order to determine a model for diffusion of drug through the beads, the following models were examined: Zero order kinetic, First order kinetic, the Higuchi model (square root of time) and the Hixon Crowell model. The results obtained are shown in Table 4. Drug release from the inert matrices as well as the methacrylate and hydrophilic polymers has been well defined by the Higuchi equation. (20, 21). In this study, the release of ibuprofen from nearly all the bead formulations obeyed from the Hixon-Crowell model. This could be due to the influence of water solubility on the rate of drug release from polymer matrix (20). Ibuprofen is sparingly soluble in water. Therfore, the rate of drug dissolution within the penetrated water could be a controlling or limiting factor in drug released from the beads. Our studies showed a decreasing trend in the rate of drug release, by increasing the Ca chloride and Na-alginate concentrations. However, in all the formulations, ibuprofen was completely released. Based on this study, it can be concluded that there is no interaction between the ibuprofen particles and the surrounding calcium gel matrix (11, 12). The results of ibuprofen release from the best formulations (Na-alginate 2% and Ca chloride 2%) in two different media (pH values of 1.2 and 7.4) showed that, there was release in the acidic medium, nor any deformation in the shape of beads. However, in pH 7.4, the drug was completely released. Other studies have reached similar results, when using Ca-alginate beads (11, 15, 22). This would make the goal of this study,which was the formulation of ibuprofen as a controlled release dosage form, feasible.

References

(1) Kakkar AP. Characterization of ibuprofen loaded microcapsules prepared by ionotropic gelation. *Indian J. Pharm. Sci.* (1995) 57: 56-60

(2) Kumar R, Gupta RB and Betageri GV. Formulation, characterization, and *in vitro* release of glyburide from proliposomal beads. *Drug Delivery* (2001) 8: 25-27

(3) Xing L, Dawei C, Liping X and Rongqing Z. Oral colon-specific drug delivery for bee venom peptide: development of a coated calcium alginate gel beads-entrapped liposome. *J. Control. Release* (2003) 93: 293-300

(4) Liu XD, Yu WY, Zhang Y, Xue WM, Yu WT, Xiong Y, Ma XJ, Chen Y and Yuan Q. Characterization of structure and diffusion behavior of Ca-alginate beads prepared with external or internal calcium sources. *J. Microencapsul.* (2002) 19: 775-782

(5) Thu B, Skjak-Braek G, Micali F, Vittur F and Rizzo R. The spatial distribution of calcium in alginate gel beads analyzed by synchron-radiation induced X-ray emission (SRIXE). *Carbohydrate Res.* (1997) 297: 101-105

(6) De souza RE, Engelsberg M, Barros J and Carvalho LB. Ultralow field overhauser images of calcium alginate gel formation. *Mol. Cryst. Liq. Cryst.* (2002) 374: 249-254

(7) Tamponnet C and Lievremont M. Production of proteoglycans by immobilized chondrocytes: Effect of divalent cations. *Biotechnology Techniques* (1991) 5: 69-72

(8) Srinivasulu B, Adinarayana K and Ellaiah P. Investigations on Neomycin Production with Immobilized Cells of *Streptomyces marinensis* Nuv-5

in Calcium Alginate Matrix. *AAPS Pharm. Sci. Tech*. (2003) 4(4): 57

(9) Thu B, Bruheim P, Espevik T, Smidsrød O, Soon-Shiong P and Skjåk-Braek G. Alginate polycation microcapsules. I. Interaction between alginate and polycation. *Biomaterials* (1996) 17: 1031-40

(10) Sweetman SC. (ed.) *Martindale, the Complete Drug Reference*. 34th ed., Pharmaceutical Press, London (2005) 1-46

(11) Pillay V, Dangor CM, Govender T, Moopanar KR and Hurbans N. Ionotropic gelation: encapsulation of indomethacin in calcium alginate gel discs. *J. Microencapsul.* (1998) 15: 215-26

(12) Fathy M, Safwat SM, el-Shanawani SM, Shawky Tous S and Otagiri M. Preparation and evaluation of beads made of different calcium alginate compositions for oral sustained release of tiaramide. *Pharm. Dev. Technol.* (1998) 3: 355-64

(13) Coppi G, Iannuccelli V and Cameroni R. Polysaccharide film coating process for freely swellable hydrogels. *Pharm. Dev. Technol.* (1998) 3: 347-53

(14) Aslani P and Kennedy RA. Effect of gelation conditions and dissolution media on the release of paracetamol from alginate gel beads. *J. Microencapsul.* (1996) 13: 601-14

(15) Pillay V and Fassihi R. *In vitro* release modulation from cross linked pellets for site specific drug delivery to gastrointestinal tract. II. Physicochemical characterization of calcium-alginate, calcium-pectinate and calcium-alginate-pectinate pellets. *J. Control. Release* (1999) 59: 243-56

(16) Falamarzian M and Varshosaz J. The effect of structural changes on swelling kinetics of polybasic/hydrophobic pH-sensitive hydrogels. *Drug Dev. Ind. Pharm.* (1998) 24: 667-9

(17) Badwan AA, Abumalooh A, Sallam E, Abukalaf A. Jawan O. A sustained release drug delivery system using calcium alginate beads. *Drug Devel. Ind. Pharm.* (1985) 11: 239-256

(18) Gehrke SH and Lee PI. Hydrogels for drug delivery systems. In: Tyle P. (ed.) *Specialized Drug Systems.* Marcell Dekker, New York (1990) 333-385

(19) Kikuchi A, Kawabuchi M, Watanabe A, Sugihara M, Sakurai Y and Okano T. Effect of Ca^{2+} -alginate gel dissolution on release of dextran with different molecular weights. *J. Control. Rel.* (1999) 58: 21-28

(20) Capan Y. Influence of technological factors on formulation of sustained release tablets. *Drug Devel. Ind. Pharm.* (1989) 15: 927-956

(21) Swarbrick J and Boylan J. *Encyclopedia of Pharmaceutical Technology.* Vol. 7, Marcel Dekker, New York (1993) 441-460

(22) Turkoglu M, Gursoy A, Eroglu L and Okar I. Effect of aqueous polymer dispersion on properties of diclofenac/alginate beads and *in vivo* evaluation in rats. *STP. Pharma. Sci.* (1997) 7: 135-140

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