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Controlled Release of Hypertensive Drug from pH/Thermo Responsive Polymeric Microbeads

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ABSTRACT
The controlled release behaviour of Acebutolol hydrochloride, from blend beads of pectin and hydroxypropyl cellulose was investigated at different pH's (1.2 & 7.4) and different temperatures (25 ^oC & 37 ^oC). These polymeric microbeads were produced by varying the concentrations of polymer, drug, crosslinker agent, calcium chloride ($CaCl_2$). The beads have been characterized by Fourier transform infrared spectroscopy (FTIR), differential scanning calorimetric (DSC), X-ray diffraction (X-RD), and scanning electron microscope (SEM) techniques. The DSC and X-RD studies showed that the polymeric micro beads exhibited with spherical shape and rough surface morphology. The results obtained from swelling studies confirmed that the pH and temperature responsive nature of polymeric micro beads under study. The release data have been analysed using an empirical equation to understand the transport of the drug containing solution through the polymeric matrices. The drug release kinetics results indicated non-Fickian model transport in the present study. Drug release was observed in a controlled manner up to 12 hrs.

Key words: *Controlled drug release, Acebutolol Hydrochloride (Antihypertensive drug), pH/temperature responsive polymers and polymeric micro beads.*

1. INTRODUCTION

Pectin is a structural heteropolysaccharide contained in the primary cell walls of terrestrial plants. Apple, quince, plume, gooseberry, oranges, cherries and grapes contain pectin. It is an essential component in the initial growth and in the ripening process and has been found to be useful in area of drug delivery [1]. It is produced commercially as a white to light brown powder, mainly extracted from citrus fruits and is used in food industry as a gelling agent particularly in jams and jellies. Pectins are a family of complex polysaccharides that contain 1, 4-linked α-D-galacturonic acid residues. The acid groups along the chain are largely esterified with methoxy groups in the natural product. Pectin is highly hydrophilic in nature. Hydrophilic matrices are widely used in oral controlled drug delivery and for the preparation of modified release formulation because of their flexibility to obtain a desirable drug release profile [2]. The release from the hydrophilic matrix is controlled by the viscous layer barrier around the tablet that opposes the penetration of solvent into the tablet [3]. Now a days, pectin is gaining importance as a polymer for modified release drug delivery formulation because of its cost effectiveness [4]. However, the major challenge of using pectin for the development of modified drug formulation is to overcome its solubility in aqueous medium which may contribute to the undesirable, premature and local release of the active medicament from the polysaccharide matrix. One of the options to reduce the high solubility of polysaccharides could be to chemically modify them without affecting their biodegradability [5-7]. Pectin polarity or high solubility can also be reduced by preparing its blend blending with another natural polymer like hydroxypropyl cellulose. For this purpose in the present study HPC is chosen for its blending which was not yet reported in literature so far.

Hydroxypropylcellulose (HPC) has been frequently utilized as a pharmaceutical additive for various purposes as a binder in tablet or granule formulations, a film-coating material and as a thickener for syrup due to its safety. Also, controlled release dosage forms [8] or bioadhesive tablets [9] have been prepared utilizing its swelling and adhesive properties in aqueous medium. However, it has not been studied on timed-release preparations with HPC regardless of such a wide utilization. Accordingly, in this study, HPC was used as a functional material for controlled release time, and was used to establish timed-release press-coated tablets.

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In view of the abundance and biocompatibility, natural polymers like polysaccharides have been used in drug-delivery applications [10-12]. Among such polymers are natural polymer pectin and HPC which are naturally occurring polysaccharides. However, their inherent drawbacks, such as poor mechanical strength, uncontrolled degradation and extensive water uptake properties, result in the uncontrolled and unpredictable release rates of the active ingredients. In order to overcome the difficulties mentioned above, blending of these two polymers and crosslinking them has been attempted to develop better formulations than those prepared from pure polymers. Blends are a better choice to develop controlled release (CR) matrices because their properties can be varied by changing the composition or by cross-linking, there by regulating the hydrophilic nature of the overall matrix [13].

Acebutolol HCl is a selective, hydrophilic beta-adrenoreceptor blocking agent with mild intrinsic sympathomimetic activity for use in treating patients with hypertension and ventricular arrhythmias. It is used as a medicine for the treatment of heart rhythm disorders and hypertension. It can be used to help the heart beat regularly and to lower blood pressure. Acebutolol hydrochloride may also reduce the frequency and severity of angina attacks.

In continuation of our research on drug delivery [14-16] in the present investigation the blend beads of pectin and HPC were prepared and crosslinked with $CaCl_2$ as a crosslinking agent, and used for acebutolol hydrochloride drug release studies. The encapsulation efficiency, equilibrium degree of swelling and ABH release rate of beads were investigated at different pHs. The effects of HPC/pectin ratio, extent of cross-linking and drug/polymer ratio on ABH release from the beads were discussed. The drug-loaded beads were characterized by fourier transform infrared spectroscopy (FTIR), scanning electron microscopy (SEM), X-ray diffraction (XRD) and differential scanning calorimetry (DSC). Release characteristics of the formulations were studied for their encapsulation efficiency, drug diffusion rates, as well as the extent of cross-linking. The results are presented here.

2. EXPERIMENTAL

2.1 Materials

Pectin (poly-D-galacturonicacid methyl ester) was purchased from HIMEDIA Chemicals, Mumbai, India. Hydroxypropylcellulose (HPC) was purchased from Aldrich chemicals; calcium chloride ($CaCl_2$) and methanol (CH_3OH) were purchased from s.d. fine chemicals, Mumbai, India. Acebutolol hydrochloride was a gift sample from Walkman Salesman Pharmaceuticals. Double distilled water was used throughout the study.

2.2 Preparation of Pectin and Hydroxy Propyl Cellulose Blend Beads

A series of pectin and hydroxyl propyl cellulose beads were developed by varying the % of ratios of PC and HPC blends, concentration of crosslinker and variation of drug. Briefly, required amount of pectin and HPC blends prepared in distilled water under constant stirring. To this, the required amount of drug was added and stirred until complete dispersion of the drug in the polymer solution. A 5 ml (different) of the drug loaded polymer blend solution was taken in hypodermic syringe and added drop wise in a short time of 20-30 sec into the aqueous methanol solution (methanol:water 80:20 V/V) containing the required amount of crosslinking agent ($CaCl_2$) under constant stirring condition. The beads were formed within 10 min. The beads were removed from aqueous methanol and washed with distilled water to remove surface adhered crosslinker. The beads were dried at 40 ^oC in vacuum oven.

2.3. FT-IR Spectroscopy

Fourier transforms infrared spectroscopy (FTIR) spectral measurements of pristine beads, drug loaded beads and pure ABH were recorded using Perkin Elmer (model Impact 410, Wisconsin, MI, and USA) spectrophotometer. The beads are finely grounded with KBr to prepare the pellets under a hydraulic pressure of 600 dynes/m^2 and spectra were scanned between 4000 to 500 cm^{-1}.

2.4. Differential Scanning Calorimetric (DSC)

DSC analysis of pristine beads, drug loaded beads and pure ABH drug were recorded on a TA instruments (Model: STA, Q_{600} USA). 10 to 12 mg of the sample was taken. The samples were heated from 30 to 400 ^oC at a heating rate of 10 ^oC/min in nitrogen atmosphere (flow rate 100 mL/min).

2.5. X-Ray Diffraction (X-RD) Studies

XRD measurements of plain drug, drug-loaded beads and plain beads were recorded with a Rigaku Geigerflex Diffractometer equipped with Ni-filtered Cu Kα radiation (λ= 0.1548 nm). The dried beads of uniform thickness were mounted on sample holder, and the patterns were recorded in the range 0 to 50^0 at a speed of 5^0/min.

2.6. Scanning Electron Microscopic (SEM):

SEM images of beads were recorded using a JSM 6400 SEM (JEOL Ltd., Akishima, Tokyo, Japan) at 55x, 200x, and 1.0Kx magnification. Working distance of 9.0 mm was maintained and the acceleration voltage used was 20 kV, with the secondary electron image (SEI) as a detector.

Table 1. Encapsulation efficiencies of different formulations

Sample code	Pectin	HPC (w/w%)	Drug (w/w%)	$CaCl_2$ (w/w%)	%EE ± S.D.
P0	80	20	00	2	70.2 ± 1.5
P1	90	10	10	2	79.6 ± 0.8
P2	80	20	10	2	83.2 ± 0.5
P3	70	30	10	2	62.8 ± 0.4
P4	80	20	20	2	67.3 ± 0.9
P5	80	20	30	2	74.2 ± 0.2
P6	80	20	20	1	80.7 ± 0.7
P7	80	20	20	4	68.2 ± 0.3

2.7. Swelling Studies

Swelling studies were conducted using both wet and dry beads. The term wet refers to the state of the beads immediately after the preparation and the term dry to beads that were left to dry for 24 h at 30^0C in air. Swelling studies of Pectin-Hydroxypropyl cellulose beads were carried out in three different conditions pH, temperature and pure water. The pH conditions were carried out in various phosphate buffer solutions (pH = 2, 3, 4, 5, 6, 8.), temperature conditions were carried out in various temperatures (25, 30 37, 40, and 45^0C.) and constant water level (25 ml). Accurately weighed amounts of beads (ranging from 0.050 to 0.055 g) were immersed in 25 ml of water and at fixed time intervals the beads were separated from the water using a stainless steel grid. Immediately, they were wiped gently with paper and weighed. The dynamic weight change of the beads with respect to time was calculated according to the formula:

$$\%SR = (W_s\text{-}W_d/W_d)\ X\ 100 \quad (1)$$

Here W_d and W_s were the weights of dried and swollen beads, respectively.

2.8. Estimation of Drug Loading and Encapsulation Efficiency

The loading efficiency of ABH in the beads was determined spectrophotometrically. About ~10 mg of the drug-loaded beads were placed in 30 mL of buffer solution and stirred vigorously for 48 h to extract drug from the beads. The solution was filtered and assayed by UV spectrophotometer (Lab India, Mumbai, India) at fixed λ_{max} value of 240 nm. The results of % drug loading and % encapsulation efficiency were calculated by following Eqs.

$$\%\ \text{Drug loading} = \left(\frac{\text{Amount of drug in MGs}}{\text{Amount of MGs}}\right) x100 \quad (2)$$

$$\%\ \text{Encapsulation efficiency} = \left(\frac{\text{Actual loading}}{\text{Theoretical loading}}\right) x100 \quad (3)$$

2.9. In vitro release studies

In vitro release studies were carried out using Tablet dissolution tester (Lab India, Mumbai, India) equipped with eight baskets. Dissolution rates were measured at 37± 0.5 ^{o}C at constant speed of 100 rpm. Drug releases from the beads were carried out in pH 1.2 and 7.4 phosphate buffer solutions at 37 ^{o}C and also 25 ^{o}C. At regular intervals of time, sample aliquots were withdrawn and analysed using UV spectrophotometer (Lab India, Mumbai, India) at the fixed λ_{max} value of 240 nm. After each sample collection, the same amount of fresh medium at the same temperature was added to the release medium to maintain the sink condition. All measurements were carried out in triplicate, and values were plotted with standard deviation errors.

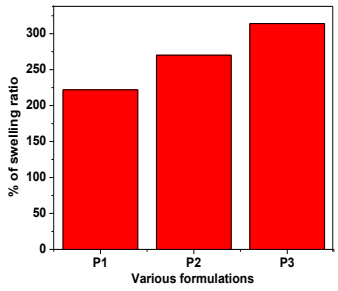
3. RESULTS AND DISCUSSION

3.1. Swelling Studies

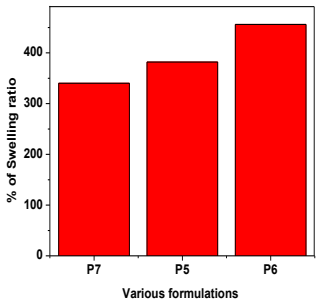
The beads swelling properties were influenced by the amount of pectin and crosslinker ($CaCl_2$). As the amount of pectin increases the swelling ratio of beads increase, it may be due to the enhancement of hydrophilic polymer chains by increase with pectin concentration. In the case of cacl2 crosslinker variation, the swelling ratio decreases with the increase of crosslinker content, it may due to the formation of polymeric chains which become rigid network as a result of contraction of microvoids. The various formulations and their swelling ratios are shown in Figure 1.

3.2. FT-IR Studies

FTIR spectra of (a) pectin, (b)HPC (c) ABH (d) plain beads and (e) drug loaded beads were shown in Figure 2. The FTIR spectroscopy was used to investigate the presence of crosslinking and chemical stability of the drug after encapsulation into the matrix. In case of (a) pectin a broad peak at 3392 cm^{-1} is attributed to -OH stretching vibration. The peak at 2939 cm^{-1} represents the -C-H stretching vibration. The peak at 1632 cm^{-1} represents acid groups. The peak at 1052 cm^{-1}



(a) *Various amounts of pectin.*



(b) *Various amounts of crosslinker.*

Figure 1: Variation of % swelling ratio with concentration of pectin (a) and crosslinker (b).

represents the -C-O-C- ethers linkage. The HPC (b), showed a broad peak at 3436 cm^{-1} due to -O-H stretching vibrations. The peak at 2975 cm^{-1} shows the aliphatic C-H stretching vibration. In case of plain beads, all the peaks of Pectin and HPC were observed in addition to a new band observed at 1655 cm^{-1}, which confirmed the -C=O stretching vibration of carbonyl group. In the case of crosslinked pectinate beads the peak intensity at 1735 cm-1 decreases due to carboxylic groups of pectin were involved in crosslinking reaction. The ionic nature of carboxyl groups and amide peaks were observed in the same region, which is confirmed the crosslinking of calcium ions with carboxyl groups of pectin.The spectral data were also to confirm the chemical stability of ABH in the beads. The FTIR spectra of plain drug, ABH (Fig 2) shows the characteristic absorption peaks at 3292 cm^{-1}, 2961 cm^{-1}, 1849 cm^{-1} and 1663cm^{-1} which indicated the OH, -CH,-C=O stretching vibrations. All characteristic peaks of drug that were observed in drug loaded beads, indicating the stability of drug after encapsulation into the polymer matrix.

3.3. Differential Scanning Calorimetric Studies (DSC)

DSC thermograms of (a) plain ABH (b) blend beads of pectin-HPC and (c) ABH-loaded of pectin-HPC beads are displayed in Figure 3. The onset melting peak of ABH is observed at 161.16 ^oC, combination of pure-blend polymers when a sharp melting peak is observed at 215.18 ^oC and with drug formulation a melting peak is observed at 225.5 ^oC in case of drug loaded beads (c). According to the above information of DSC graph, the drug melting point 161.16 ^oC is not observed either in plain Pectin-HPC beads or the drug loaded Pectin-HPC beads, which suggests that the drug is molecularly dispersed in the polymer matrix.

3.4. XRD Studies

X-RD analysis can provide a clue about crystallinity of the drugs in crosslinked beads. XRD patterns recorded for (a) drug (b) plain beads (c) drug loaded beads are presented in Fig: 4. Here, drug peaks were observed at 2theta = 7^0, 16^0, 20^0 and 21^0 due to the crystalline nature of drug. These peaks are not found either in plain beads or in the drug loaded beads, suggesting that the drug is molecularly dispersed in the beads.

3.5. Scanning Electron Microscopy Studies

Fig: 5 shows scanning electron micrographs of (a) drug loaded group of beads, taken at 55X magnification, and (b) the P3 formulation of stimuli responsive single bead taken at 200 X magnification. From these SEM graphs it is observed that the beads are spherical in shape with rough surface.

3.6. In Vitro Release Studies

3.6.1. Drug Release Kinetics

Drug release kinetics was analysed by plotting the cumulative release data versus time and by fitting these data to the exponential equation of the type [17].

$$M_t/M_\alpha = kt^n \qquad (4)$$

Here, M_t/M_α represents the fractional drug release at time t; k is a constant characteristic of the drug-polymer system and n is an empirical parameter characterizing the release mechanism. Using the least squares procedure, we have estimated the values of n and k for all the eight formulations and these values are given in Table 2. If n = 0.5, then drug diffuses and releases from the polymer matrix following a Fickian diffusion. For n > 0.5, anomalous or non-Fickian type drug diffusion occurs. If n=1, a completely non-Fickian release kinetics is operative. The intermediate values ranging between 0.5 and 1.0 are attributed to the anomalous type transport [19]. The values of k increased with increasing drug into the beads, but the n values increased with increasing drug. This indicates the presence of the interactions between the beads and drug as studied from the release kinetics represented by Eq 4. proposed by Peppas et al., and from the results given in table 4.4.1. The values of exponent n are found to range between 0.220 and 0.558 at pH-1.2 whereas 0.572 and 0.884 at pH-7.4 as calculated from the empirical

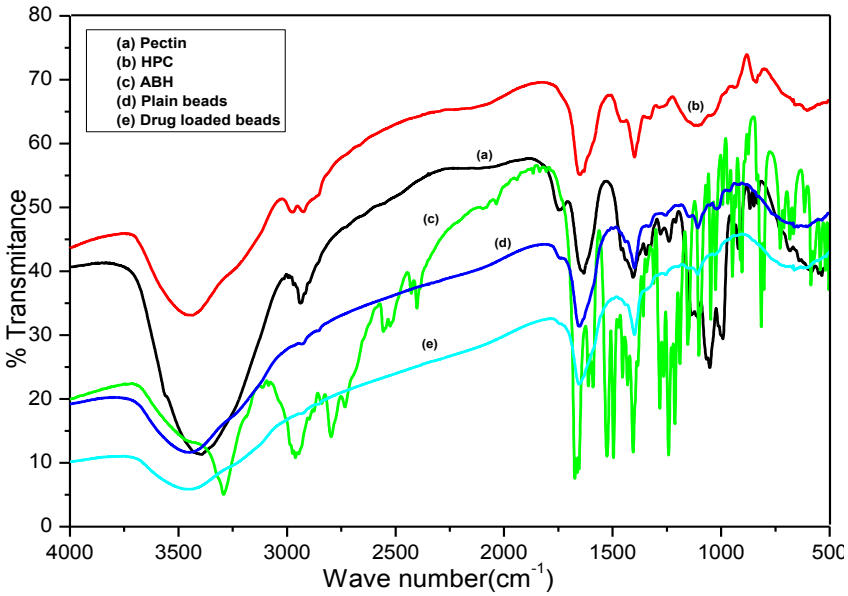


Figure 2: FT-IR spectra of (a) pectin (b) HPC (c) ABH (d) plain beads and (e) drug loaded beads.

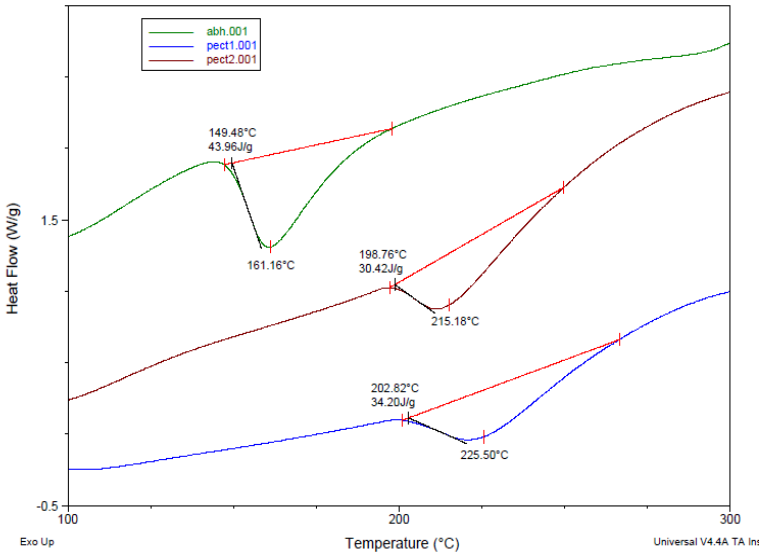


Figure 3. DSC thermograms of (a) plain drug (b) plain microbeads and (c) drug loaded micro beads.

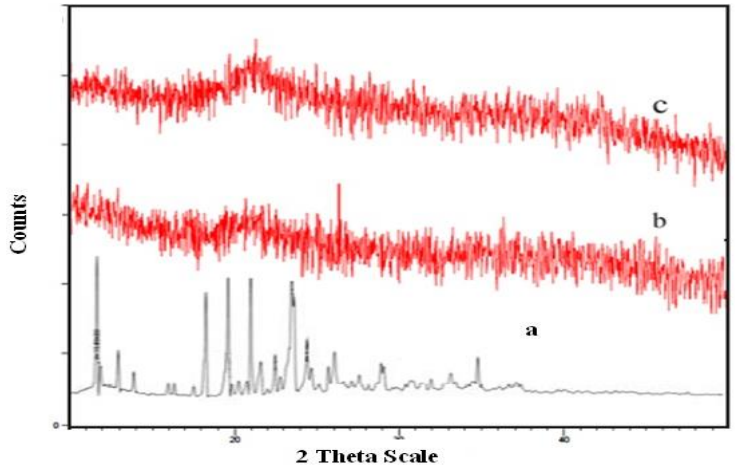


Figure 4: X-ray diffraction spectra of (a) ABH (b) plain beads (c) drug loaded beads.

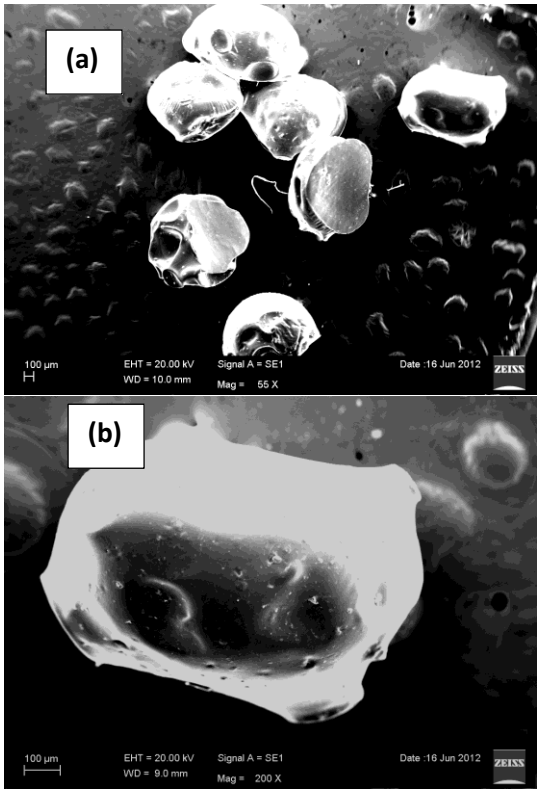


Figure 5: SEM images of (a) drug loaded group of beads (b) drug loaded single bead.

equation, which indicated that drug release showed the Fickian transport in pH-1.2 to non-Fickian transport in pH-7.4. The values of the correlation coefficient, 'r' is calculated and included in (4.4.1), which falls in the range of 0.932 to 0.994 in pH = 1.2 where as it falls in the region of 0.917 to 0.991 pH-7.4, respectively, indicating a good fit of the experimental data. This is due to the reduction in the regions of low microviscosity of the medium and closure of the microcavities in the swollen beads.

The influence of the different composition ratios of Pectin and HPC in the drug loaded beads P1, P2 and P3 (10, 20, 30 wt % of HPC, respectively) was investigated in this experiment. From **Fig: 6.** It may be noted that % of cumulative release decreases with the increase of HPC concentration. Because, increase of HPC amount which forms dense network structure, so low amount of HPC formation P1 is high release studies compare with higher amount of HPC formation P3. This reason is applicable for both gastric (pH = 1.2) condition and intestinal (pH = 7.4) conditions.

3.6.2. Effect of Drug Loading

Figure 7 shows the in-vitro release studies data of drug (ABH) loaded beads P2, P4 and P5 at different amounts of drug loading (10, 20 and 30 wt%, respectively) at pH-1.2&7.4. This pH's are used in in-vitro release experiments were carried out in gastric and intestinal pH conditions. The preparation of beads in the pH-7.4 condition release studies were higher, because lower hydrogen bonding since the drug is basic nature. Whereas the beads in the pH-1.2 condition release studies were lower, because more hydrogen bonding and slow release studies of beads in the acidic media due to the basic nature of the drug which leads the neutralization result which further leads to more ionization of drug which in respusiner show only rules. The release data shows that the P5 beads containing higher amount of ABH (P5) displayed faster and higher release rates than those formulations containing lower amount of ABH. A prolonged release rate was observed in the P2 beads because it contains lower amount of drug. Notice that the release rate becomes quite slower at the lower amount of drug in the beads, due to the availability of more free void spaces through which a lesser no of drug molecules will transport. Similar behavior was observed in both pH media studied.

3.6.3. Effect of Crosslinking Agent

The % cumulative release versus time curves of beads P5, P6, P7 are displayed in Figure 8 for varying amounts of $CaCl_2$ (% of 1,2 and 4) at a fixed amount of drug (20 wt%). In-vitro release experiments were carried out in gastric and intestinal pH (1.2 and 7.4) conditions. This is attributed to an increase in the extent of crosslinking, leading to the formation of a rigid network structure. So, the % cumulative release is quite fast and larger at lower amount of $CaCl_2$ (10%), whereas the release is quite slower at higher amount of $CaCl_2$ (40%). The % cumulative release is slower when the beads containing higher amount of $CaCl_2$ was used, it may be due to the polymeric chains become rigid because of the contraction of microvoids, thus decreasing the % cumulative release of drug through the beads.

4. CONCLUSIONS

Stimuli responsive polymers offer great advantages in drug delivery. Instead of acting passively as pure drug carries, they will interact and respond to the environmental setting. Discussion of a series of pectin and hydroxypropyl cellulose beads was developed by varying the % of ratios of pectin and HPC, concentration of crosslinker and variation of drug. Drug loaded beads were subjected in vitro release studies indicate that they may be useful for sustained drug release applications.

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