Surface Morphology and Release Behaviors of Theophylline Loaded Sodium Alginate Gel Beads

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Abstract

Theophylline loaded alginate beads were prepared by ionic cross linking technique. Beads were prepared by dropping a drug-alginate solution in 5% (W/V) calcium chloride for surface cross-linked beads. The beads were characterized by swelling index, Scanning Electron Microscope SEM) and *in vitro* drug release. The swelling index was highest in formulation 4 (12.29% in 5 hours) and formulation 3 showed the lowest swelling (6.91% in 4 hours). The surface morphology of the different bead formulations were studied using scanning electron microscopy (SEM). Surface of beads with various amount of sodium alginate reveals that smooth, dense and closely packed drug-polymer bonding is obtained when the amount of alginate is increased. In vitro dissolution of beads was carried out in USP rotating basket method at 100rpm for 8 hours. The dissolution data were treated with zero order, first order, Higuchi, Korsmeyer-Peppas, Hixson-Crowell model. Most of the formulations were fitted to Korsmeyer's model. Finally it can be concluded that with the increasing alginate concentration, the release rate of Theophylline was decreased.

Keywords: Theophylline, ionic cross-linking technique, sodium alginate, swelling index, release kinetics.

Introduction

Natural hydrophilic polymers, owing to their characteristic biocompatibility and biodegradability properties, are widely exploited in the pharmaceutical industry for the development of novel drug delivery systems (Shilpa A. *et al.*, 2003). Among these polymers, alginate is one that has been widely used in numerous biomedical applications, processed in various dosage forms e.g. tablets, capsules, beads, rafts, liquid suspensions (Draget K.I. *et al.*, 1997).

Calcium-induced alginate gel beads have been developed in recent years as a unique vehicle for drug delivery system. (Bodmeier R. *et al.*, 1989; Bodmeier R. *et al.* 1993). The beads were prepared using ionotropic gelation technique (Lim F. *et al.* 1980; Segi N. *et al.*, 1989) where gelation of anionic polysaccharide sodium alginate, the primary polymer of natural origin, was achieved with oppositely charged calcium ions, acting as counter ion, (Lim LY. *et al.*, 1997) to form instantaneous microparticles.

Theophylline, an alkaloid found in leaves of *Camelia sinensis* is used clinically as a bronchodilator in the management of Chronic Obstructive Pulmonary Disease (COPD). Our aim is to develop a sustain release preparation of Theophylline to provide desirable serum concentrations for prolonged periods without frequent dosing thereby providing patient compliance (ZhilingYu *et al.*, 1996)

The beads were evaluated with respect to surface morphology by scanning electron microscopy (SEM), swelling index and *in-vitro* drug release in water medium.

Materials and Methods

Materials: Theophylline anhydrous (Eskayef Bangladesh Ltd), Sodium Alginate (BDH Chemicals Ltd., England), Calcium chloride (Merck, Germany) were used in this study from the indicated sources.

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Preparation of Alginate gel beads: Different concentrations (0.75 to 2.5 gm/100 ml) of w/v Sodium alginate solution were prepared by dissolving in distilled water with gentle heat and agitation to have homogenous dispersion. The solution was heated in water bath with continuous stirring. A clear solution will appear within 30 to 40 minutes. The gel solution was then taken in a 23 gauge hypodermic needle fitted with 10 ml syringe and was added drop wise to 5% calcium chloride solution. After the beads formed, they were separated, washed with distilled water, dried in air for 24-48 hours. (D. Nagasamy Venkatesh *et al.*, 2008; Ahmed A. El-Zatahry, 2008).

Here, different formulations of Theophylline (1gm) having alginate polymer of 0.75, 1, 1.5, 2 and 2.5gm incorporated with the formulation code F 1, F 2, F 3, F 4 and F 5 respectively was prepared.

Characterization of Theophylline loaded sodium alginate gel beads

Surface morphology of the beads by scanning electron microscopy: Scanning Electron Microscope (SEM) was used to study the morphology of the prepared beads. Scanning electron microscopy was performed using Hitachi (Model: S-3400 N, Japan) scanning electron microscope having different magnifications and the micrographs are presented.

Swelling study: The extent of swelling was measured in terms of % weight gain by the beads. The swelling behaviors of all the formulations were studied. In this test 20 mg of beads from each formulation was kept in petridish containing distilled water. At the end of 1 hour, the beads were withdrawn, soaked with tissue paper and weighed. Then for every 1 hour, weights of beads were noted and the process was continued till the end of 8 hours, % weight gain by the beads was calculated by the following formula (Yeole PG, 2006).

Swelling Index (SI) = {$(W_t - W_0)/ W_0$)] x 100

Here, W_t = Mass of swollen beads at time t

W_0 = Mass of dry beads at t=0

In-vitro **release studies of Theophylline from beads:** *In vitro* release studies of prepared beads were carried out using USP rotating basket method in 900ml distilled water of 37±0.5ºC at a rotational speed of 100rpm. Dissolution was carried out for a total period of 8h using distilled water as dissolution medium. At periodic time intervals, 5ml of sample withdrawn suitably diluted and absorbance was measured at 271nm. Five milliliters of fresh dissolution media was added each time to maintain the sink conditions (Das .M.K, 2008).

Kinetic models: The suitability of several equations that are reported in the literature to identify the mechanisms for the release of Theophylline was tested with respect to the release data. The data were evaluated according to the following equations:

Zero-order equation:

$Q_t = K_0 t$ …………..................... (1)

Higuchi equation based on Fickian diffusion :

$Q_t = K_H \sqrt{t}$ …………….............. (2)

Where, Q is the amount of drug release in time t, k_0, and k_H are rate constant of zero order and Higuchi rate equations respectively (Higuchi T., 1961; Higuchi T., 1963; Donbrow M *et al.*, 1983).

First order model:

$LogC = LogC_o - kt/2.303$……… (3)

Where, C = cumulative percent of drug release, Co = the initial concentration of drug and k = first order rate constant (Donbrow M *et al*, 1983).

Korsmeyer-Peppas model:

$Log (M_t/M_f) = logk + nlogt$…….. (4)

Where M_t is the amount of drug release at time t; M_f is the amount of drug release after infinite time; k is a release rate constant incorporating structural and geometric characteristics of the dosage form; n is the diffusional exponent indicative of the mechanism of drug release (Merchant HA *et al.*, 2006; Korsmeyer RW, 1983).

Hixson-Crowell's cube root equation:

$(100-W) 1/3 = 1001/3-kt$………. (5)

Where W= % of drug released at time t, k= Hixson Crowell release kinetics (Singh P *et al.*, 1967; Deasai S.J *et al.*, 1966).

Mean Dissolution Time (MDT):

$$MDT = \left(\frac{n}{n+1}\right) k^{-\frac{1}{n}} \quad ……………… (6)$$

Where n = release exponent and k = release rate constant. A higher value of MDT indicates a higher drug retaining ability of the polymer and vice-versa (Mockel JE *et al.*, 1993).

Results and Discussion

Effect of sodium alginate on surface morphology of Theophylline beads: Five different alginate concentrations were considered to investigate the effect of different polymer content on surface morphology of the Theophylline beads. Sodium alginate was used at five different concentrations i) 0.75, ii) 1, iii) 1.5, iv) 2, v) 2.5 % w/v.

In case of F 2, particle surface was rough (Figure 1a). Large particles were observed in the surface of the beads. Rod-shaped crystals with sharp corners were visible because of the thin polymer coat in the case of F 2 (Figure 2). Comparatively, in case of F 3 (Figure 1b), beads were more spherical in shape. Here, rod shaped drugs were visible (Figure 3).

But beads in F 4 were smooth, and homogenous in nature (Figure 1c and Figure 4). In the formulation mixture drug-polymer ratio was 1:2 and a uniform drug-polymer binding was assumed in the microsphere. And it was observed from the SEM image of the beads that the surface was more looked like a layer of mixture of drug and polymer rather than a layer of only polymer (Figure 4).
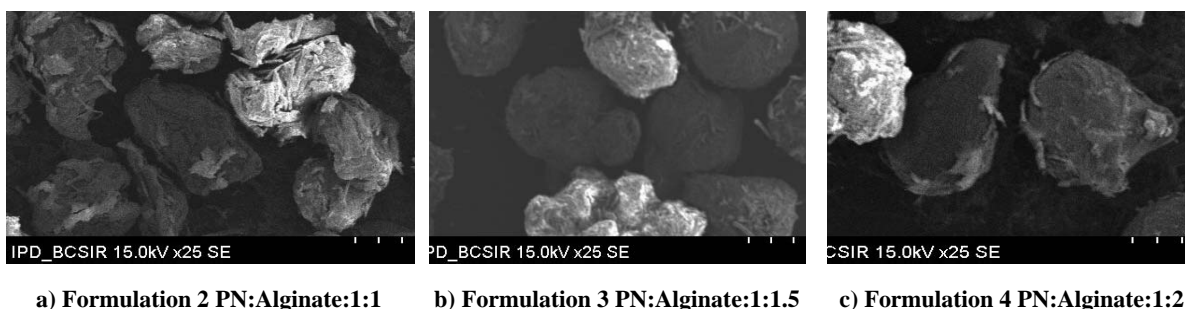

| a) Formulation 2 PN:Alginate:1:1 | b) Formulation 3 PN:Alginate:1:1.5 | c) Formulation 4 PN:Alginate:1:2 |

Figure 1: Effect of sodium alginate on surface morphology of Theophylline beads at magnification X25

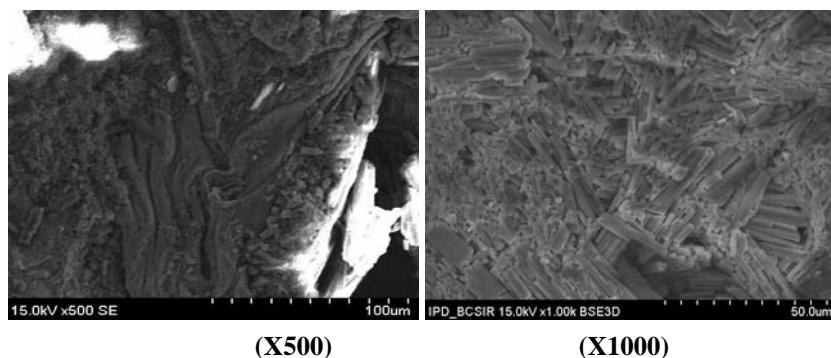(X500)   (X1000)

Figure 2: Scanning electron microscopy photomicrographs of formulation 2

(X500)   (X2000)
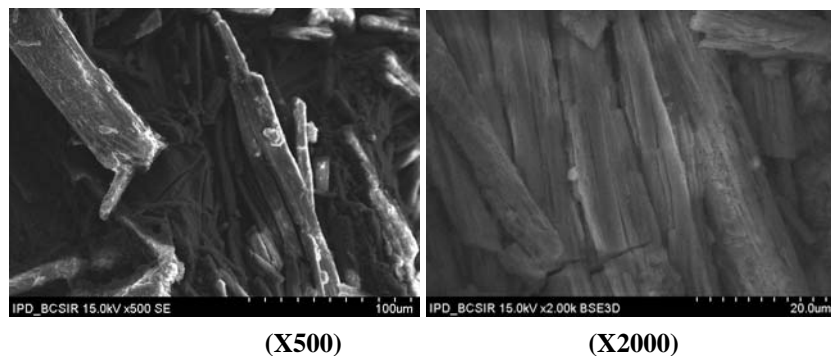
Figure 3: Scanning electron microscopy photomicrographs of formulation 3

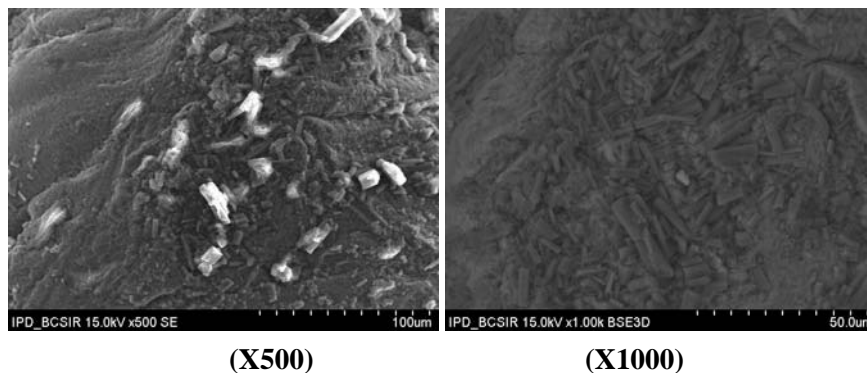(X500)   (X1000)

Figure 4: Scanning electron microscopy photomicrographs of formulation 4

Swelling study of Theophylline loaded alginate beads: The formulation from number 1 to 5 has different alginate concentration i.e. 0.75 gm to 2.5 gm with constant Theophylline loading. Among these formulations F 1 swelled up to 4 hour. It shows swelling of 7.83%. F 2 (10.44%), F 3 (6.91%) and F 4 (12.29%) swelled high up to 5 hours (Table 1 and Figure 5). Alginate based F 5 swelled high up to 4 hour with swelling index of 8.28%. Thus formulation 4 showed the highest swelling when Theophylline: Alginate ratio is 1gm: 2gm.

Table 1: Data for swelling index of Theophylline loaded Alginate beads

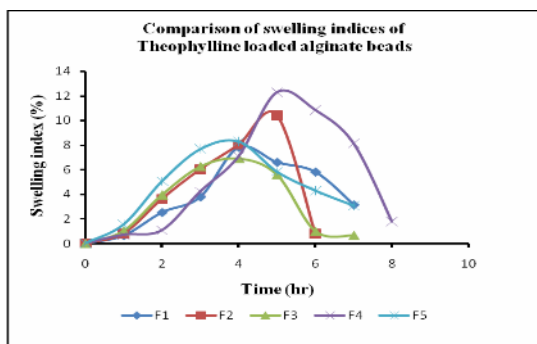| Time(hr)	F1	F2	F3	F4	F5
0	0.63	0	0	0	0
1	2.52	0.80	1.01	0.71	1.53
2	3.79	3.61	3.95	1.07	5.05
3	7.83	6.02	6.25	4.21	7.67
4	6.62	8.03	6.91	7.07	8.28
5	5.83	10.44	5.59	12.29	5.83
6	3.15	0.80	0.99	10.86	4.29
7	0.63	-	0.66	8.14	3.07
8	-	-	-	1.79	-

Figure 5: Comparison of swelling indices of Theophylline loaded Alginate beads

***In-Vitro* Release Kinetics:** From Figure 6, a release profile of Theophylline from alginate beads were obtained. F 1, F 2, F 3, F 4 and F 5 showed 100.7%, 71.9%, 58.2%, 50.1% and 34.6% release respectively at 8 hours. So, it was observed that drug release rate has been decreased with increase amount of alginate. As the weight of the alginate increases, its hydrophobicity increases, leading to better precipitation of polymer at the boundary phase of droplets. When the bead surface wets by the water media the alginate starts to partially hydrate, forming a gel layer. Initial burst effect of soluble beads from the external layer is released. The media penetrates into the beads increasing the thickness of the viscous gel layer and soluble bead is released by diffusion from the gel layer and by exposure through beads erosion. The prolongation of the release rate from the alginate beads with increase of alginate concentration reflects the concomitant increases in gel strength which is a determining factor in this case since the release of drugs in alginate matrices are mainly through the diffusion of the drug through the pores of the polymer network which can be significantly reduced in size by increasing the alginate concentration (Ahmed A. El-Zatahry, 2006).

In case of F 1 and F 2, the polymer content 0.75gm and 1gm was not sufficient to retard the release of drug from the surface of the beads. This phenomenon is attributed to the fact of surface erosion or initial degradation of beads.

The highest percentage of drug release within 8 hours is from F 1 where alginate is 0.75g. But in F 5 where the alginate amount is 2.5g, Theophylline release from that formulation was 34.6%. The

highest sustaining effect was observed in F 4 (contain 1:2 Theophylline-alginate) 50.1% for 8 hour as it swells much observed from swelling study.

From SEM photomicrographs (Figure 2), we can also interpret that in F 2; the extent of cross linking is lower as alginate percentage is lower. So, the drug release is also higher than F 3, F 4 and F 5. Rod-shaped crystals with sharp corners were visible because of the thin polymer coat in the case of F 2.

Comparatively, in F 4, the cross linking is adequate and release rate of drug indicates sustaining action. SEM photomicrographs shows strong cross linking. Here, rod shaped drugs are closely entrapped within the cross link (Figure 4).
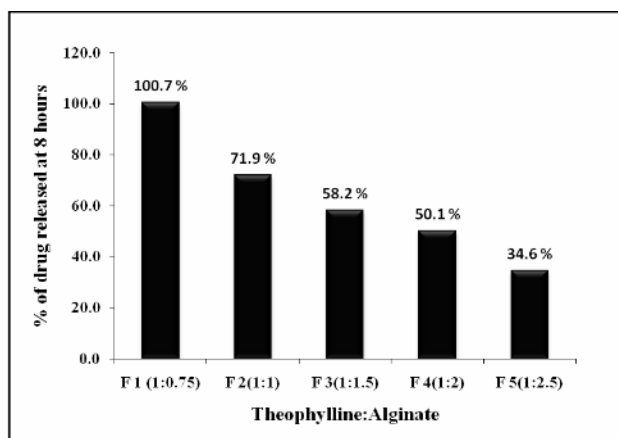

Figure 6: Comparative release profile of beads containing different ratios of Theophylline-Alginate

Data treatment of Theophylline from alginate based beads in light of rate constant, R^2 and MDT value: Alderman reported that when the hydrophilic matrix tablet enters an *in vitro* dissolution medium, drug particles initially pass into solution from the surface (immediate release). The solid matrix also begins to swell (polymer relaxation) as soon as hydration with solvent molecules, diffusion of the dissolved drug and erosion of gelatinous viscous polymer layer into aggregates of granules and these in turn disaggregates into fine particles that release their drug content by dissolution.

Table 3 shows that F 1 to F 5 exerts good linearity for the Korsmeyer's equation, as their R^2 value is from 0.941 to 0.968. Their n values were indicator of drug release through diffusion mechanism.

Table 2: Interpretation of R-squared values of different release profile of alginate based Theophylline beads

Formulation	Coefficients of correlation, R^2				
	Zero order	First order	Higuchi	Korsmeyer	Hixson-Crowell
1	0.866	0.870	0.866	0.941	0.861
2	0.955	0.965	0.955	0.992	0.952
3	0.879	0.890	0.879	0.900	0.872
4	0.806	0.814	0.806	0.890	0.801
5	0.923	0.928	0.923	0.968	0.917

Table 3: Interpretation of release rate constant and successive fractional dissolution time (hr)

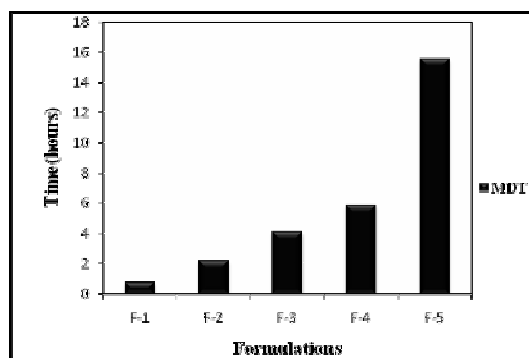| Formulation	From Korsmeyer kinetics		
	K_k	n	MDT(hr)
1	0.732	0.23	0.77
2	0.416	0.48	2.17
3	0.363	0.39	4.12
4	0.329	0.37	5.89
5	0.237	0.35	15.52

Figure 7: Successive fractional dissolution time (hour) of alginate based Theophylline from beads of F 1 to F 5

Table 4: Best fitted model and release mechanism of formulation 1 to formulation 5

Formulation	Best fitted model	n (Release Exponent)	Release mechanism
1	Korsmeyer	0.23	Fickian (case 1) diffusion
2	Korsmeyer	0.48	Non-Fickian (anomalous) diffusion
3	Korsmeyer	0.39	Fickian (case 1) diffusion
4	Korsmeyer	0.37	Fickian (case 1) diffusion
5	Korsmeyer	0.35	Fickian (case 1) diffusion

The MDT values of different formulations manifest the effect of polymer. F 1 contains least amount of alginate and shows MDT value of 0.77 hours from Table 3. This means drug release rate will be faster for this formulation. As, the concentration of alginate increases, the drug release rate gradually becomes slower and MDT value becomes gradually higher. That's why the MDT value for F 5 is 15.52 hours, because of highest amount of alginate.

Conclusion

The morphology, swelling and release behaviors of Theophylline loaded alginate beads were investigated in this study. Polymer-drug ratio influences the drug release pattern and surface morphology. As the amount of alginate is increased the drug release was decreased. But, up to a certain increase in alginate amount shows marked rise in swelling as well as drug release from the gel layer. It can be concluded that alginate has the ability to retard the drug release to a considerable extent. But proper adjustment of drug-polymer ratio can influence the therapeutic efficacy.

Acknowledgement

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