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Intragastric floating drug delivery of Ambroxol Hydrochloride using pectin and carbonate salts

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Abstract

The purpose of this work was to develop intragastric floating drug delivery by a means of calcium pectinate gel (CaPG) and zinc pectinate gel (ZnPG) beads. The CaPG and ZnPG beads containing carbonate salt, as a gas-forming agent, were prepared by dispersing carbonate salt in pectin solution and then extruding into either neutral or acidified solution of calcium chloride and zinc acetate respectively. The effect of factors such as type of carbonates, percentage of carbonates, gelation medium, drug loading, on floating and release properties was investigated. To overcome limitations of various approaches for imparting buoyancy, porous beads were prepared by incorporation of carbonate salts into pectin solution. Acidity of gelation medium increased the pores in the structure of beads containing calcium carbonate and zinc acetate. This is due to carbon dioxide generated from reaction of carbonate salts with acid. The highly porous beads prepared with carbonate salts and acidified gelation medium showed a good floating ability with fast drug release.

Keywords: Pectin; Calcium pectinate; Zinc pectinate; Floating drug delivery; Ambroxol hydrochloride

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INTRODUCTION

Natural biodegradable polysaccharides like pectin, guar gum, chitosan, carrageenans, sodium alginate and gellan gum have been used in controlled drug delivery [1], [2], [3]. Multiparticulate systems obtained by ionotropic crosslinking of these polymers have been used to develop floating drug delivery. Pectin is an inexpensive, non-toxic polysaccharide extracted from citrus peels or apple pomaces, and has been used as a food additive, a thickening agent and a gelling

agent [4,5]. Calcium pectinate hydrogels are stable in low pH solution, and are being investigated as a carrier material for different controlled release systems. Various approaches to induce buoyancy in crosslinked gel beads, some of which include freeze-drying, entrapment of gas or gas forming agents, use of volatile oils or fixed oils, have been used [6], [7] and [8]. These approaches are complicated, as they require specific equipment and handling techniques with limited acceptance. The oil containing beads have limitations of coalescence of oil droplets yielding beads of greater particle size distribution, volatilization or leaching of oil [9]. The floating dosage forms with carbonate salts as buoyancy imparting agent are simple to prepare as compared to other techniques. Their floating property is based on the evolution of carbon dioxide when in contact with acidic environment. Floating drug delivery systems act by prolonging the gastric residence time of the dosage forms. The gel beads are multiple-unit systems which avoid ''all or- none'' emptying from the stomach during migrating myoelectric complex (MMC) motility of the stomach, hence they are more advantageous than single-unit systems [10]. In the current study, a floating system employing carbonate salts as gas-forming agents dispersed in a CaPG and ZnPG matrix was prepared, for the delivery of ambroxol hydrochloride (a mucolytic agent in the treatment of variety of respiratory disorders). The effect of formulation and processing variables, including various cations (Ca, Zn), type and amount of carbonates, type of gelation medium on formation, floating and in vitro drug release properties of the obtained beads were studied.

MATERIALS AND METHODS

Materials

Low methoxy pectin with degree of methylesterification (DE) of 27% and Ambroxol hydrochloride were generous gifts from JCPL, Jalgaon, India. Sodium bicarbonate ($NaHCO_3$), calcium carbonate ($CaCO_3$) and potassium carbonate (K_2CO_3) were purchased from Pure Chem Laboratories, Pune. All other chemicals were standard pharmaceutical grade or analytical grade.

Peparation of blank beads

Beads without carbonate salts

The CaPG and ZnPG beads were prepared by ionotropic gelation method. Pectin was dispersed in water with agitation and kept in sonicator for half an hour to remove air bubbles. The dispersions of pectin (5% w/w) were dropped using a nozzle of 0.80-mm inner diameter into 5% w/v calcium chloride and 3% w/v zinc acetate with gentle agitation at room temperature. The gel beads formed were allowed to stand in the solution for 20 min, separated and washed three times with distilled water. The beads were air-dried at 37^0C for 12 hour

Beads containing carbonate salt

The beads containing carbonate salt were prepared by dissolving or suspending carbonate salt i.e. $NaHCO_3$, $CaCO_3$, K_2CO_3 (each in the concentration of 5%w/v and 10%w/v) in pectin solution . The mixture was dropped using a nozzle of 0.80-mm inner diameter into either neutral or acidified (containing 0.1 M hydrochloric acid or 10% v/v acetic acid) solution of each 5% w/v calcium chloride and 3% w/v zinc acetate with gentle agitation at room temperature. The CaPG and ZnPG beads formed were then separated, washed and air-dried at 37 ^{0}C for 12 hours

Preparation of drug-loaded beads

The drug-loaded CaPG and ZnPG beads were prepared by suspending ambroxol hydrochloride (i.e. 2.5% and 5.0% w/v) in the pectin solution and in the mixture of pectin and carbonate salt, then dropping the mixture into either neutral or acidified solution of each 5% w/v calcium chloride and 3% w/v zinc acetate with gentle agitation. Thus drug loaded beads without carbonate salt and with carbonate salt were obtained. Table 1 and Table 2 shows compositions of various batches of CaPG and ZnPG beads prepared

Table 1 Composition of CaPG beads

	CaPG									
Batch No.	A1	A2	A3	A4	A5	A6	A7	A8	A9	A10
Amount of pectin (g)	1	1	1	1	1	1	1	1	1	1
Amount of drug (g)		0.5	1	0.5	0.5	0.5	1	1	1	0.5
Calcium carbonate(%w/w)				5		5	10	5		
SBC[a] (%w/w)					5				5	5
Amount of $CaCl_2$ (%w/v)	5	5	5	5	5	5	5	5	5	5
Acetic acid 10% (v/v) (ml)						5	5			5
0.1N HCl (ml)								5	5	

a = Sodium bicarbonate

Table2 Composition of ZnPG beads

	ZnPG									
Batch No.	B1	B2	B3	B4	B5	B6	B7	B8	B9	B10
Amount of pectin (g)	1	1	1	1	1	1	1	1	1	1
Amount of drug (g)		0.5	1	0.5	0.5	0.5	1	1	1	0.5
Calcium carbonate(%w/w)				5		5	10	5		
SBC[a] (%w/w)					5				5	5
Amount of zinc acetate (%w/v)	3	3	3	3	3	3	3	3	3	3
Acetic acid 10% (v/v) (ml)						5	5			5
0.1N HCl (ml)								5	5	

a = Sodium bicarbonate

Characterization of beads

Percent entrapment efficiency

Calibration curve of the standard Ambroxol hydrochloride was prepared. Standard drug was dissolved in water and sufficiently diluted to make the concentrations in the range of 5-25 µg/ml and absorbance at 242nm was taken. Beads containing theoretical concentration of 10 mg of drug were taken from each batch and placed in 50 ml phosphate buffer, pH 7.4, and mechanically shaken on magnetic stirrer (EQUIP TRONICS Magnetic Stirrer, Model EQ-770) at 200 rpm for 12 h. The resultant dispersions were filtered and analyzed at 242 nm using UV spectrophotometer (VARIAN CARY 100 scan UV-Visible Spectrophotometer). The entrapment efficiency was determined by the following formula:

$$\text{Entrapment efficiency (\%)} = AQ/TQ \times 100$$

Where AQ is the actual quantity of drug and TQ is the theoretical quantity of drug in beads.

Particle size analysis

The mean diameter of 50 dried beads was determined by optical microscopy (Model BH2, Metzer biomedical, Mumbai). The microscope eyepiece was fitted with a micrometer by which the size of the beads could be determined.

Buoyancy of gel beads

The obtained beads were studied for their buoyancy property at 37 ± 2 ^{0}C by placing 50 beads in 50 mL of each water and simulated gastric fluid without pepsin (SGF, pH 1.2). Vessels were shaken at 100 rpm. The percentage of floating samples was measured by visual observation.

***In vitro* drug release studies**

Release studies were performed by using the USP basket method at 75 rpm and 37^{0}C in 900 mL of test medium (i.e., SGF, pH 1.2). Beads containing theoretical concentration of 50 mg of Ambroxol hydrochloride were used for each dissolution study. Samples were taken at appropriate time intervals and after suitable dilution assayed spectrophotometrically at 242 nm.

RESULTS AND DISCUSSION

Preparation of gel beads

First the drug loaded beads without carbonate salt were prepared. Dense structured beads were obtained without carbonate salts. The CaPG and ZnPG beads containing carbonate salt were produced by dispersing $NaHCO_3$ or $CaCO_3$ in concentration of 5%w/w and 10w/w. The beads containing K_2CO_3 could not be produced due to the formation of viscous gel before extrusion though the needle. Incorporation of $NaHCO_3$ (5% w/w) into pectin solution prior to bead formation resulted in porous-structured gel beads while the beads containing $CaCO_3$ showed the dense, non-porous structure. Beads could not be formed by using 10% w/w of $NaHCO_3$. During the formation of the CaPG and ZnPG beads containing $CaCO_3$ using acidified gelation medium, carbonate salts are reacted with acid (acetic acid or hydrochloric acid) to produce carbon dioxide. The evolving gas permeates though the bead structure leaving gas bubbles or pores, resulting in the highly porous beads responsible for greater floating ability. Composition of the batches of CaPG and ZnPG beads with Pectin:drug ratio 1:0.5 and 1:1 is shown in Table 1 and Table 2

Percent entrapment efficiency

Table 3 Percent entrapment efficiency of beads

CaPG	A2	A3	A4	A5	A6	A7	A8	A9	A10
% entrapment efficiency	63.7	62.4	68.25	69.8	75.8	78	74	76.5	73.5
ZnPG	B2	B3	B4	B5	B6	B7	B8	B9	B10
% entrapment efficiency	63.4	62	68.18	69.3	76.2	77.8	74.5	76	73.1

Percent entrapment efficiency of CaPG and ZnPG beads was found in the range of 62-78 % . Conventional bead (A2, A3, B2 and B3) showed lower entrapment than the beads containing carbonate salts. Acidified gelation medium may decrease the solubility of drug and hence increase the entrapment. This can be observed by greater entrapment efficiency of A5-A10 than A2, A3 and A4. 0.1N HCl as an acidifying agent gives higher entrapment than acetic acid (10% v/v) (Table 3). Increased concentration of carbonate salt (i.e.,10% $CaCO_3$) causes increased entrapment efficiency. CaPG beads showed relatively greater entrapment efficiency than ZnPG beads (Table 3). This may be due to the greater crosslinking ability of calcium cations than that of zinc cations. A7 and B7 containing 10% $CaCO_3$ prepared in acidified gelation medium (10% v/v acetic acid) showed greater entrapment than other batches.

Particle size of gel beads

The mean diameter of dried CaPG and ZnPG beads containing different carbonate salts is shown in Table 4. Incorporation of $NaHCO_3$ and $CaCO_3$ significantly increased the size of gel beads than that of the beads without carbonate salt. Increased amount of $NaHCO_3$ produced irregular shaped and ruptured beads. As percentage of $CaCO_3$ increased from 5% to 10%, the size of the air-dried beads increased. The beads shrank down during air-drying due to water evaporation from the structure.

Table 4 Mean diameter (mm) of dried CaPG and ZnPG beads containing different carbonate salts [no. of beads (n) = 50]

Batch no.	A1	A2	A3	A4	A5	A6	A7	A8	A9	A10
Mean diameter (mm)	1.17	1.19	1.16	1.43	1.53	1.56	1.61	1.75	1.82	1.73
Batch no.	B1	B2	B3	B4	B5	B6	B7	B8	B9	B10
Mean diameter (mm)	1.14	1.16	1.18	1.40	1.55	1.52	1.60	1.71	1.83	1.70

Floating property of beads

Floating tests were performed in SGF as well as in water. The results showed that the conventional beads sank immediately on immersion in the test media. The beads containing carbonate salts showed different floating properties depending on the type and amount of the carbonate salt added in the formulation (Fig. 1 and Table 5). Fig.1 demonstrated the floating kinetics of some formulations in SGF. Beads containing 5% $CaCO_3$ were able to float immediately on gastric fluid and remained buoyant after the test period of 5h. In gastric fluid, the beads containing 5% $NaHCO_3$ exhibited a good floating ability; approximately 80% beads floated after the lag time of 5 min (e.g., Fig. 2 and table 5). This may be due to release of CO_2 gas from $NaHCO_3$ in acidic media. Lower floating ability of these beads was observed in neutral media because of no CO_2 gas formation. The beads containing $CaCO_3$ those gelled in acidified gelation medium exhibited a good floating ability (100% floating) in all test media, irrespective of pH of the medium. Their buoyancy was not influenced by the amounts of drug added as nearly all of the porous beads remained buoyant after the buoyancy test period (Table 5).

Table 5 Floating property of drug-loaded CaPG and ZnPG beads containing different carbonate salts, n=50

Formulation	% Beads floated			
	CaPG			
	Distilled water		SGF	
	5 min	5h	5 min	5h
A4 (5% CaCO3)	50	0	70	60
A5 (5% $NaHCO_3$)	50	0	80	60
A6 (5% $CaCO_3$ + acetic acid)	100	70	100	80
A7 (10% $CaCO_3$ + acetic acid)	100	100	100	100
A8 (5% $CaCO_3$ + HCl)	100	80	100	100
A9 (5% $NaHCO_3$ + HCl)	100	90	100	100
A10 (5% $NaHCO_3$ + acetic acid)	80	70	100	90
	ZnPG			
	Distilled water		SGF	
	5 min	5h	5 min	5h
B4 (5%CaCO3)	50	0	70	50
B5 (5% $NaHCO_3$)	60	0	90	50
B6 (5% $CaCO_3$+acetic acid)	100	60	100	70
B7 (10% $CaCO_3$ + acetic acid)	100	100	100	100
B8 (5% $CaCO_3$+HCl)	100	80	100	100
B9 (5% $NaHCO_3$+HCl)	100	80	100	100
B10 (5% $NaHCO_3$+acetic acid)	90	70	100	90

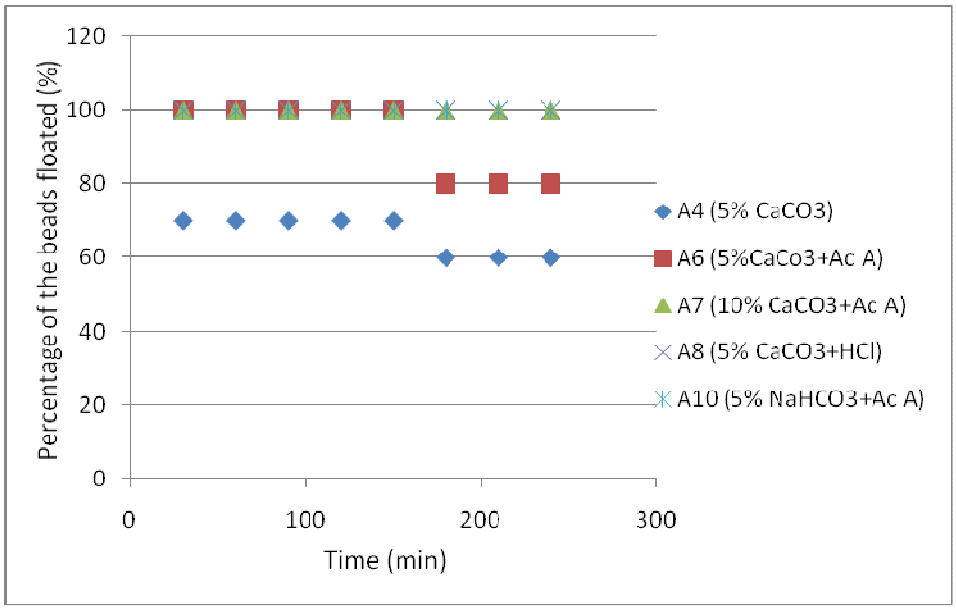

Fig 1- Floating kinetics of CaPG beads containing $NaHCO_3$ and $CaCO_3$ prepared in neutral and acidified gelation medium tested in SGF (Ac A- Acetic acid)

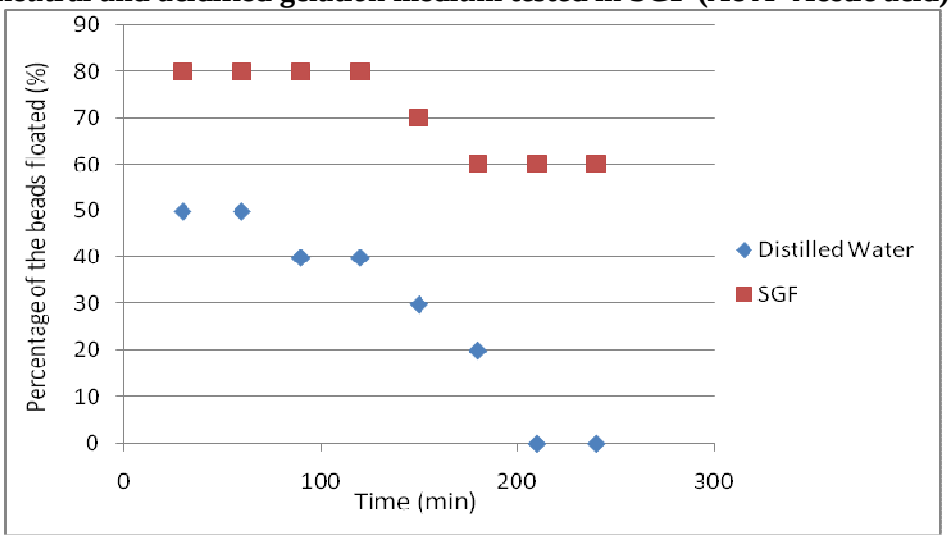

Fig 2- Floating kinetics of CaPG beads, A8 (5% $NaHCO_3$) in SGF and Distilled water.

***In vitro* drug release studies**

Effect of formulation variables on drug release

The release of ambroxol hydrochloride from beads was significantly slower than the dissolution of ambroxol hydrochloride powder because of the entrapment of drug in rate controlling polymer matrix. Fig. 4 shows the drug release from CaPG beads with different types and amounts of carbonate salts. Ambroxol hydrochloride was released from the beads containing $NaHCO_3$ more quickly than from those containing $CaCO_3$ due to their more porous structure. The beads containing $NaHCO_3$ disintegrate more readily in the test media due to the increased water uptake. Although $CaCO_3$ is present as an insoluble dispersion in medium with neutral pH, it becomes water-soluble and produces CO_2 in acidic media resulting in porous structure. Thus, the faster drug release from the beads containing 10% $CaCO_3$ may be resulted from more porous

structure than those with 5% $CaCO_3$ [11]. Effect of different cations used for crosslinking on drug release from beads is shown in Fig. 3. Beads prepared with zinc cations as crosslinking agent showed sustained release of drug than the beads prepared with calcium cations.

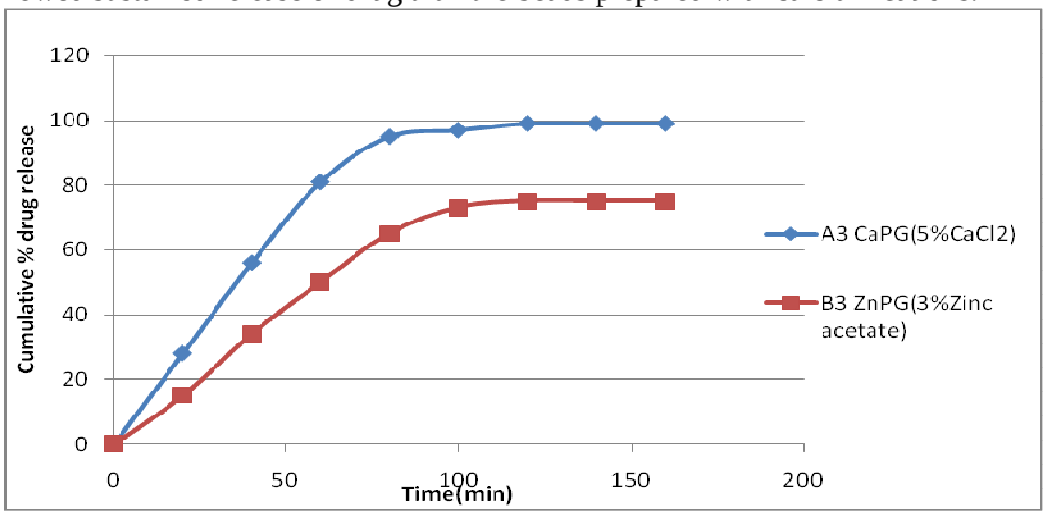

Fig 3- Effect of different cations used as gelation medium on release of drug from beads

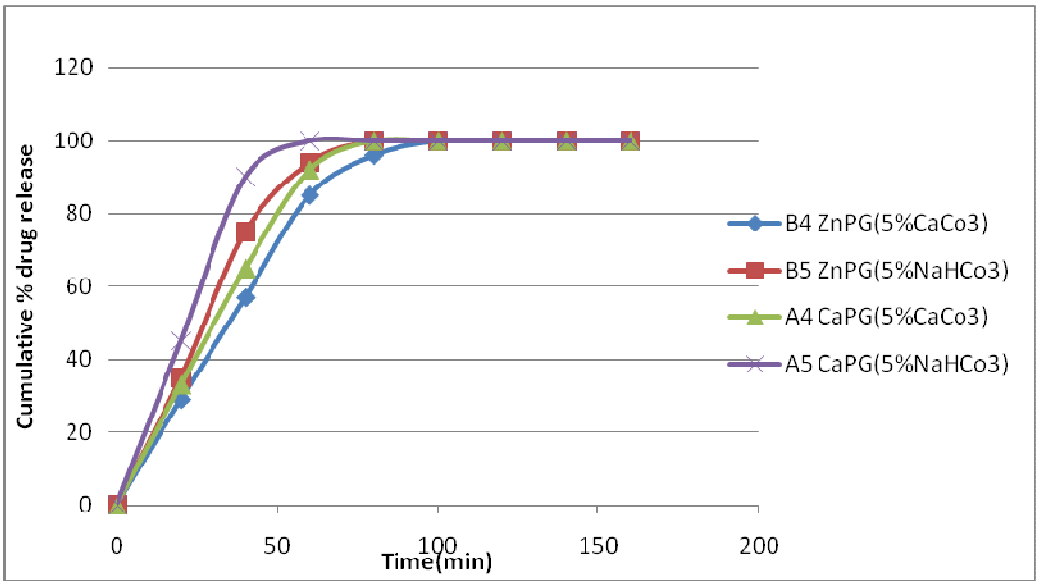

Fig 4- Effect of type and concentration of carbonate salt on Ambroxol hydrochloride release from air dried CaPG beads containing carbonate salt

Effect of the gelation medium

Fig. 5 shows the effect of medium used for bead formation on drug release from air-dried CaPG beads containing 5% $CaCO_3$. The CaPG beads containing 5% $CaCO_3$ those gelled in acidified medium released the drug faster than those gelled in neutral medium. It is most likely that acidified gelation medium helps to produce CO_2 gas, resulting in the porous structure. The beads those gelled in mixture of $CaCl_2$ and hydrochloric acid released the drug more quickly, comparing to those gelled in $CaCl_2$ and acetic acid. It is possible that the calcium ions in the

matrix structure were replaced faster by protons from the stronger acid solution of hydrochloric acid.

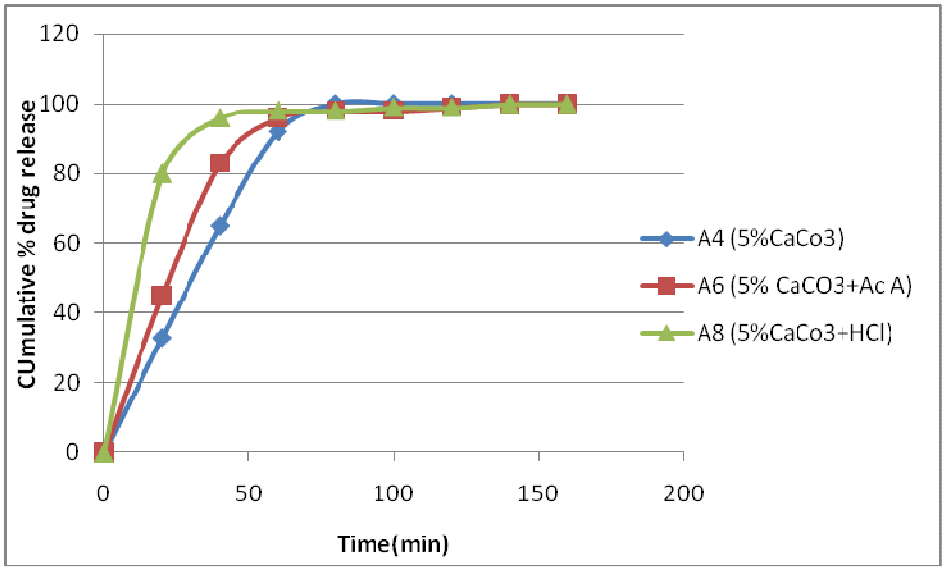

Fig 5- Effect of processing variables on drug release from CaPG beads containing carbonate salt

CONCLUSION

An intragastric floating drug delivery system using CaPG and ZnPG beads containing carbonate salt was designed and tested. CaPG beads showed greater floating ability than ZnPG beads. The release of ambroxol hydrochloride from CaPG beads containing carbonate salts depended on the formulation variables tested. Acidifying of gelation medium increased the pores in the structure of beads containing $CaCO_3$. This is because $CaCO_3$ reacted with acid to produce CO_2, and the evolving gas permeated though the matrix structure leaving gas bubbles or pores. It is obvious that the highly porous beads showed a good floating ability and a fast drug release. A7 i.e., CaPG with 10% $CaCO_3$ Prepared in acidified gelation medium(10%v/v acetic acid) showed greater entrapment and floating ability was found 100% in SGF after 5h of test period but drug release was faster in comparison with other batches. The results indicated that the beads using Zinc acetate, $CaCO_3$ and high drug loading could prolong the drug release but buoyancy of the beads using these conditions seemed to be decreased. This work can be extended to obtain prolonged drug release and better floating ability inside stomach by optimizing the formulation

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