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STUDY OF FACTORS AFFECTING THE ENCAPSULATION EFFICIENCY AND DRUG RELEASE FROM CALCIUM ALGINATE BEADS

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ABSTRACT

Although many studies have been carried out on calcium alginate (Ca-Alg) beads as a matrix for drug delivery system, optimization of the preparation parameters are limited and not clear. Values widely varied by authors and sometimes there is contradiction! In this work, an inclusive study has been carried out to investigate the optimum conditions for encapsulation of brilliant blue (BB) as a model drug using Ca-Alg beads. Results show that by increasing $CaCl_2$ concentration from 0.5 – 5.0 % (w/v) the encapsulation efficiency (EE) increases from 62 - 90 % and delays the release rate in phosphate buffer at pH 7.4, simulated intestinal fluid (SIF). By increasing the alginate concentration from 1 - 3 % (w/v), the release of BB was found to follow this order at the first 2h: 1 % > 2 % > 3 % after which it was as follow: 1 % > 3 % > 2 %. This change in the results is due to bursting and disruption of the beads using 3% (w/v) alginate after 2 h. Two techniques were used to support this explanation: a) swelling of dried beads, b) beads bursting. Also, the release kinetic results using 1 – 3 % (w/v) alginate revealed shifting from Fickian to anomalous to case II Transport mechanism, respectively, whereas the SEM showed an improvement of the gel beads morphology with increase in alginate concentration. On overall, 2 % alginate was found to be the optimum concentration. Also, Ca-Alg beads showed negligible swelling percent of 60 % in acid medium (pH 1.2) compared to 5000 % in alkaline medium, (pH 7.4) indicating that Ca-Alg beads can be used as a matrix for targeting drug to the intestine.

Keywords: Calcium alginate beads; controlled intestinal drug release; swelling, brilliant blue, biodegradable polymer.

1. INTRODUCTION

Drug delivery systems have been extensively studied over the last years and polymers are now being studied as a method of controlling the release of drugs **[Xiao-Peng et al, (2007)]**. Biodegradable polymers are one of the key materials for these devices, and have advantages over nondegradable implants. The main advantage is that biodegradable devices degrade and are absorbed by the body during and/or after drug release this allows us to bypass the need for surgical removal of the device **[Akihiko et al, (1999)]**. One of the most known used polysaccharide in biotechnology is alginate **[Steve et al., (2007)]**. Alginate is a water-soluble linear polysaccharide extracted from brown seaweed and is composed of alternating blocks of 1–4 linked α-L-guluronic and β-D-mannuronic acid residues **[Meera et al., (2006)]**. Alginate has the ability to form hydrogel in presence of multivalent cations like Ca^{+2} in aqueous medium **[Gombotz et al. (1998)]**. Alginate shows excellent features such as immunogenecity **[Cappai et al, (1995)]**, biocompatibility **[Gerd et al, (1997)]**, bioadhesion **[Peppas et al, (1985)]** and non-toxicity **[Smidsrod et al, (1990)]**, these features make it a very attractive biomaterial for use in many types of application like wound dressing **[Kneafsey et al., (1996)]**, scaffold for tissue engineering **[Biji & Jayakrishnan (2005)]** and pharmaceutical industries **[Vandenberg & De La Noüe (2001) and Chretien & Chaumeil (2005)]**.

Although many authors **[Skjåk-Braek et al, (1989) and Anil & Willem (2005)]** have studied Ca-Alg beads as a matrix for drug delivery system. optimization of the preparation parameters were not clear. Also, there are many conflicts between authors and this was the main reason for doing this work. For examples, **[Bajpai et al., (2005)]** reported that using high alginate concentration 4% (w/v) gave stable beads for drug delivery system. whereas **[Arica et al., (2002)]** reported that beads prepared with 1% (w/v) alginate sustained the release of 5-fluorouracil. Also the concentration of $CaCl_2$ as cross-linking agent showed various results; **[Gaserod et al., (1998)]** reported that by increasing the concentration of $CaCl_2$ to 3% (w/v) should increase the porosity of beads, leading to higher diffusion of entrapped drug. While **[Sankalia et al., (2005)]** found that using 0.5% (w/v) of $CaCl_2$ gives weak gel due to insufficient cross-linking of alginate. **[Kim & Lee (1992)]** reported that

calcium ion content in the gel beads leveled off after 6 min of curing time in $CaCl_2$ solution, and there was little variation in the release of blue dextran from alginate gel beads cured for more than 6 min. **[Yotsuyanagi et al., (1987)]** reported that an approximately 70 h curing was necessary to reach constant weight of alginate gels.

Thus, this work is aiming to unveil the contradiction in results by many authors by studying comprehensively the influence of preparation parameters including alginate concentration, calcium chloride concentration, curing time and drying process on the encapsulation efficiency and the release rate using brilliant blue as a model drug. Also, swelling of the beads in simulated gastric and intestinal fluids was studied and the morphology of beads was visualized using SEM. To our knowledge, the optimization study in this work was inclusive, covering many novel aspects, which are essential for any scientist who is working on calcium alginate beads as a carrier for drug delivery systems.

2. MATERIALS AND METHODS

2.1. Materials

Alginic acid sodium salt from brown algae was purchased from Fluka, brilliant blue R 250 (BB, Mw 825) was purchased from Aldrich; calcium chloride anhydrous was purchased from Gen Lab. All other reagents were of analytical grade and used as received.

2.2. Methods

As a general rule, all experiments were carried out in triplicate and data are means ± SD (n = 3).

2.2.2. Preparation of calcium alginate beads

Sodium alginate was dissolved in bidistilled water at various concentrations 1, 2, 3 and 4 % (w/v), then BB 25 % (w/w) was added and suspended thoroughly by stirring. Three milliliters of this solution was dropped into a 15 ml of gelling solution through a disposable plastic syringe using a 23G needle at a dropping rate of 1 ml/min under mild agitation for various time 30 - 120 min. The gelling solution contained $CaCl_2$ 0.5 - 5 % (w/v). The formed beads were collected, washed with 20 ml bidistilled water and dried at room temperature for 24 h or used in the wet state.

2.2.3. Encapsulation efficiency

The gelling and washing solutions remaining after removal of the beads were assayed for BB by UV/Vis spectrophotometer (Shimadzu) at 590 nm using a stander curve of known concentration in the range of 1.25 – 30 mg/l with correlation coefficient $R^2 = 0.9998$.

The encapsulation efficiency was calculated from the difference between the initial amount of BB dissolved in alginate solution and the amount of BB measured in the gelling and washing solution **[Shi et al., (2006)]** as shown in the following formula:

$$\text{Encapsulation efficiency \%} = [(M_i - M_g) / M_i] \times 100. \quad (1)$$

Where M_i is the initial amount of BB dissolved in alginate solution and M_g is the amount of BB measured in the filtered solution.

2.2.4. Swelling study

Swelling studies were conducted using both wet and dry beads. The term wet refers to the state of the beads immediately prepared and the term dry to beads that were left to dry for 24 h in air till constant weight. Swelling studies of Ca-Alg beads were carried out in simulated intestinal fluid of 10 mM phosphate buffer (pH 7.4) and in simulated gastric fluid of 10 mM HCl buffer (pH 1.2). Accurately weighed amounts of beads were incubated in 25 ml of swelling solution at 37°C under shaking at 100 rpm. At predetermined time intervals, the beads were separated from the medium using a stainless steel grid. Immediately, they were wiped gently with filter paper and weighed. The swelling percent of the beads was calculated according to the formula:

$$\text{Swelling percent \%} = [(Ws - W_i) / W_i] \times 100 \quad (2)$$

Where Ws is the weight of the beads in the swollen state and W_i is the initial weight of the beads.

2.2.5. In vitro release study

The in vitro release studies were performed in 10 mM phosphate buffer pH 7.4. Accurately weighed amounts of beads were placed in conical flasks containing 25 ml of the release medium. The samples were incubated at 37°C under shaking at 100 rpm. At predetermined time intervals, samples of 3 ml were withdrawn from the release medium and

were replaced with fresh phosphate buffer solution. The concentration of BB in the solution was assayed by UV/Vis spectrophotometer (Shimadzu) at 590 nm.

2.2.6. Morphology of the beads

The surface of the beads was examined using scanning electron microscopy (SEM, S-590, HITACHI). Prior to observation, samples were mounted on metal grids, using double-sided adhesive tape and coated by gold under vacuum before observation.

3. RESULTS AND DISCUSSION

3.1. Morphology of the Beads

Scanning electron micrographs of air dried Ca-Alg beads prepared with 3% (w/v) $CaCl_2$ and 1,2 and 3% (w/v) alginate concentration were illustrated in Fig. 1. At 1% (w/v) alginate, the dry beads completely lost its spherical shape (Fig. 1A) and the surface show highly roughness and large cracks (Fig. 1B) caused by collapsing of the polymer layers during dehydration due to low mechanical strength of the gel. By increasing the alginate concentration to 2% (w/v), beads remained its spherical shape (Fig. 1C) and the surface morphology was improved, but still showed large cracks (Fig. 1D). Further increase in alginate concentration to 3% (w/v) increases the viscosity leading to non spherical (elongated) beads (Fig. 1E), which have smooth surface with smaller pores size due to the high gels beads mechanical strength (Fig. 1F). These results indicated that the surface morphology of Ca-Alg beads improved by increasing alginate concentration whereas increasing alginate concentration above 3% made preparation of the beads difficult because the solution becomes too viscous for dropping and non spherical (elongated) beads were formed.

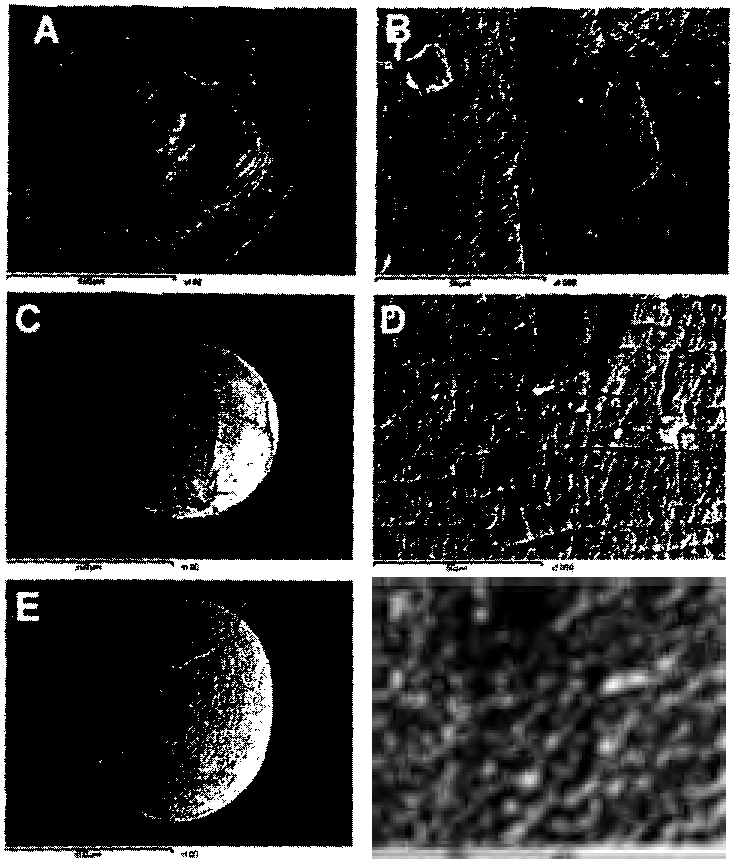

Fig. (1): SEM micrographs of air dried calcium alginate beads prepared with 3% $CaCl_2$ and different concentrations of alginate: 1% (w/v) alginate beads (A) and surface morphology (B); 2 % (w/v) alginate beads (C) and surface morphology (D); 3 % alginate beads (E) and surface morphology (F).

3.2. Encapsulation efficiency

3.2.1. Effect of alginate concentration.

The effect of alginate concentration on the encapsulation efficiency was studied using 1 – 4 % (w/v) alginate beads hardened with 3% (w/v) $CaCl_2$ and cured for 30 min. Figure 2 shows a gradual increase in the EE from 86 – 93 % when alginate concentration was increased from 1 – 4 % (w/v). However, the EE % of beads using 4 % alginate was close to that of 3 % alginate, thus for further optimization, 1- 3 % (w/v) alginate were used.

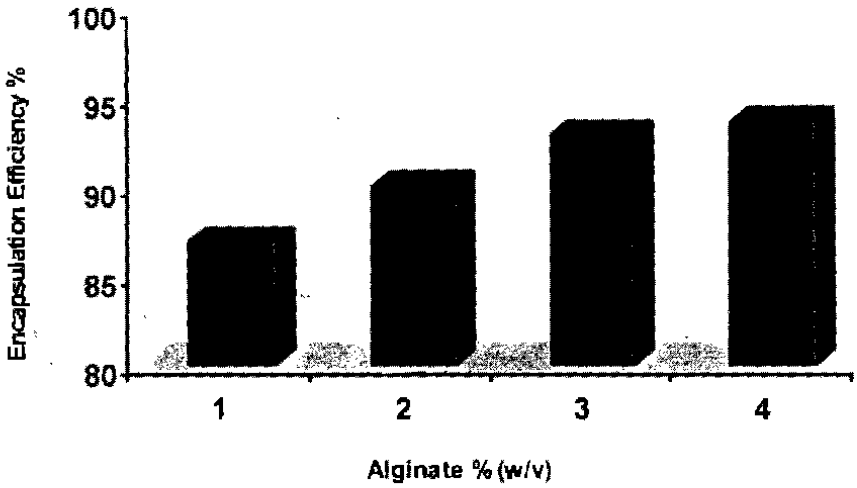

Fig. (2): Effect of alginate concentration on the encapsulation efficiency.

This increase in the EE can be explained as follow, increasing the alginate concentration provided more binding sites of alginate for Ca^{2+} ions resulting in the formation of a more compact gel membrane, with smaller pores size so leaching of BB to the curring medium during preparation decreased **[Sankalia et al., (2005); Shi et al., (2006) and Arica et al., (2005)].**

3.2.2. Effect of $CaCl_2$ concentration.

Keeping the alginate concentration and curing time fixed at 2 % and 30 min, respectively, and increasing $CaCl_2$ concentration from 0.5 – 5 % (w/v) significantly increased the EE % from 62 – 90 % reaching a plateau after 3% (w/v) $CaCl_2$ as shown in Fig. 3.

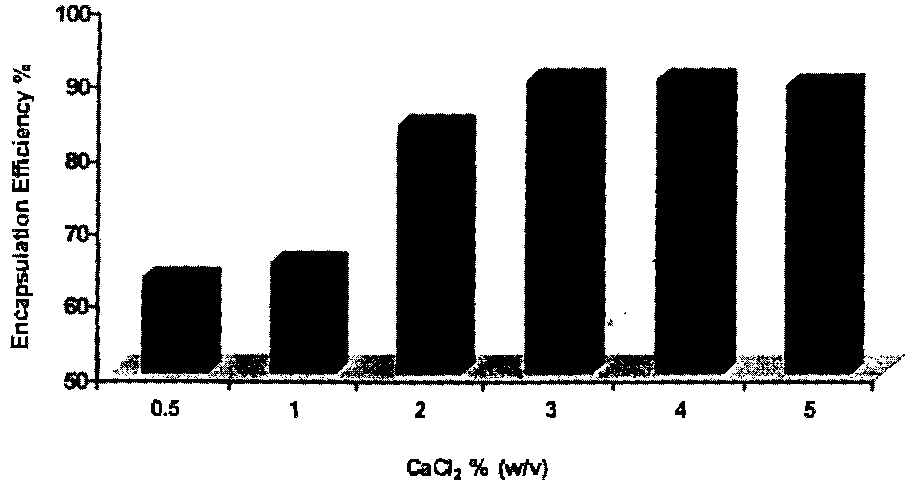

Fig. (3): Effect of $CaCl_2$ concentration on the encapsulation efficiency.

This can be explained as follow, at low concentration of $CaCl_2$ 0.5 & 1 % (w/v) the amount of Ca^{+2} ions were insufficient for fast cross-linking of alginate and the formed gels have low mechanical strength and large pores size so leakage of BB to the external medium took place leading to decrease of the EE. While at high concentration of $CaCl_2$, 2 & 3 % (w/v) the cross-linking of alginate was more efficient and quick due to a great quantity of Ca^{+2} ions were available to cross-link alginate, so strong gels with smaller pores size were formed, which reduced leakage of BB during preparation. Further increasing in $CaCl_2$ concentration more than 3% (w/v) showed no effect on encapsulation efficiency due to saturation of carboxylate group of alginate with Ca^{2+} ions **[Ali & Anish (2004); Bhopatkar et al., (2005) and Anil et al., (2003)]** thus for further optimization, 0.5 - 3 % (w/v) $CaCl_2$ were used.

3.2.3. Effect of curing time

Increasing the gelation time from 30 - 120 min during preparation of Ca-Alg beads using 2 % (w/v) sodium alginate and 3 % (w/v) $CaCl_2$ solution decreased EE from 90 – 84 % as shown in Fig. 4. The ionic interaction between carboxylate group in alginate and the small bivalent calcium ions was so quick. Further soaking of the alginate beads in the $CaCl_2$ solution lead to more leaching of BB. This may be due to the high solubility of BB in aqueous medium **[Kim & Lee (1992)]**. Thus, a curing

time of 30 min, which gives the maximum EE has been chosen for further experiments.

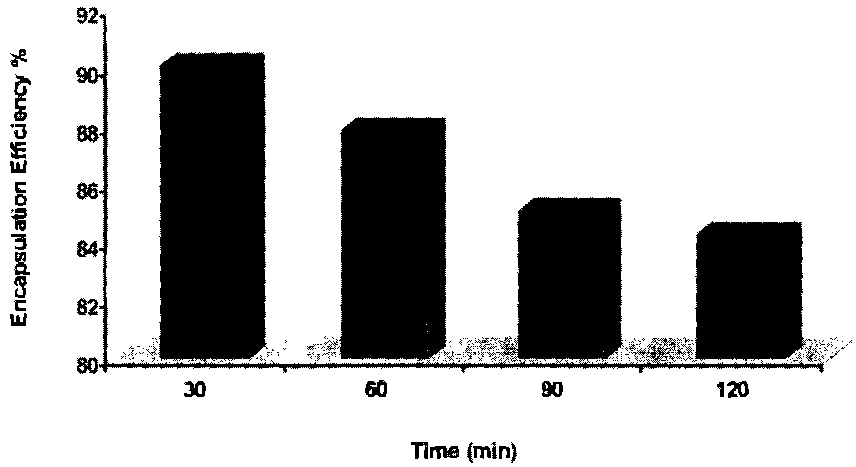

Fig. (4): Effect of curing time on the encapsulation efficiency.

3.3. In vitro release study

As described previously **[Akihiko et al., (1999)]** the release of low molecular weight drugs depends on diffusion through pores while drugs with high molecular weight as protein releases through swelling and disintegration of polymeric matrix. In our case, BB was used as model drug for low molecular weight drugs so its release was expected to be controlled by diffusion mechanism but we noticed that the release profile obeyed another mechanism according to the preparation condition.

3.3.1. Effect of $CaCl_2$

Increasing $CaCl_2$ concentration from 2 to 3 % (w/v) and keeping the alginate concentration and curing time at 2 % (w/v) and 30 min. respectively decreased the release rate of BB in phosphate buffer, pH 7.4 (simulated intestinal fluid), which is in agreement with previous studies **[Bhopatkar et al., (2005) and Anil et al., (2003)]**. For example, the release percent after 120 min was 66 and 84 % using 3 and 2 % (w/v) $CaCl_2$, respectively as shown in Fig. 5.

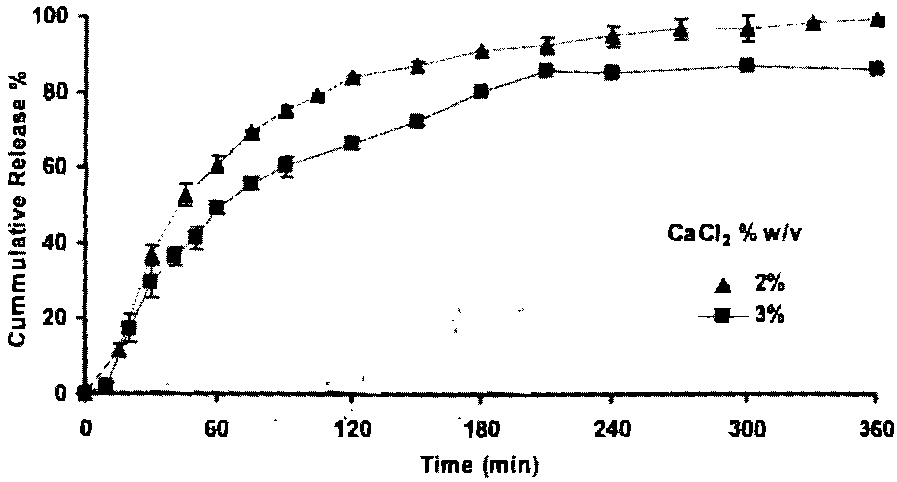

Fig. (5): Effect of $CaCl_2$ concentration on release rate of BB in phosphate buffer. pH 7.4 at 37 °C and 100 rpm.

This can be explained by the fact that at higher concentration of $CaCl_2$ cross-linking of alginate was more efficient, so strong gel with smaller pores size was formed, which retarded penetration of dissolution medium into the beads, which in turn decreased the release rate **[Ali & Anish (2004)]**. Also the efficient cross linking of alginate beads at higher $CaCl_2$ retarded disintegration of beads which take place due to the presence of phosphate ions in the buffer (phosphate buffer) which have a high affinity for Ca^{+2} ions. **[Dainty et al., (1986)]** reported that the disruption of Ca-Alg beads occurred faster in phosphate buffer above pH 5.5 by chelating action of phosphate ions, at these higher pH values, the affinity of phosphate ions toward calcium ions is higher than that of alginate, and solubility of calcium phosphate complex is high.

3.3.2. Effect of alginate concentration

Increasing the alginate concentration from 1 - 3 % (w/v) at constant $CaCl_2$ concentration and curing time of 3 % (w/v) and 30 min. respectively showed a significant effect on the release of BB in phosphate buffer pH 7.4. The rate of release could be divided into two sections, a) before two hours: The release of BB was found to follow this order: 1 % > 2 % > 3 % and b) after two hours: the release of BB was as follow: 1 % > 3 % > 2 % as shown in fig.6.

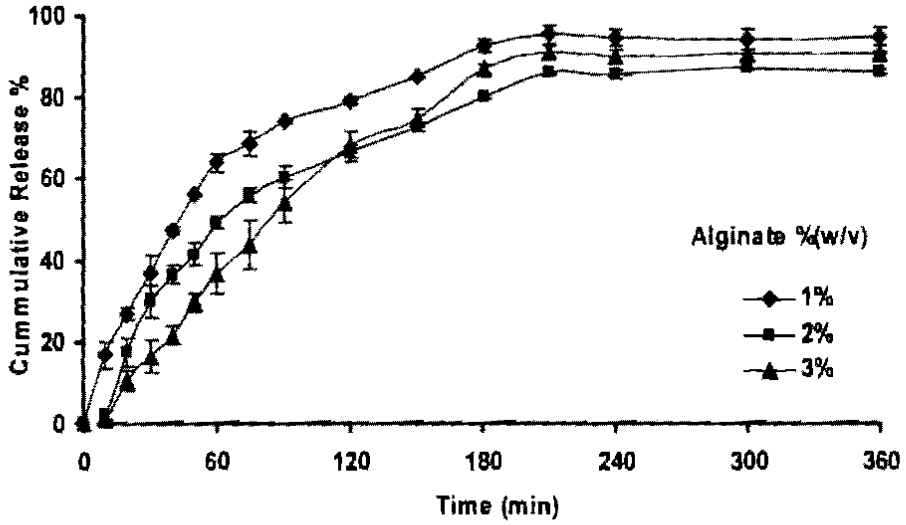

Fig. (6): Effect of alginate concentration on the release rate of BB in phosphate buffer pH 7.4 at 37 °C and 100 rpm.

For the rate of release before two hours, i.e. 1 % > 2 % > 3 %, this could be explained by the fact that increasing the alginate concentration increases the viscosity and provided more number of binding sites of alginate for Ca^{2+} ions resulting in the formation of a more stable and compact gel membrane with smaller pore size so penetration of dissolution medium into beads retarded and the release rate decreased **[Shi et al., (2006)].**

This was also supported by studying the release kinetics as shown in Fig. 7 where the release of drug from simple swellable polymeric matrix follow power law expression **[Pornsak et al., (2007)]** as shown in equation 3.

$$\text{Log } [M_t/M_\infty] = \log K + n \log t \qquad (3)$$

Where $[M_t/M_\infty]$ is the drug released fraction at time t, K is a constant and n is the release exponent.

There are three scenarios for n values:

1) If $n \leq 0.5$, the mechanism is called Fickian and the release is diffusionally controlled.

2) If $n \geq 0.85$, the mechanism is called case II Transport and the release is depending only on the relaxation/swelling of the polymer.
3) If $0.5 < n < 0.85$, the mechanism is called non Fickian (anomalous) and the release is depending on both the diffusion and relaxation of the polymer.

The increase in alginate concentration from 1 - 3 % (w/v) tended to increase the n values. Alginate concentration of 1% (w/v) showed n = 0.55 being close to Fickian mechanism due to large pore size and low mechanical strength of beads, which disintegrated rapidly so the release depended only on diffusion mechanism. Further increase of alginate concentration to 2 % increased n value to 0.64 following anomalous transport (non Fickian) due to increase in the gel mechanical strength so the release undergoes through diffusion and swelling (relaxation) of the polymer network. While using 3 % alginate, the n value increased to 0.97 shifting the release mechanism from anomalous transport to case II transport, which depended mainly on swelling/relaxation of the polymer network.

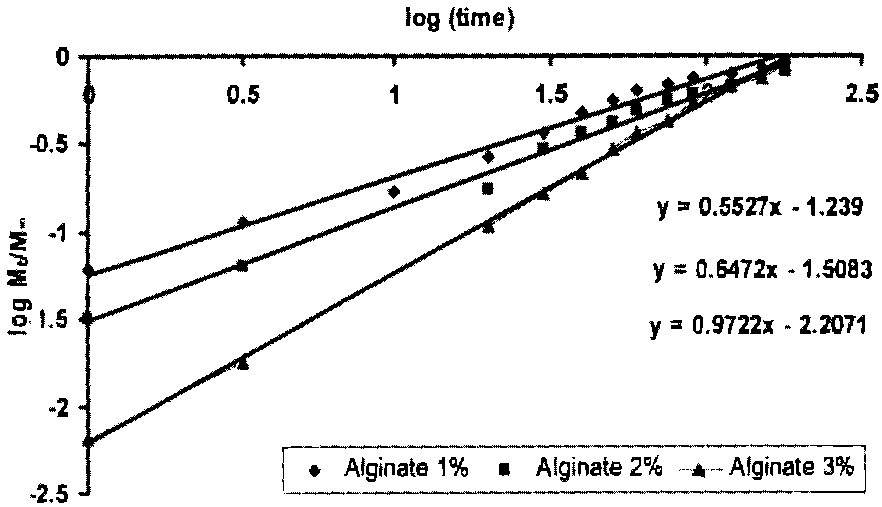

Fig. (7): Release kinetics of brilliant blue from calcium alginate beads.

For the rate of release after two hours, i.e. 1 % > 3 % > 2 %, the rate of release using 3 % (w/v) alginate started to be faster than that of 2 % (w/v) alginate as shown in Fig 6. To understand this unexpected behavior, swelling study for Ca-Alg beads of 2 % and 3 % (w/v) alginate concentration was carried out in phosphate buffer pH 7.4 as shown in Fig.8.

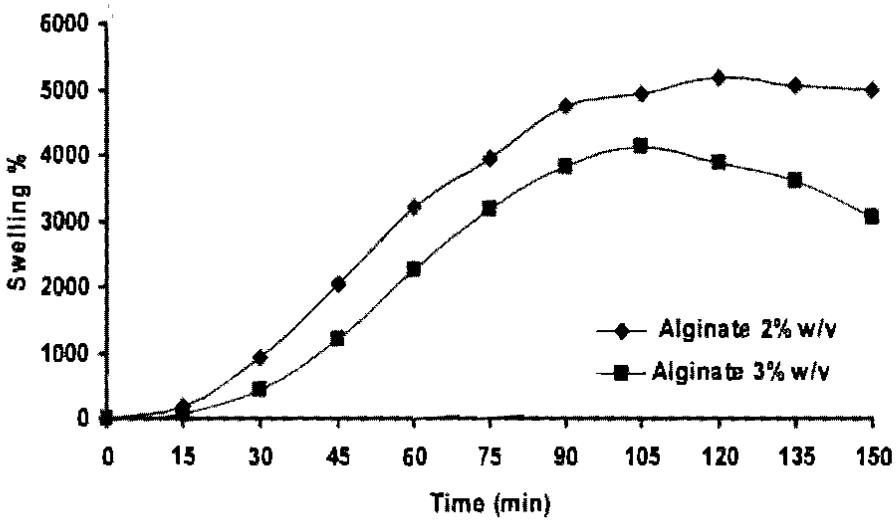

Fig. (8): Effect of alginate concentration on swelling percent of dry beads in phosphate buffer pH 7.4 at 37 °C and 100 rpm.

Two observations were noticed from the swelling study. The first, that beads prepared with 3 % (w/v) alginate showed lower swelling percent than that of 2 % (w/v) alginate, which was in harmony with the release results and release kinetics. The second was bursting and disruption of beads prepared with 3 % (w/v) alginate after 2 h while no bursting in case of 2 % (w/v) alginate, which showed a decline in swelling percent after 2 h for 3% (w/v) alginate beads. The latter was supported by the optical images of the beads after incubation in the release medium as shown in Fig. 9. This may be due to the higher osmotic pressure inside beads prepared with 3 % (w/v) alginate compared to that prepared with 2 % (w/v) alginate **[Shu & Zhu (2002)]**.

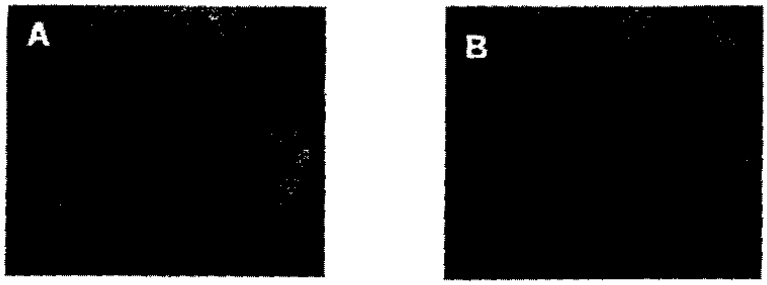

Fig. (9): Optical images showing bursting of beads after incubation in SIF buffer. (A): 2% (w/v) alginate, (B): 3% (w/v) alginate.

From above results and discussion, we noticed that use of higher alginate concentration could i) increase the mechanical strength of beads, ii) increase the EE, iii) delayed the drug release. But use of highly viscous alginate solution may create some other complications such as i) non homogenous cross-linking of beads as highly viscous medium of droplet could retard the diffusion of Ca^{+2} ions into the interior of beads, ii) inability to use hypodermic syringe to prepare smaller beads where the size of dried beads were increased from 544 to 638 µm with increasing alginate concentration from 2 to 3% (w/v), respectively , iii) improper mixing of drug with alginate solution, iv) bursting of beads due to the high osmotic pressure **[Bajpai & Rasika (2005)]**.

3.3.3. Effect of drying

The release was carried out for wet beads after immediately prepared and for beads dried in air for 24 h till constant weight. The release profile shows that the drying of beads accelerates the release rate as shown in Fig. 10.

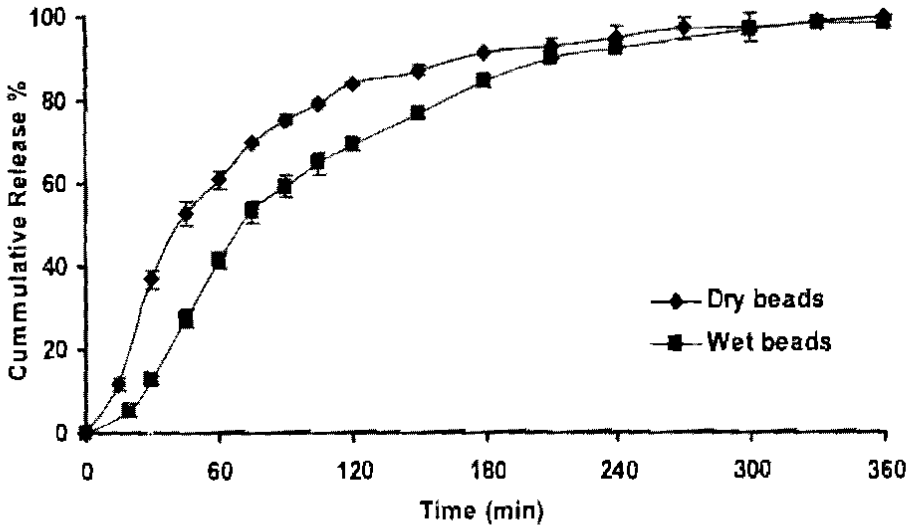

Fig. (10): Effect of drying on the release rate of BB in phosphate buffer pH 7.4 at 37 °C and 100 rpm.

This may be due to the dehydration of alginate gel leading to formation of cracks and large gaps on the surface of beads which accelerate the release of BB through it **[Sezer & Akbuğa (1999)]**.

3.4. Swelling study

Swelling studies were carried out to investigate the behavior of Ca-Alg beads in the release medium (gastro intestinal track) by monitoring the swelling percent and disintegration of the wet and dry beads in acidic medium pH 1.2 (simulate gastric medium) and in alkaline medium pH 7.4 (SIF). The swelling of wet Ca-Alg beads in alkaline medium as shown in Fig.11 exhibited a swelling of 236 % at 60 min and then began to disintegrate. This was due to the presence of Na^+ ions in the phosphate buffer which undergo ion-exchange with the Ca^{2+} ions present within the alginate chains. So the repulsion force between the negatively charged carboxylate group (i.e. $-COO^-$ groups) of alginate increased and the degree of cross-linking decreased due to loss of Ca^{2+} ions. This ultimately results in a rather loose structure and hence the beads take up more water until bursting of the beads take place and the beads start to disintegrate **[George & Nikolaos (2006)]**.

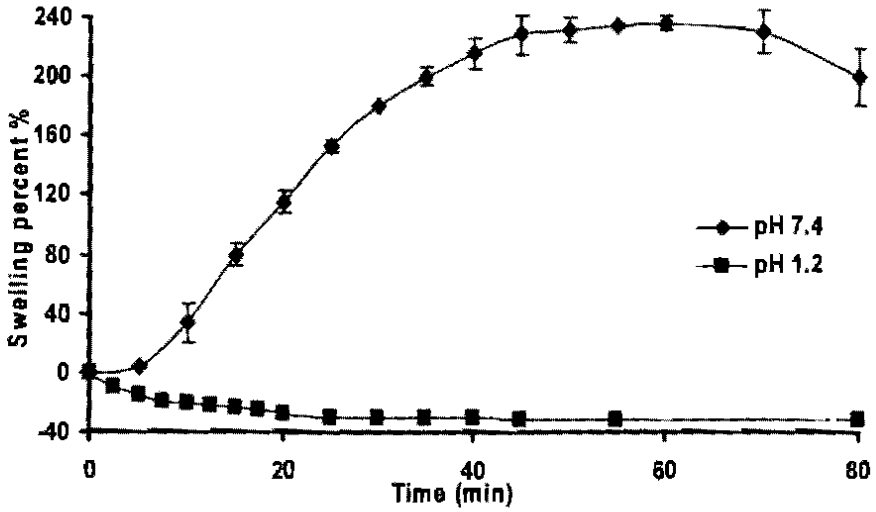

Fig. (11): Swelling percent of wet beads in HCl buffer, pH 1.2 and phosphate buffer, pH 7.4 at 37 °C and 50 rpm.

The same beads tend to shrink when exposed to acidic environment, pH 1.2. **Ouwerx et al., (1998)** have shown that at low pH values < 4, the carboxylate groups of alginate are protonized and hence the electrostatic repulsion among these groups decreased and shrinkage is favored so the interior water rejected out side the bead and a decrease in its weight take place.

On the other hand the swelling of the dried beads show high degree of swelling compared to wet beads as shown in Fig. 12. Calcium alginate beads exhibited nearly 5000 % swelling percent in phosphate buffer, pH 7.4 at 120 min then beads started to disintegrate. This was due to the hydration of the dried beads and the ion exchange mechanism between Na^{+} and Ca^{2+} ions, which was explained previously **[George & Nikolaos (2006)]**. The dried beads showed a very small swelling of 60% in HCl buffer without disintegration. This was due to hydration of the hydrophilic groups of alginate **[Bajpai & Rasika (2005)]**. These results indicated that Ca-Alg beads have a resistance towards acidic medium while it shows highly swelling percent and disintegration in alkaline medium. This phenomenon can be exploited in targeting the release of drugs to the intestinal region.

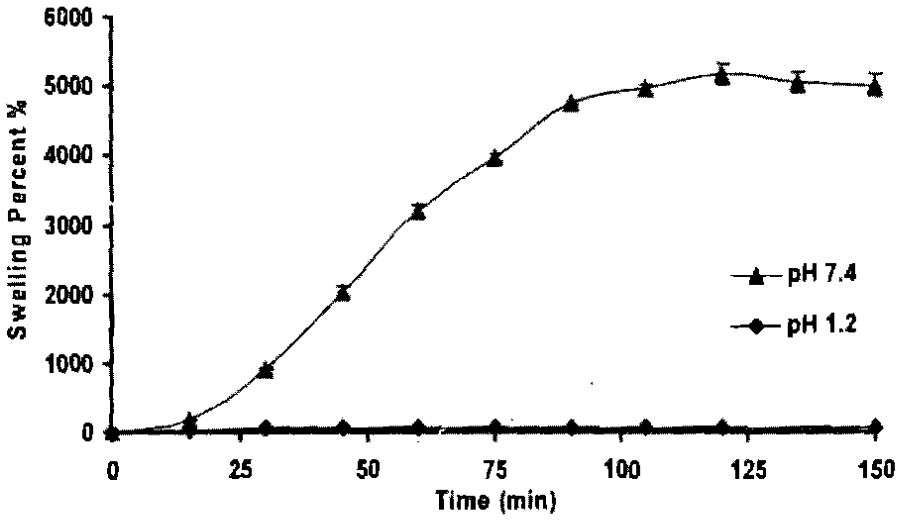

Fig. (12): Swelling percent of dried beads in HCl buffer, pH 1.2 and phosphate buffer, pH 7.4 at 37 °C and 50 rpm.

CONCLUSION

The optimum conditions for preparing alginate beads based on calcium chloride were studied inclusively. Results showed that Ca-Alg beads prepared using 2 % (w/v) alginate and hardened with 3% (w/v) $CaCl_2$ and cured for 30 min are showing the most suitable conditions for controlled Brilliant Blue release. It could also be appropriate for relatively low molecular weight drugs. Beads were in the spherical form, micrometer range, following anomalous mechanism with a maximum swelling of 5000 % in pH 7.4 compared to 60 % in pH 1.2. The Ca-Alg beads could be used for targeting drugs to the intestine.

REFERENCES

Akihiko, K.; Minako, K.; Atsushi, W.; Masayasu. S.; Yasuhisa, S.; Teruo, O.; Effect of Ca^{+2} alginate gel dissolution on release of dextran with different molecular weights. Journal of Controlled Release, 58, 21–28 (1999).

Ali N.; Anish T.; In situ cross-linking of sodium alginate with calcium and aluminium ions to sustain the release of theophylline from polymeric matrices. IL Farmaco, 59, 999-1004 (2004).

Anil, K. A.; Deepak, B.; Seiichi, T.; Hiroshi, T.; Willem, F. S.; Chitosan-alginate multilayer beads for gastric passage and controlled intestinal release of protein. Drug development and industrial pharmacy, 29(6) 713-724 (2003).

Anil, K. A.; Willem, F. S.; Chitosan-alginate multilayer beads for controlled release of ampicillin. International journal of pharmaceutics, 290. 45-54 (2005).

Arica, B.; Çaliş, S.; Atilla, P.; Durlu, N. T.; Çakar, N; Kaş, H. S.; Hincal. A. A.; In vitro and in vivo studies of ibuprofen-loaded biodegradable alginate beads. Journal of Microencapsulation, 22(2), 153-165 (2005).

Arica, B.; Çaliş. S.; Kaş, H. S.; Sargon, M. F.; Hincal, A. A.; 5-Fluorouracil encapsulated alginate beads for the treatment of breast cancer. International journal of pharmaceutics, 242, 267-269 (2002).

Bajpai, S. K.; Rasika, T.; Investigation of water uptake behaviour and stability of calcium alginate-chitosan bi-polymeric beads: Part-1. Reactive and Functional Polymers. 66(6). 645-658 (2005).

Bhopatkar, D.; Anal, A. K.; Stevens, W. F.; Ionotropic alginate beads for controlled intestinal protein delivery: effect of chitosan and barium counter ions on entrapment and release. Journal of Microencapsulation, 22(1) 91-100 (2005).

Biji B.; Jayakrishnan A.; Self cross-linking biopolymers as injectable in situ forming biodegradable scaffolds. Biomaterials. 26. 3941-3951(2005).

Cappai, A.; Petruzzo, P.; Ruiu, G.; Congiu, T.; Dessy, E.; Deseta, W.; Cruz, G.; Brotzu, G.; Evaluation of new small barium alginate microcapsules, International Journal of Artificial Organs, 18. 95–102(1995).

Chretien, C.; Chaumeil; J. C.; Release of macromolecular drug from alginate-impregnated microspheres. International journal of pharmaceutics, 304. 18-28 (2005).

Dainty, A. L.; Goulding, K. H.; Robinson, P.K.; Sinpkins. I.; Trevan, M. D.; Stability of alginate-immobilized algal cells. Biotechnology bioengineering, 28, 210-216 (1986).

Gåserød, O.; Smidsrød. O.; Skjåk-Braek G.; Microcapsules of alginate-chitosan-I A quantitative study of the interaction between alginate and chitosan. Biomaterials, 19. 1815-1825 (1998).

George P.; Nikolaos B.; Swelling studies and in vitro release of verapamil from calcium alginate and calcium alginate–chitosan beads. International Journal of Pharmaceutics, 323, 34–42 (2006).

Gerd, K.; Anja, P.; Christoph, R.; Patrik, G.; Beate, K.; Hans-Jürgen H.; Ulrich. Z.; Biocompatibility of mannuronic acid-rich alginates. Biomaterials, 18(10). 707-713 (1997).

Gombotz, W. R..; Wee. S. F.; Protein release from alginate matrices. Advanced drug delivery reviews. 31, 267–285 (1998).

Kim. C.; Lee. E.; The controlled release of blue dextran from alginate beads. International journal of pharmaceutics. 79, 11–19 (1992).

Kneafsey. B. O.; Shaughnessy. M.; Condon, K.C.; The use of calcium alginate dressing in deep hands burns. Burns. 22. 40-43 (1996).

Meera, G.; Abraham. T. E.: Polyionic hydrocolloids for the intestinal delivery of protein drugs: Alginate and chitosan - a review. Journal of Controlled Release 114, 1–14 (2006).

Ouwerx, C.; Velings, N.; Mestdagh, M. M.; Axelos, M. A. V.; Physico-chemical properties and rheology of alginate gel beads formed with various divalent cations. Polymer Gels and Networks, 6, 393–408 (1998).

Peppas, N.A.; Buri, P.A.; Surface, interfacial and molecular aspects of polymer bioadhesion on soft tissues. Journal of Controlled Release, 2. 257-275 (1985).

Pornsak, S.; Nartaya, T.; Kingkarn, K.; Swelling, erosion and release behavior of alginate-based matrix tablets. European Journal of Pharmaceutics and Biopharmaceutics, 66, 435–450 (2007).

Sankalia, G. M.; Rajshree. C. M.: Jolly M. S.; Vijay B. S.; Papain entrapment in alginate beads for stability improvement and Site-Specific Delivery: physicochemical characterization and factorial optimization using neural network modelling. AAPS PharmSciTech. 6 (2) Article 31(2005).

Sezer, A. D.; Akbuğa J.; Release characterization of chitosan treated alginate beads: II. Sustained release of low molecular weight drug from chitosan treated alginate beads. Journal of Microencapsulation, 16(6) 687-696 (1999).

SHI, X.W.; DU, Y. M.; LI, J.; SU, X.L.; YANG J.H.; Release characteristics of brilliant blue from calcium-alginate beads coated with quaternized chitosan. Journal of Microencapsulation, 23(4), 405–415 (2006).

Shu, X. Z.; Zhu. K.J.; The release behaviour of brilliant blue from calcium–alginate gel beads coated by chitosan: the preparation method effect. European Journal of Pharmaceutics and Biopharmaceutics, 53, 193–201 (2002).

Skjåk-Braek, G.; Grasdalen, H.; Smidsrød, O.; Inhomogeneous polysaccharide ionic gels. Carbohydrate Polymers, 10, 31-54 (1989).

Smidsrod, O.; Skjak-Break, G.; Alginate as immobilization matrix for cells. Trends in Biotechnology, 8, 71-78 (1990).

Steve, W. N. U.; Mel, S. L.; Song–Shu, L.; Err-Cheng, C.; Shih-Jung L.; Development of a biodegradable alginate carrier system for antibiotics and bone cells. Journal of Orthopaedic Research, 25(1), 62-72 (2007).

Vandenberg, G.W.; DE LA Noüe, J.; Evaluation of protein release from chitosan-alginate microcapsules produced using external or internal gelation. Journal of Microencapsulation, 18(4), 433–441 (2001).

Xiao-Peng, W.; Tian-Ning, C.; Zhan-Xiao, Y.; Modelling and simulation of drug delivery from a new type of biodegradable polymer micro-device. Sensors and Actuators A, 133, 363–367 (2007).

Yotsuyanagi, T.; Ohkubo, T.; Ohhashi, T.; Ikeda, K.; Calcium induced gelation of alginic acid and pH-sensitive reswelling of dried gels. Chemical and Pharmaceutical Bulletin, 35(4) 1555–1563 (1987).

دراسة العوامل المؤثرة على كفائة حبيبات الكالسيوم ألجينات على تغليف الدواء ومعدل خروجه من الحبيبات

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يهدف هذا البحث لعمل دراسة مكثفة لتحضير كبسولات من الكالسيوم ألجينات التى تحتوى على أزرق البريلينت كنموذج للعقاقير والمواد الفعاله المختلفه حيث تم دراسة تـــاثير تركيز كل من الألجينات وكلوريد الكالسيوم والزمن اللازم للتشبك على مدى كفائة الألجينات لتغليف أزرق البريلينت ومعدل خروجه من الكبسولات وكذلك توصيف الكبسولات باســتخدام الميكرسكوب الإلكترونى كما تم دراسة معدل إنتفاخ الكبسولات فى أوساط محاكيـــة للمعـــدة والأمعاء فى جسم الإنسان حيث أظهرت الدراسة إمكانية إستخدام كبسولات الكالسيوم الجينات لتوجيه خروج العقار فى منطقة الأمعاء.