Effect of Various Excipients on Theophylline-loaded Alginate Beads Prepared by Ionic Cross Linking Technique

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ABSTRACT: Theophylline loaded sodium alginate beads were prepared by ionic cross linking technique using calcium chloride ($CaCl_2$) as cross linking agents. The purpose of this work was to prepare sodium alginate beads as a device for the extended release of theophylline. Different excipients like sodium carboxy methyl cellulose, polyethylene glycol 4000, hydroxy propyl methyl cellulose, sodium starch glycolate, Eudragit L 100 and sodium lauryl sulphate were used to fabricate theophylline-alginate beads and their effect on drug release were investigated. In this study, the beads were characterized and evaluated in respect to their surface morphology, swelling index (SI) and *in-vitro* release characteristics. Beads were prepared by dropping a hot aqueous theophylline-alginate or theophylline-alginate-excipient solution into electrolyte solution. Alginate cross linked with electrolytes and beads were formed with entrapped drug. Beads were collected by decanting the solution and dried at room temperature. Surface of beads with various excipients revealed that smooth, dense and closely packed drug-polymer bonding was obtained when the excipients were changed. Beads in F 1 contain Eudragit L 100 that swelled highest at 3 hours with SI of 10.74 %. Sodium starch glycolate beads (F 4) swelled high up to 9.93 % at 2 hours. Dissolution studies were carried out in 900 ml of distilled water for 8 hours. Most of the formulations were fitted to Higuchi model. The drug release rate are shown in decreasing order: Eudragit L 100>Sodium carboxy methyl cellulose> Sodium lauryl sulphate> Sodium starch glycolate>Hydroxy propyl methylcellulose 5 cps>Polyethylene glycol 4000. The use of Eudragit L 100 was found to be promising because it released about 69 % of theophylline within 8 hours. It was found that among the hydrophilic polymers used, Sodium carboxy methyl cellulose showed 49 % theophylline release within 8 hours. The lowest amount of drug release was found with HPMC 5 cps and PEG 4000 which was about 26 % of drug release.

Key words: Theophylline, ionic cross-linking technique, sodium alginate beads, swelling index, release kinetics.

INTRODUCTION

Theophylline is a bronchodilator, which is used in treating Chronic Obstructive Pulmonary Disease (COPD). Conventional dosage forms of theophylline are administered 3–4 times a day to avoid large fluctuations in plasma concentrations. It is rapidly absorbed and eliminated. Our aim was to develop a sustained release preparation of theophylline to provide desirable serum concentrations for prolonged periods without frequent dosing, thereby providing patient compliance.[1]

The main concern of this study was to prepare good sustained release sodium alginate based beads of theophylline by the ionic cross-linking technique using different excipients like Eudragit L 100, Sodium carboxy methyl cellulose (SCMC), Sodium lauryl sulphate (SLS), Sodium starch glycolate (SSG), Hydroxy propyl methyl cellulose (HPMC) 5 cps, Polyethylene glycol (PEG) 4000 were used to fabricate Theophylline-alginate beads

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and their effect on drug release were investigated. Since alginate gel can easily be formed by this ionic interaction in aqueous medium, gel beads are commonly obtained by dropping solutions of alginate into solution of electrolyte.[2]

The use of Eudragit L 100, a copolymer based on methacrylic acid and methacrylic acid methyl ester, in preparing theophylline beads was done successfully.[3] Sodium lauryl sulphate is used as dispersing agent and sodium carboxy methyl cellulose is an anionic water soluble polymer. Their effect on beads showed modified release of theophylline. Sodium starch glycolate absorbs water rapidly, resulting in swelling which leads to rapid disintegration of beads. Hydroxy propyl methyl cellulose and polyethylene glycol can be formed to transparent, tough, flexible film that can reliably control drug release.[4,5,6]

The present study deals with the use of various excipients in theophylline-alginate beads prepared by ionic cross linked technique to observe the *in vitro* release characteristics, swelling study and surface morphology.

MATERIALS AND METHOD

Theophylline anhydrous (Eskayef Bangladesh Ltd), Sodium Alginate (BDH Chemicals Ltd., England), Calcium chloride (Merck, Germany), Eudragit L 100 (Merck, Germany), Hydroxy propyl methyl cellulose 5 cps (Merck, Germany), Polyethylene glycol 4000 (Merck, Germany), Sodium carboxy methyl cellulose (Merck, Germany), Sodium lauryl sulphate (Merck, Germany), Sodium starch glycolate (Merck, Germany), used in this study were obtained from the indicated sources.

Preparation of alginate beads by ionic cross linking technique. Sodium alginate solution was prepared by dissolving in distilled water with gentle heat and agitation to have homogenous dispersion. Theophylline and different excipients were added to alginate solution. Calcium chloride ($CaCl_2$) solution was prepared as 5 % solution. The solution was continuously stirrer with glass rod while heating in the thermostatic water bath until clear solution appeared. Heating was done up to 30-40 minutes. When all the ingredients were mixed completely a gel was formed, then it was taken in a 23 gauze hypodermic needle fitted with 10 ml syringe and was added drop wise to 5 % calcium chloride solution.

Upon addition, the solution was being mechanically stirred using stirrer. The distance of nozzle from the solution was about 5 cm. When the gel was poured into the electrolyte solution as droplets, they became spherical and it became hard since the temperature was below the gelling point of alginate. Thus alginate beads were prepared. The prepared beads were allowed to stand in the solution for 15 minutes, and then the beads were decanted, washed with distilled water, dried in air for 36-48 hr.[7,8]

Characterization of theophylline loaded alginate beads

Surface morphology: 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 in Figure 1 to 8. Prior to examination the beads were placed on carbon tape and then placed on a disk to examine the surface.

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.[9]

Swelling Index (SI) = $\{W_t - W_0\}/ W_0)] \times 100$

Here, W_t= Mass of swollen beads at time t

W_0= Mass of dry beads at t=0

***In vitro* dissolution study:** *In-vitro* dissolution studies were carried out using USP XXX apparatus Type-II (Basket Apparatus) in 900 ml distilled water of 37±0.5ºC at a rotational speed of 100 rpm. Dissolution samples were withdrawn at appropriate intervals up to 8 hours and then filtered through 0.45 µm filters. The drug content was determined spectrophotometrically at λ_{max} = 271nm in the filtrate either directly or after appropriate dilution with the dissolution media. The dissolution study for each batch was performed in triplicate.

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: [10-13]

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.

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.

Determining the correlation coefficient assessed fitness of the data into various kinetic models. The rate constants, for respective models were also calculated from slopes.

RESULTS AND DISCUSSION

Surface morphology. The drug release from Eudragit L 100 is due to formation of pores and channels and due to swelling of polymer up to some extent. The resultant beads were more spherical and had a smooth surface.[14] Surface morphology also attributes to this fact in Figure 1 and 2.

Table 1. Different formulations of alginate beads prepared with various excipients

Batch code	Theophylline (gm)	Sodium alginate (mg)	Polymer 2 (mg)	Polymer name
1	1	900	100	Eudragit L 100
2	1	900	100	Sodium carboxy methyl cellulose
3	1	900	100	Sodium lauryl sulphate
4	1	900	100	Sodium Starch Glycolate
5	1	900	100	HPMC 5 cps
6	1	900	100	Polyethylene glycol 4000

Table 2. Data for swelling index of alginate based theophylline beads with various excipients

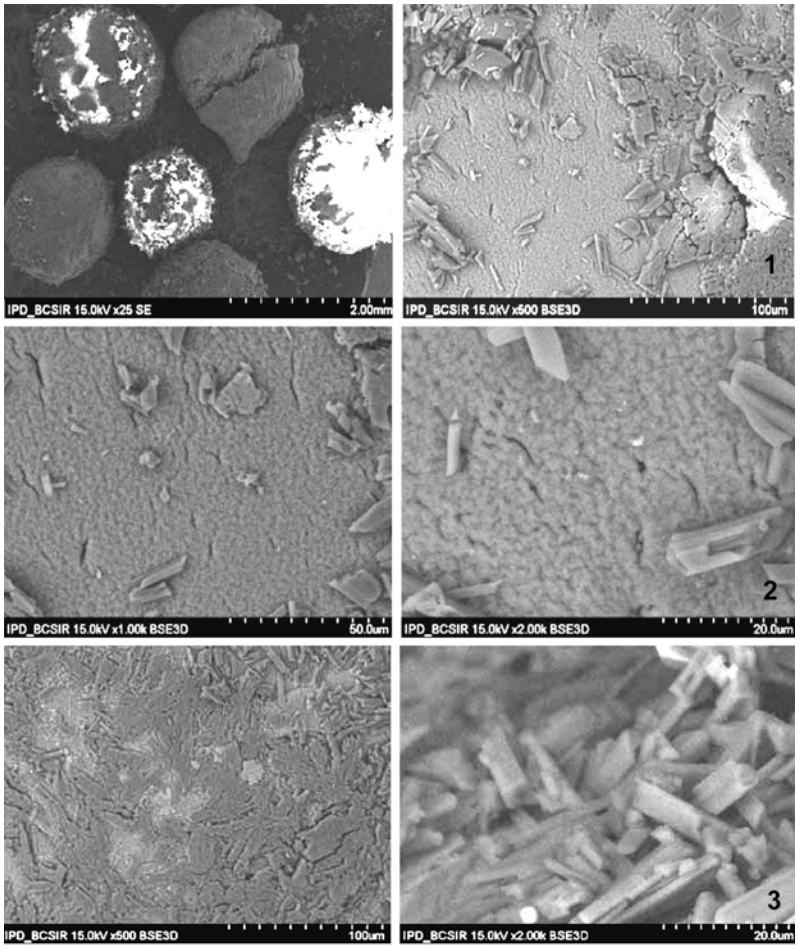
Time(hr)	F 1(Eud L 100)	F 2 (SCMC)	F 3 (SLS)	F 4 (SSG)	F 5 (HPMC 5cps)	F 6 (PEG 4000)
0	0	0	0	0	0	0
1	2.99	3.10	1.85	8.60	1.67	0.53
2	5.52	4.52	3.44	9.93	3.00	3.56
3	10.74	5.52	5.19	9.37	4.67	5.21
4	7.98	6.86	6.04	8.61	8.67	4.56
5	5.22	9.66	7.41	8.44	5.00	3.26
6	4.22	5.10	7.78	8.27	3.67	1.95
7	3.68	2.76	8.15	7.29	2.67	0.98
8	-	-	6.67	5.96	1.67	0.33

SEM of Formulation 3 with SLS shows that the surface texture is rough compared with Na-CMC. The dense network of drug-polymer-SLS increases the tortuisity, as evident from Figure 4 thus delaying the release of the drug and retarding the penetration of water required to make the beads swell for

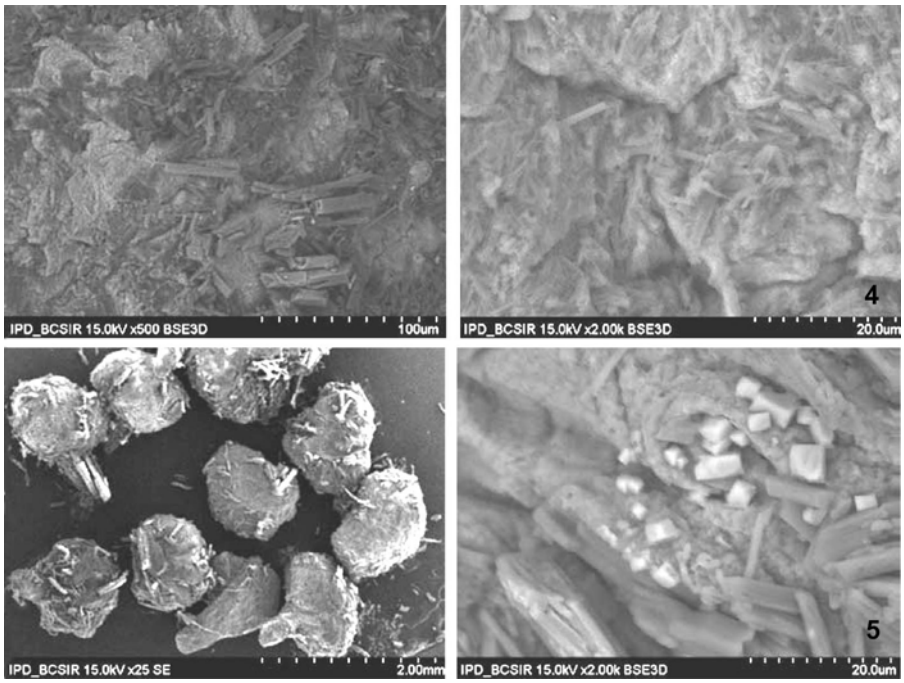
disintegration. Surface morphology of beads with sodium starch glycolate (Formulation 4) reveals that drug crystal is on the surface (Figure 5). SSG is used to control the release of drugs and the size of the beads. From SEM photomicrographs (Figure 6), we can interpret that in F 6 (PEG 4000) the surface morphology is visualized as dense structure. As a result the extent of drug release is only 26 % at the end of 8 hours.

Table 3. R-squared values and release rate of different kinetic models of the formulations

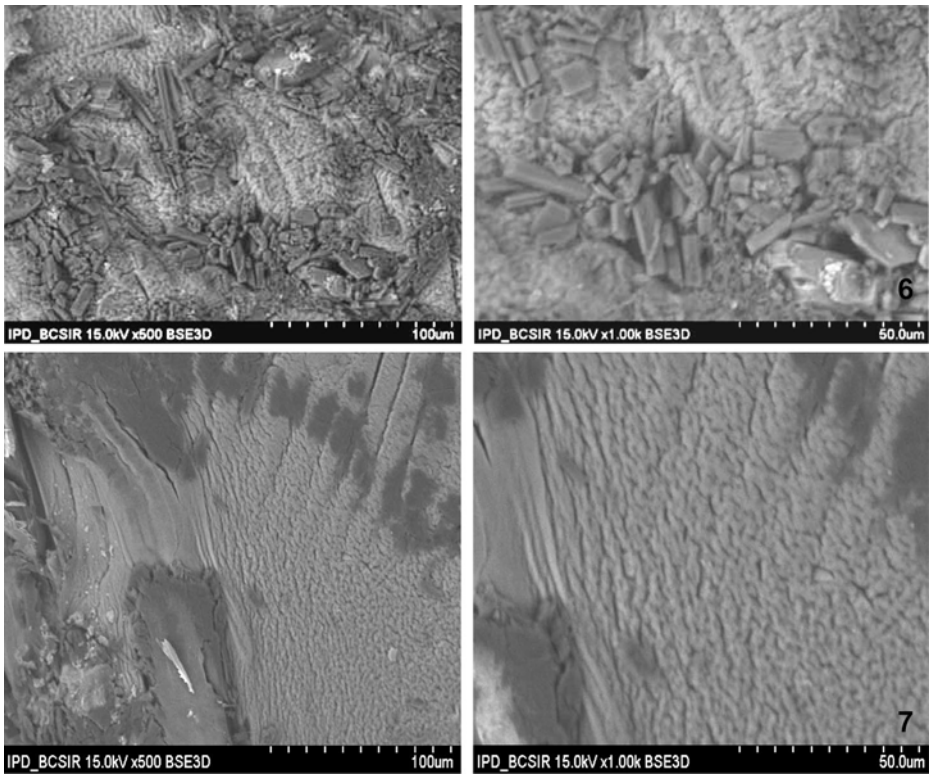
Formulations	Kinetic models					
	Zero-order		Higuchi		First order	
	R^2	Release Rate (K_o)	R^2	Release Rate (K_H)	R^2	Release Rate (K_1)
1	0.934	42.80	0.966	25.83	0.961	1.783
2	0.977	40.89	0.973	36.63	0.971	1.773
3	0.894	30.08	0.934	23.01	0.905	1.846
4	0.643	16.10	0.709	2.19	0.664	1.926
5	0.906	20.04	0.867	16.83	0.903	1.903
6	0.934	17.46	0.923	12.49	0.935	1.917



Figs. 1-3: 1. Scanning electron microscopy photomicrographs of formulation 1 at X25 and X500. 2. Scanning electron microscopy photomicrographs of formulation 1 at X1000 and X2000. 3. Scanning electron microscopy photomicrographs of formulation 2 at X500 and X2000.



Figs. 4-5: 4: Scanning electron microscopy photomicrographs of formulation 3 at X500 and X2000. 5. Scanning electron microscopy photomicrographs of formulation 4 at X25 and X2000



Figs. 6-7: 6. Scanning electron microscopy photomicrographs of formulation 5 at X500 and X1000. 7. Scanning electron microscopy photomicrographs of formulation 6 at X500 and X1000

Swelling study. Swelling study of alginate based theophylline beads with different excipients prepared in $CaCl_2$ solution was carried out. The formulations were prepared using drug: alginate: excipient in 1 g: 900 mg: 100 mg ratio. Beads in F 1 contain Eudragit L 100, which is resistant to gastric juice but dissolves readily at above pH 5.5. They are used to control the active substance from the matrix. In water media it swells highest at 3 hours with SI of 10.74 % (Table 2). Sodium carboxy methyl cellulose containing F 2 beads showed highest swelling at 5th hour (9.66 %). F 3 swelled high up to 7th hour (8.15 %). F 4 contains sodium starch glycolate that is used as disintegrant in formulations. It has enormous swelling capacity through rapid water uptake. In this study, the beads swelled high up to 9.93 % within 2 hours. Its enormous swelling helps to disintegrate the beads for long hours after the drug intake time. Hydroxy propyl methyl cellulose 5 cps swelled high up to 4 hours with SI of 8.67 % (F 5). Polyethylene glycol is hydrophilic in nature and their viscosity increases with increasing molecular weight. PEG 4000 (F 6) is used as controlled release agent, which shows 5.21 % swelling at 3 hours (Table 2). The comparison of swelling indices of theophylline beads with various excipients is shown in Figure 8.

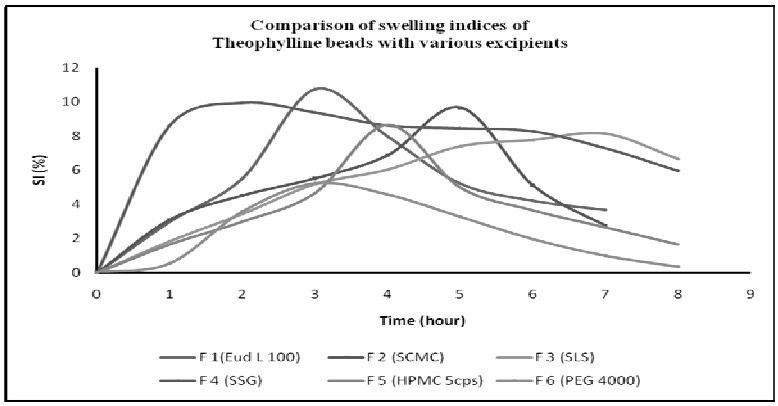


Figure 8. Comparison of swelling indices of theophylline beads with various excipients

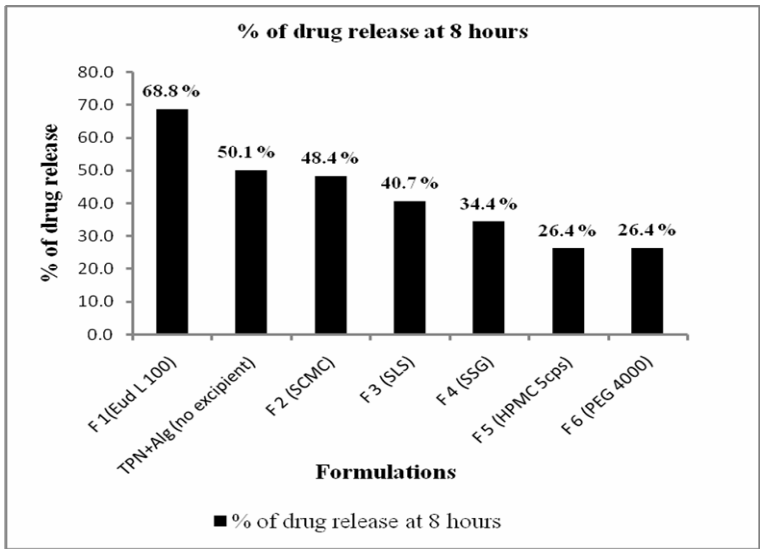


Figure 9. Percent of drug released from the formulations at 8 hours

***In vitro* Release Kinetics.** When a hydrophilic matrix comes into contact with an aqueous medium, it absorbs water, hydrates and swells to form a gel through which the dissolved drug diffuses out. In case of water soluble polymers, dissolution of the polymer results in a gradual erosion of this gel layer. However, at higher concentrations, the polymer chains entangle to a greater degree culminating in "virtual cross-linking" and therefore formation of a stronger gel layer. Eudragit L 100 was used to prepare beads which give about 69 % (Figure 9) of drug release up to 8 hours. Within 1.5 hours about 40 % of drug was released. The drug release from Eudragit L 100 is due to formation of pores and channels and due to swelling of polymer up to some extent. Surface morphology also attributes to this fact in Figures 1 and 2. Sodium carboxy methylcellulose (SCMC) is water soluble sustained release polymer, which shows about 49 % drug release at 8 hour. Sodium lauryl sulphate and sodium starch glycolate releases about 40.7 % and 34.4 % of theophylline (Table 3). The drug release amount is nearly same for formulation with HPMC 5 cps beads and PEG 4000. HPMC is a hydrophilic polymer used to retard the release of drugs from the beads. Correlating with formulation 4 reveals that addition of polymers can modify the release of theophylline. From Table 3 it was found that % release of beads containing only theophylline and alginate was 50.12%, and when polymers are used along with alginate the release characteristics were fairly modified. The release data obtained were fitted into different kinetic models (Table 3).

CONCLUSION

Theophylline loaded alginate beads containing various excipients were prepared successfully by ionic cross linking technique. Apart from the natural water soluble polymer, namely, sodium alginate, the use of different excipients further prolongs the release of the drug. Polymethacrylate Eudragit L 100 showed maximum prolongation of drug release. Hence, further studies can be extended taking Eudragit L 100 and sodium carboxy methyl cellulose as the release controlling copolymer. The dense network of drug-polymer-excipient delays the release of the drug and retards the penetration of water required to make the beads swell for disintegration. More extensive study can be done when excipients are used to obtain regular and spherical beads, their effect on drug release should be investigated.

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