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Development and *in vitro* Evalution of New Generation Superporous Hydrogel Beads ($SPHB_S$) Containing Fluconazole

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Abstract

The preparation of superporous hydrogels based beads (SPHBs) with various concentrations of polymers such as guar gum,sodium alginate and hydroxy propyl cellulose combination. The superporous hydrogels beads containing carbonate salt, as a gas-forming agent, were prepared by dispersing carbonate salt in polymers solution and then extruding into either neutral or acidified solution of calcium chloride and citric acid. Acidity of gelation medium increased the pores in the structure of beads containing sodium bi carbonate. This is due to carbon dioxide generated from reaction of carbonate salts with citric acid. The effect of selected factors, such as polymer combination, per-centage of sodium bi carbonates, per-centage of citric acid and per-centage of calcium chloride. The characterization studies were performed by measurement of apparent density, porosity, swelling studies, mechanical strength studies, particle size, fourier transform infrared spectroscopy (FTIR), scanning electron microscope (SEM) and differential scanning calorimetry (DSC).

INTRODUCTION

Fluconazole is a 1,2,4-triazole based drug that has established an exceptional therapeutic record for Candida infections, including oropharyngeal and esophageal candidiasis, vulvovaginal candidiasis, candidemia, and disseminated candidiasis. It is an antifungal agent of choice for the treatment of infections by Candida albicans and Cryptococcus neoformans due to its potent activity, excellent safety profile, and favorable pharmacokinetic characteristics[1].

Hydrophilic polymers based hydrogels are cross-linked, with a network structure, which are able to absorb large amounts of water, and are water insoluble.[2-4] For the pharmaceutical purpose they are distinctive carriers for controlled drug delivery, release control can be governed by both swelling and biodegrading properties.[5-7] The swelling properties of hydrogels are mainly related to the elasticity of the network, the presence of hydrophilic functional groups in the polymer chains, the extent of cross-linking, and porosity of the polymer. The physical char-acteristics of hydrogels including their swelling ratio also depend on the balance between attractive and repulsive ionic interactions and solvent-mediated effects.[8,9] due to their high water affinity and biocompatibility, hydrogels based on poly (acrylic acid) and its derivatives,[10,11] chitosan, [12] alginate[13] and collagen,[14] have attracted the attention. However, these nonporous hydrogels swell slowly and exhibit low loading capacities,[15,16] which restrict their use in effective drug delivery. A new generation of hydrogels, which swells and absorbs water very rapidly, has been developed. Examples of this new generation are superporous hydrogels (SPHs), which swell to equilibrium size in a short period of time.[17-21]. Several important properties of SPHs, such as fast swelling, large swelling ratio, and surface slipperiness, make them an excellent candidate material to develop gastric retention devices.[22] Due to poor mechanical strength of conventional SPHs (CSPHs), they are difficult to handle without breaking.[23]

The scope of the present study was to investigate the influence of some processing parameters on size and shape of alginate beads containing theophylline as a model drug, prepared by ionotropic gelation.

MATERIAL AND METHODS

Fluconazole gife sample obtained from Ranbaxy (M) Sdn Bhd (Sungai Petani,Malaysia).Guar gum, HPMC and calcium chloride purchesed from R&M Chemicals (Rssex.UK). Sodium Alginate were supplied from A.R Alatan Sains (K) Sdn Bhd (Malaysia). Sodium bi carbonate and citric acid from Bendosen Laboratory Chemicals. All other chemicals were used of AR grade .

Preparation of internal phase

The internal phase was prepared by homogination (table 1). Required quantity of polymers (guar gum, HPMC and sodium alginate) were added subsequently 50 ml of deionized water in a beaker, keep the mixer for swelling 24 hours followed by fluconazole and sodium bi carbonate added to the above mixers with glass rode with care.

Preparation of external phase

For the preparation of external phase (citric acid and calcium chloride) were added to the 50 ml of deionized water in a 100 ml beaker with continuous stirring.

Preparation of drug-loaded $SPHB_S$

The drug-loaded superporous hydrogel beads were prepared by injection. The internal phase injected to the external phase with the help of 5 ml syringe (Needle size - 0.50×25mm) the

beads were prepared by dropping from a distance of about 10cm. Incorporation of $NaHCO_3$ containing polymers solution into external phase (citric acid and calcium chloride), the porous beads could be formed because of released (Co_2) gas and burst of the bead happen before the wall was sufficiently hardened by calcium chloride. The beads were kept for curing in external phase for 60 min followed by filtered and dried.

EVALUATION OF SUPERPOROUS HYDROGEL BEADS

Optical microscopic study

The mean diameter of 50 dried beads and porous diameter was determined by optical microscopy (Model 70 G camera scope 9-DN-117 M Olympus, Japan).

Scanning electron microscopy study

Morphological examination of the surface structure of the dried beads were carried out using Scanning electron microscopy (Phenom world EMS 550X). For examination of the pores structure of the beads, they were placed on sample holder and then examined by a scanning electron microscope.

Density measurements

Pieces of $SPHB_S$ were taken and weighed in order to determine the mass of each piece. A hydrophobic solvent such as hexane that is not absorbed by $SPHB_S$ was used for this purpose. By the use of forceps, a piece of the polymer was immersed in a predetermined volume of hexane in a graduated cylinder, and the increase in the hexane volume was measured as the volume of the polymer. The density was calculated [24] from the following eq. 1:

Density = M SPHB /V SPHB,→ (1)

where, V SPHB is the volume of solvent displaced by SPHB and M SPHB is the mass of the SPHB.

Porosity measurements

The two main prerequisites of $SPHB_S$ are swelling and porosity**.** Determination of porosity, dried $SPHB_S$ were immersed in hexane over night and weighed after excess hexane on the surface was blotted. The porosity was calculated from eqn. 2:

Porosity = V P /V T, → (2)

where, V P (= V T - V SPHB) is the pore volume of SPHB and V T is the total volume of the SPHB. Total volume of SPHB can be measured from its dimensions, as it is cylindrical in shape.

Swelling studies

The equilibrium swelling ratio can be calculated from eqn. 3:

Where, Q is the equilibrium swelling ratio, M_s is the mass in the swollen state, and M_d is the mass in the dried state. At the beginning of each experiment, the dried gel was measured gravimetrically to obtain M_d and then it was immersed in an excess of distilled water for swelling. At various time intervals, the hydrogel was removed from the water and weighed when excessive water on the surface was blotted to determine M_s. [17] When the weight became constant it was considered as ms and the time was considered as swelling time.

$Q = (M_s - M_d)/M_{d,}$ → (3)

RESULTS AND DISCUSSION

In the development of the super porous beads containing fluconazole using sodium bi carbonate are reacted with citric acid to generate carbon dioxide. The evolving gas permeates through the hydogel structure leaving gas bubbles or pores (Fig 1) resulting in the highly porous and fragile beads. A large amount of the beads were predominantly spherical in form, although some were found to be elongated or irregular. Shape of the super porous beads was experimental after air-drying. This is due to the consequence of the shrinkage occurring during the drying process of the resultant beads. In many drying processes, migration of soluble solid or moisture to the marginal layers of the solid as the solvent is removed.

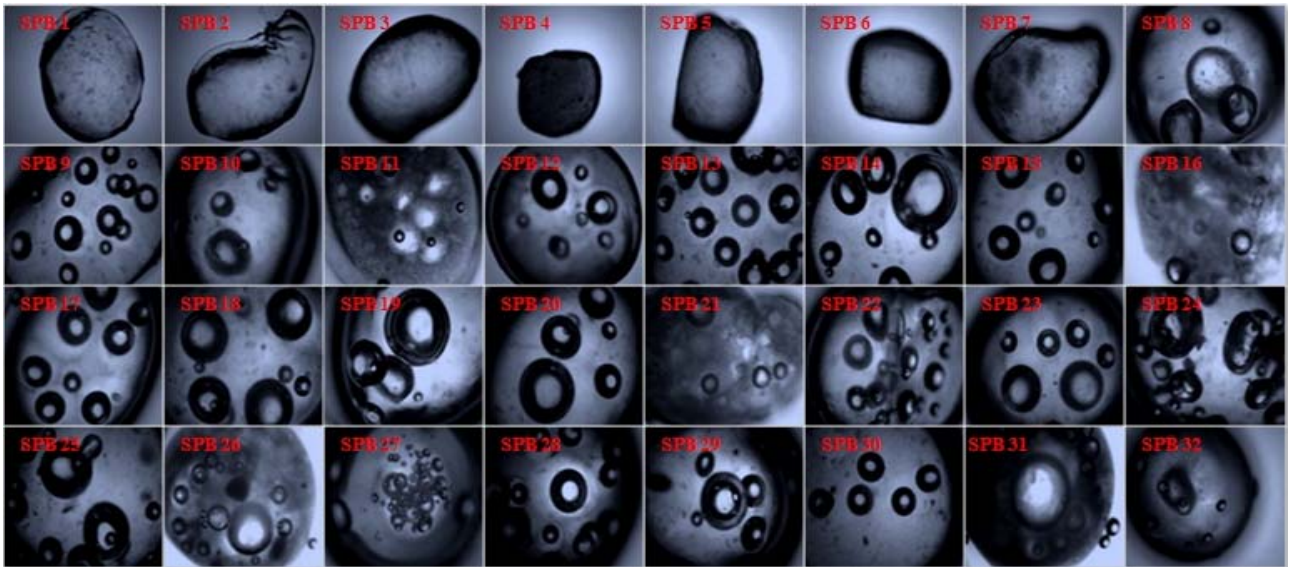

Figure 1. Optical microscopy pictures of super porous beads containing various ratio of sodium bicarbonate, citric acid and calcium chloride

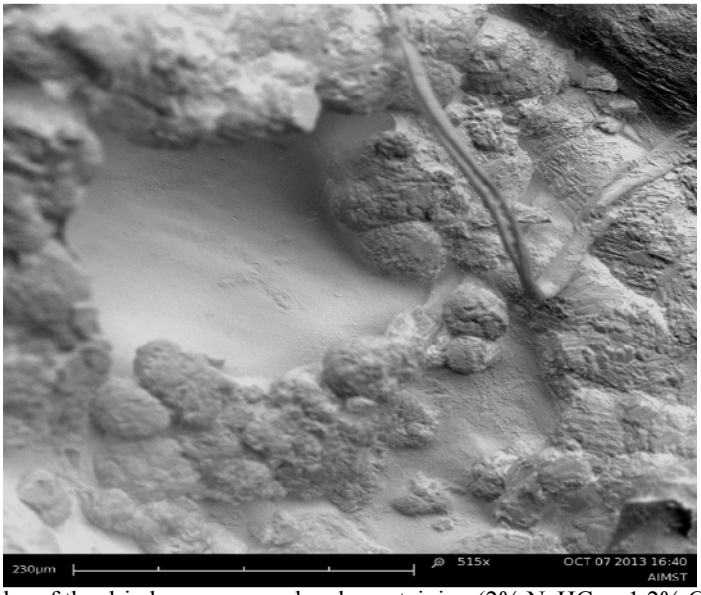

Figure 2: SEM photography of the dried superporous beads containing (2% $NaHCo_3$, 1.2% Citric acid and 2% $CaCl_2$)

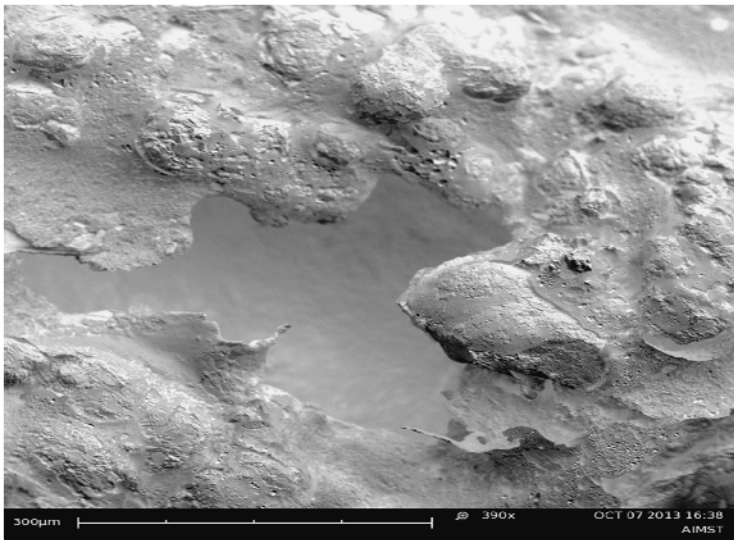

Figure 3: SEM photography of the dried superporous beads containing (3% $NaHCo_3$, 1.8% Citric acid and 2% $CaCl_2$)

The scanning electron micrographs of dried super porous beads containing various ratio of sodium bi carbonate, citric acid and $CaCl_2$ are shown in Figs. 2 and 3. The rough surface of super porous beads due to divalent calcium cations present in calcium salt. The evolving CO_2 gas infuses through the hydogel structure leaving gas bubbles or pores resulting in the highly porous-structured beads. Also, the increase in sodium bi carbonate and citric acid concentration caused increase in porous structure of the formed beads. These findings indicated the differences porous size of beads. Although increase in concentration of calcium salt, resulting harden surface of beads which affect the formation of pores.

The apparent density is an important parameter of super porous beads. The density was significantly decreased from 0.62 g/cc (SPB_S12) to 0.39 g/cc for the formula SPB_S22 which consists of 3% $NaHCo_3$ and 1.8% citric acid, as the concentration of calcium chloride increased and apparent density also increased from 0.71 g/cc (SPBs27) to 0.78 g/cc for the formula SPBs32 due to formation thick layer of beads (tab 2) .

Porosity is an important derived properties of super porous beads. The value of porosity studies of showed higher values in the optimized formulations SPB_S17 and SPB_S22, due to less concentration of calcium salt. The Porosity was significantly decreased from 55.56 % to 51.54 % for the formula SPB_S27 and SPB_S32 which consists of 6 % and 8 % of calcium salt.

Table 1. Composition of super porous beads

Formulation Code	*Internal phase*						*External phase*			*Diameter of beads (µm)*	*Pore size of beads in radius (µm)*
	Fluconazole (g)	**GG (g)**	**HPMC (g)**	**SG (g)**	**$NaHCo_3$ (g)**	**Deionised water (ml)**	**Citric acid (g)**	**Calcium chloride (g)**	**Deionised water (ml)**		
SPBs1	0.15	0.1	--	0.1	0.5	50	0.3	1	50	703.13	--
SPBs2	0.15	0.2	--	0.3	0.5	50	0.3	1	50	846.20	--
SPBs3	0.15	0.3	--	0.4	0.5	50	0.3	1	50	796.30	--
SPBs4	0.15	0.4	--	0.5	0.5	50	0.3	1	50	622.14	--
SPBs5	0.15	0.3	0.2	0.4	0.5	50	0.3	1	50	419.25	--
SPBs6	0.15	0.4	0.3	0.5	0.5	50	0.3	1	50	725.35	--
SPBs7	**0.15**	**0.5**	**0.4**	**0.6**	**0.5**	**50**	**0.3**	**1**	**50**	**1430.25**	**--**
SPBs8	0.15	0.2	--	0.3	1.0	50	0.6	1	50	1904.85	25.20
SPBs9	0.15	0.3	--	0.4	1.0	50	0.6	1	50	1331.64	20.66
SPBs10	0.15	0.4	--	0.5	1.0	50	0.6	1	50	1411.22	32.40
SPBs11	0.15	0.3	0.2	0.4	1.0	50	0.6	1	50	1580.71	16.42
SPBs12	**0.15**	**0.4**	**0.3**	**0.5**	**1.0**	**50**	**0.6**	**1**	**50**	**1832.61**	**21.45**
SPBs13	0.15	0.2	--	0.3	1.5	50	0.9	1	50	1612.81	21.60
SPBs14	0.15	0.3	--	0.4	1.5	50	0.9	1	50	1633.45	36.40
SPBs15	0.15	0.4	--	0.5	1.5	50	0.9	1	50	1640.61	24.20
SPBs16	0.15	0.3	0.2	0.4	1.5	50	0.9	1	50	1630.97	16.60
SPBs17	**0.15**	**0.4**	**0.3**	**0.5**	**1.5**	**50**	**0.9**	**1**	**50**	**1479.67**	**26.20**
SPBs18	0.15	0.2	--	0.3	1.5	50	0.9	2	50	2025.91	49.60
SPBs19	0.15	0.3	--	0.4	1.5	50	0.9	2	50	1676.87	27.80
SPBs20	0.15	0.4	--	0.5	1.5	50	0.9	2	50	1748.65	28.20
SPBs21	0.15	0.3	0.2	0.4	1.5	50	0.9	2	50	1011.91	21.60
SPBs22	**0.15**	**0.4**	**0.3**	**0.5**	**1.5**	**50**	**0.9**	**2**	**50**	**1569.32**	**23.40**
SPBs23	0.15	0.2	--	0.3	1.5	50	0.9	3	50	1739.15	30.20
SPBs24	0.15	0.3	--	0.4	1.5	50	0.9	3	50	1815.25	39.40
SPBs25	0.15	0.4	--	0.5	1.5	50	0.9	3	50	1681.547	40.12
SPBs26	0.15	0.3	0.2	0.4	1.5	50	0.9	3	50	1514.72	42.40
SPBs27	**0.15**	**0.4**	**0.3**	**0.5**	**1.5**	**50**	**0.9**	**3**	**50**	**1370.27**	**11.20**
SPBs28	0.15	0.2	--	0.4	1.5	50	0.9	4	50	2391.97	18.20
SPBs29	0.15	0.3	--	0.4	1.5	50	0.9	4	50	2462.27	30.21
SPBs30	0.15	0.4	--	0.5	1.5	50	0.9	4	50	2019.97	19.60
SPBs31	0.15	0.3	0.2	0.4	1.5	50	0.9	4	50	1731.87	13.42
SPBs32	**0.15**	**0.4**	**0.3**	**0.5**	**1.5**	**50**	**0.9**	**4**	**50**	**1059.57**	**14.60**

Table 2. Characteristics of optimized Formulations of superporous beads

Optimized formulation code	*Apparent density*(g/cc)*	*% porosity**	*Swelling ratio**
SPB_S12	0.62 ± 0.01	65.01 ± 2.03	60.09 ± 0.63
SPB_S17	0.41 ± 0.04	79.45 ± 2.11	72.13 ± 0.41
SPB_S22	0.39 ± 0.02	85.13 ± 3.53	75.57 ± 0.54
SPB_S27	0.71 ± 0.01	55.56 ± 2.19	62.02 ± 0.32
SPB_S32	0.78 ± 0.03	51.54 ± 2.55	71.43 ± 0.01

*mean ± SD, n=3

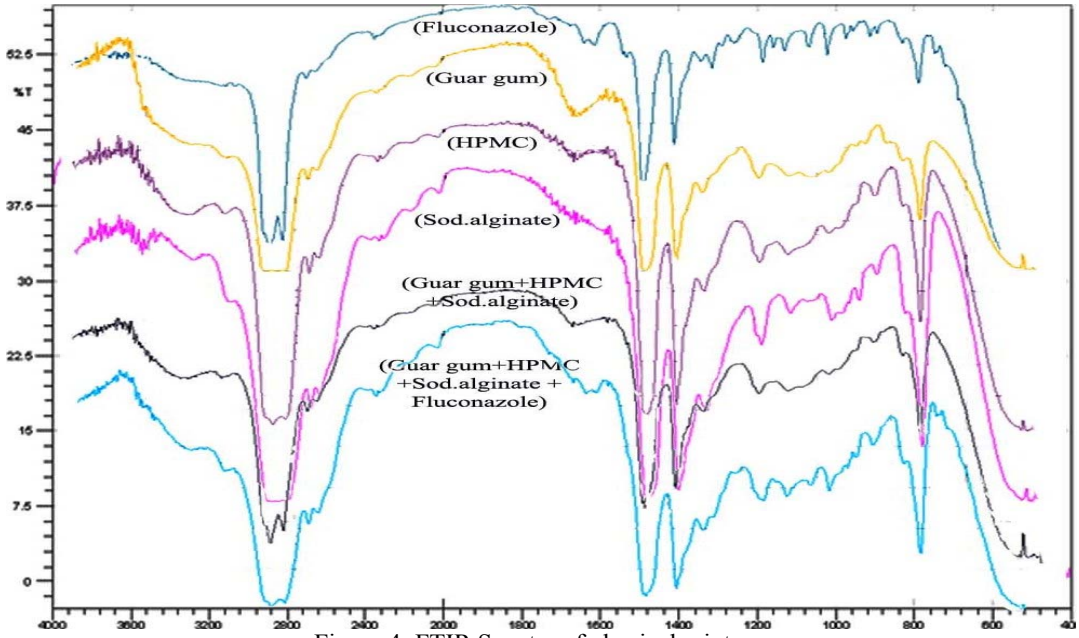

Figure 4: FTIR Spectra of physical mixture

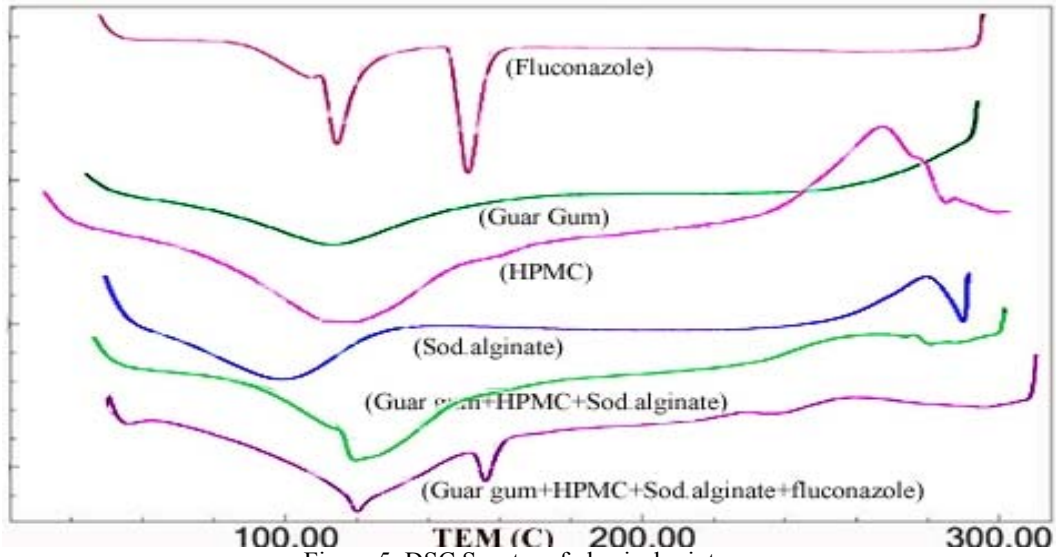

Figure 5: DSC Spectra of physical mixture

Fluconazole compound formed the polymer active with no disturbance in the functional group; therefore a polymerized active constituent has no change of effect after polymerizations (fig 4).

The DSC studies of fluconazole showed a sharp endothermic peak at 145.85°C and another peak at 107.30°C which may be related to moisture. The DSC curve of the sodium alginate polymer showed a broad endothermic peak at 119.29 °C and 257.73°C. The DSC curve of the HPMC showed at 90.64°C.combination of three polymer endothermic peak at 112.20°C. Physical mixture of polymer combination and drug showed a peak at 106.37°C and 142.36°C. From the results of DSC study (fig)it can be concluded that there was no significant drug- excipient interaction (fig 5).

The *in vitro* release profile of fluconazole from superporous hydrogel beads formulations SPB_S12, SPB_S17, SPB_S22, SPB_S27 and SPB_S32 were conducted in diffusion medium pH 7.4. The formulations SPB_S12 and SPB_S17 containing sodium bi carbonate, citric acid and calcium chloride in the ratio of 2.0:1.2:2.0 and 3.0:1.8:2.0 showed 95.57% and 95.87% drug release respectively at 4 hours. Whereas formulations SPB_S22, SPB_S27 and SPB_S32 containing sodium bi carbonate, citric acid and calcium chloride in the ratio of 3.0:1.8:4.0, 3.0:1.8:6.0 and 3.0:1.8:8.0 showed 94.16%, 96.22 and 92.98% drug release respectively at 4 hours (fig 6).

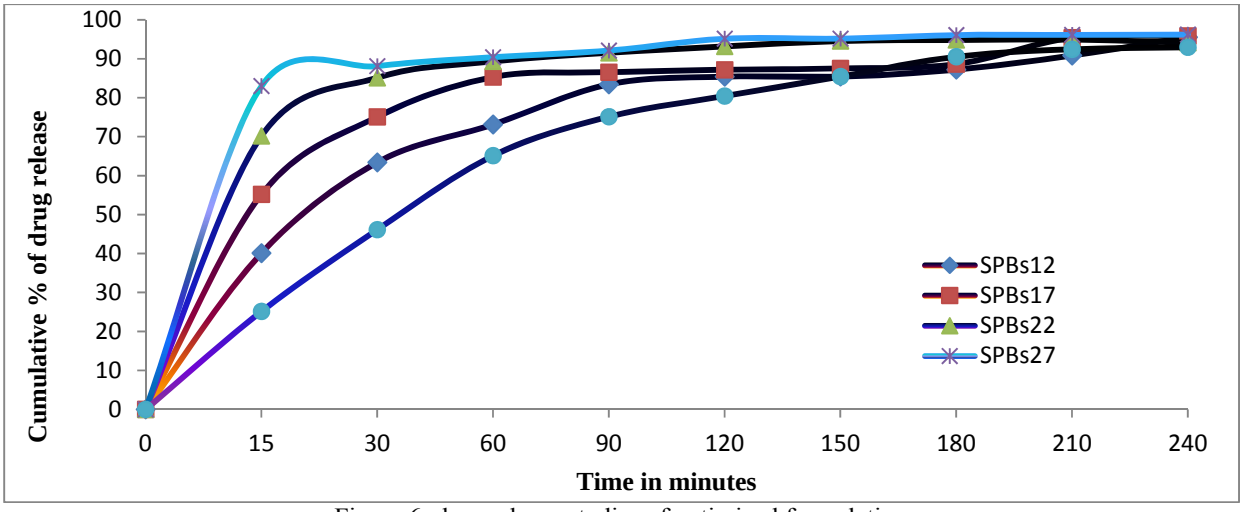

Figure 6: drug release studies of optimized formulation

CONCLUSION

Tripolymer based superporous hydrogel showed good porosity and swelling index. Higher the concentration of calcium salt higher will be the density and lower will be the porosity. The increase in calcium salt concentration is beneficial from mechanical strength point of view, but at the same time the decrease in porosity of the beads which leads to slower the diffusion of drug. The DSC, IR showed no incompatibility between the drug and excipients.

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