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Optimization of the entrapment efficiency and release of ambroxol hydrochloride alginate beads

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ABSTRACT

The objective of the current study was to optimize the composition of alginate beads to produce ambroxol hydrochloride alginate beads with optimum specifications. The study employed beads based on sodium alginate solution (2% w/v) as the main component with calcium chloride solution as crosslinking agent as the prototype beads. The beads were prepared by syringe method. The effect of viscosity modifiers on the morphology, entrapment efficiency and drug release was studied. The prototype beads were spherical semitransparent with entrapment efficiency (EE) of 23%. Incorporation of polyvinylpyrrolidone (PVP) as a viscosity modifier produced spherical semitransparent beads with higher EE values compared with the prototype. Addition of carboxymethyl cellulose (CMC) produced oval opaque beads which have larger size and higher EE values compared with the prototype beads or those containing PVP only. Replacement of CMC with hydroxypropyl methyl cellulose (HPMC) produced semitransparent spherical beads with significant increase in the EE. Monitoring the drug release rate from different beads, the all the tested beads were able to retain the drug in the stomach condition. In the intestinal conditions the release rate depended on the composition of the beads with prototype beads librating most of its contents in the first 15 minutes. Formulations containing either CMC or HPMC were able to retard the drug release in the intestinal phase. In conclusion the study developed beads with optimum entrapment and release of ambroxol hydrochloride.

INTRODUCTION

Alginate is a polysaccharide which contains varying amounts of 1,4'-linked β-D-mannuronic acid, α-L-guluronic acid residues. As biocompatible and biodegradable biopolymer, it can form a bioadhesive stable gel especially in the presence of divalent cations such as calcium or barium. These properties have been employed in development of controlled release drug delivery system (Rasel and Hasan, 2012). Sodium alginate has been tested for sustained and controlled oral delivery of drugs with no evidence for mucosal damage (Kanjanabat and Pongjanyakul, 2011; Rajesh *et al*., 2012). The effect of divalent cations on alginate solution is widely used in preparation of solid beads for controlled drug delivery (Kanaka Durga Devi1 *et al.*, 2010). These beads are acid resistant and can liberate the drug slowly in acidic environment. Ionotropic gelation technique (Poncelet *et al*., 1999) is the most widely used technique with the majority of researchers employing syringes manually or mechanically via pump to simply drip alginate solution into a solution of divalent cation. This is expected to form beads (Takka and Gürel, 2010). This strategy is considered traditional and is being modified in many ways to control the size and shape of the beads. The major problem in preparation of beads is poor entrapment of hydrophilic drugs which tend to escape to the external aqueous environment during the process of beads production. Taking into consideration the fact that the majority of drug candidates requiring controlled release delivery systems are hydrophilic, it is important to optimize the entrapment efficiency of these drugs into the beads. The characteristics of beads depend on the composition of alginate based system. Addition of other excepients can affect size, shape, entrapment efficiency and release of drugs from such beads (Rangaraj *et al*., 2010). Accordingly the objective of the current study was to optimize the composition of alginate beads to produce beads with optimum specifications. To achieve this Ambroxol HCl was selected as model drug. Ambroxol is an active metabolite of the mucolytic agent bromhexine and is

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used in the treatment of bronchitis to improve expectoration. It is rapidly absorbed after oral administration followed by rapid elimination requiring three doses per day for optimum therapeutic efficacy (Kubo *et al*., 2004). The effect of viscosity modifiers such as hydroxypropyl methylcellulose (HPMC), sodium carboxy methylcellulose (NaCMC) and Polyvinyl pyrrolidone (PVP) on the characteristics of beads was investigated.

MATERIALS AND METHODS

Materials

Ambroxol was obtained as gift sample from Pharco pharmaceuticals, Alexandria. Sodium alginate (AR grade) was purchased from M.P. Biomedicala, LLC, France. Calcium Chloride was purchased from Al-Nasr Chemical Company, Cairo Egypt. Hydroxypropyl methylcellulose (HPMC E5) was supplied as a gift sample from Sigma pharmaceutical industries, Egypt. Polyvinyl pyrrolidone (PVP K30) was purchased from Sigma Chemical Company, St. Louis, USA. Sodium carboxy methylcellulose (CMC) was purchased from Nice Chemicals, Kerala, India. All other chemicals used in the present study were of analytical grade.

Spectrophotmetric determinations

The concentrations of ambroxol hydrochloride were determined by UV Spectrophotometry. This employed a spectrophotometer,Thermo Fisher Scientific, USA. Determinations were performed at 248nm and the calibration curve was linear (R^2 = 0.9975) in the concentration range of 12-40 µg/ml.

Preparation of drug- loaded beads by manual syringe method

The beads were prepared according to the composition presented in Table 1. Sodium alginate was dissolved in distilled water at 60°C under magnetic stirring for 2 hours in order to obtain 100 ml of polymer solution with concentration of 2% (w/w). HPMC or CMC were dispersed in the alginate solution if required. This was achieved by sprinkling the polymer powder on the surface of the alginate solution while stirring. The specification of beads prepared by this method depends on the inner diameter of the needle. Accordingly, 10 ml syringes fitted with a needle having a size of 21G were employed in preparation of all formulation. Sodium alginate solution (2% w/v) in presence or absence of other polymers with drug being solubilized in was introduced drop wise into the gelling solution (2% w/v aqueous calcium chloride with or without viscosity modifier, Table 1) while being gently stirred at 25°C. The stirring was continued for 15 minutes and the calcium alginate beads were harvested by filtration (Badarinath *et al*., 2010).

Determination of entrapment efficiency and drug content

The entrapment efficiency of the drug into the beads was determined after separation of the beads from the free drug remaining in solution. The entrapment efficiency (EE) was calculated using the equation:

EE (%) = [(Total drug added – amount of free drug)/total drug added] x 100

The drug content in the beads was determined by crushing known amount of dry beads a mortar with a pestle before soaking in 100 ml of phosphate buffer (pH of 7.4) with continuous stirring using overhead stirrer for 60 minutes. This provided complete swelling and bursting of the beads. The resultant dispersion was filtered through 0.45 µm membrane filter and the concentration of drug in the solution was determined spectrophotometrically after appropriate dilution using phosphate buffer (pH of 7.4) (Narra *et al*., 2012).

The drug content was calculated as the percentage drug load was given by the formula:

% Drug load = (WD / WB) x100

Where, WD is the amount of drug loaded in beads and WB is the weight of beads.

Particle morphology and particle size measurement

The beads were placed on a dark background and were photographed in presence of the measuring meter using a digital camera. The bead size was measured using Microsoft Powerpoint software with the taking the measuring meter as the reference scale. The average size of 50 beads was recorded (Mandal *et al*., 2010).

The average diameter of the beads was calculated using the following formula:

$X = \sum (X_i) / N$

X = Average particle diameter, Xi = Individual diameter of beads, N = Number of beads.

Determination of dissolution rate

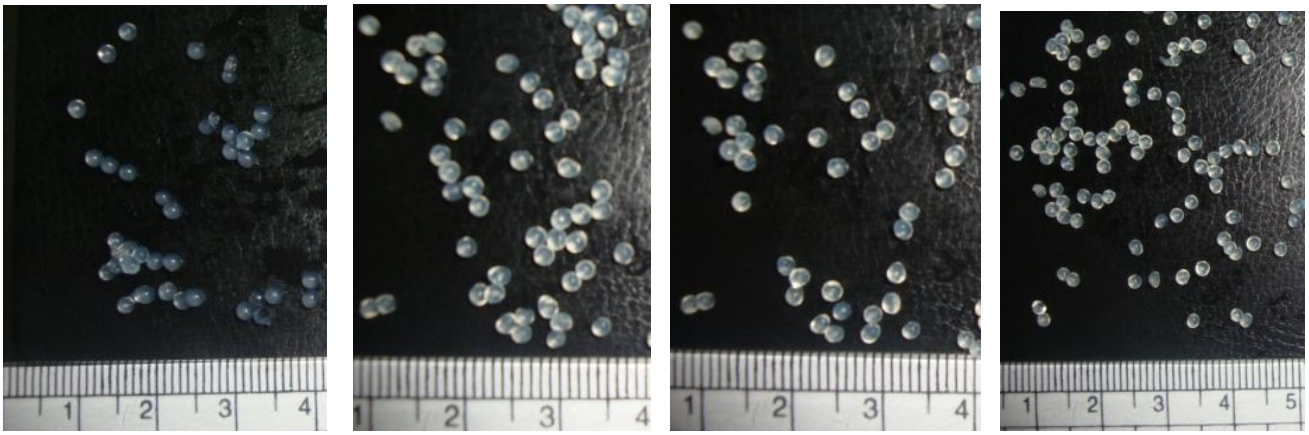
In vitro release studies of prepared microbeads were carried out using USP type 2 dissolution (paddle method) apparatus at 50 rpm. The release studies were performed in both stomach and intestinal environment. The stomach phase was conducted for 2 hours during which the drug release was monitored in 0.1N HCl. For the intestinal phase, the release study was conducted for a total period of 6 hours using 900 ml of phosphate buffer (pH 6.8) for first 4 hours at the end of which the pH was adjusted using 1N sodium hydroxide solution to 7.4 and the release was continued for the rest of the period. The temperature of the dissolution medium was maintained at 37±1°C. At periodic time intervals, 5 ml of samples were withdrawn, filtered immediately and drug content was determined spectrophotometrically at 248nm. Fresh dissolution media (5 ml) was added each time to compensate the dissolution medium. The cumulative percentage of drug release was plotted as a function of time to create the release profile. This was used to calculate the release efficiency (RE) which was calculated from the area under the release curve at time t (determined using the non-linear trapezoidal rule) and expressed as a percentage of the area of the rectangle described by 100% release in the same time (El Maghraby and Alomrani, 2009).

Table 1: The composition of the tested formulations.

Formula code	sodium alginate (%w/v)	Drug (%w/v)	Crosslinking agent Ca Cl2 (%w/v)	Viscosity modifiers agent PVP(%W/V)	Na CMC	HPMC
F1	2%	0.50%	2%	0	0	0
F2	2%	0.50%	2%	2%	0	0
F3	2%	0.50%	2%	3%	0	0
F4	2%	0.50%	2%	4%	0	0
F5	2%	0.50%	2%	2%	1%	0
F6	2%	0.50%	2%	2%	2%	0
F7	2%	0.50%	2%	2%	3%	0
F8	2%	0.50%	2%	0	2%	0
F9	2%	0.50%	2%	2%	0	0.50%
F10	2%	0.50%	2%	2%	0	1%
F11	2%	0.50%	2%	2%	0	2%

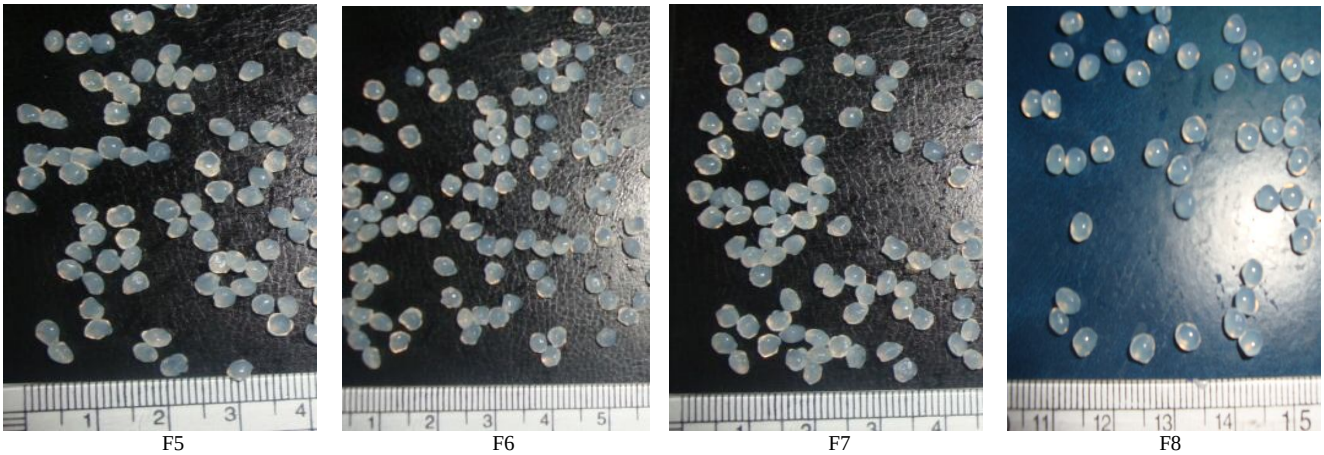
Table 2: The characteristics of the prepared beads

Formula code	Entrapment efficiency (%)	Particle size (µm)	Drug cotent (%)	Release efficiency (%)
F1	23 ± 0.43	2000 ± 0.001	2 ± 0.08	91± 1.34
F2	25.66 ± 0.19	2022 ± 133	2.4 ± 0.04	78.39 ± 1.67
F3	ND	2035 ± 145	ND	ND
F4	26.85 ± 0.54	2041 ± 151	ND	ND
F5	27.43± 2.11	2747± 252	ND	ND
F6	38.54 ± 0.31	2770 ± 227	3.94 ± 0.04	69.66 ± 0.26
F7	29.07 ± 0.26	2793 ± 220	ND	ND
F8	29.9 ± 1.91	3133 ± 48	2.81 ± 0.06	75.92 ± 1.01
F9	29.23 ± 0.36	2062 ± 295	ND	ND
F10	46.86 ± 0.32	2069 ± 302	ND	ND
F11	53.73 ± 0.15	2078 ± 341	4.54 ± 0.09	65.93 ± 0.65



F1 F2 F3 F4

Fig. 1: Photographs of sodium alginate beads in absence and presence of increasing concentrations of PVP as viscosity modifier. Formulation details are in Table 1.



F5 F6 F7 F8

Fig. 2: Photographs of sodium alginate beads in presence carboxymethyl cellulose as hydrophilic polymer. Formulation details are in Table 1.

RESULTS AND DISCUSSION

Beads preparation

The aim of this study is to optimize the composition of alginate beads to produce beads with optimum specifications and to study the effect of viscosity modifiers such as hydroxypropyl methylcellulose (HPMC), sodium carboxy methylcellulose (CMC) and polyvinyl pyrrolidone (PVP) on the characteristics of beads.

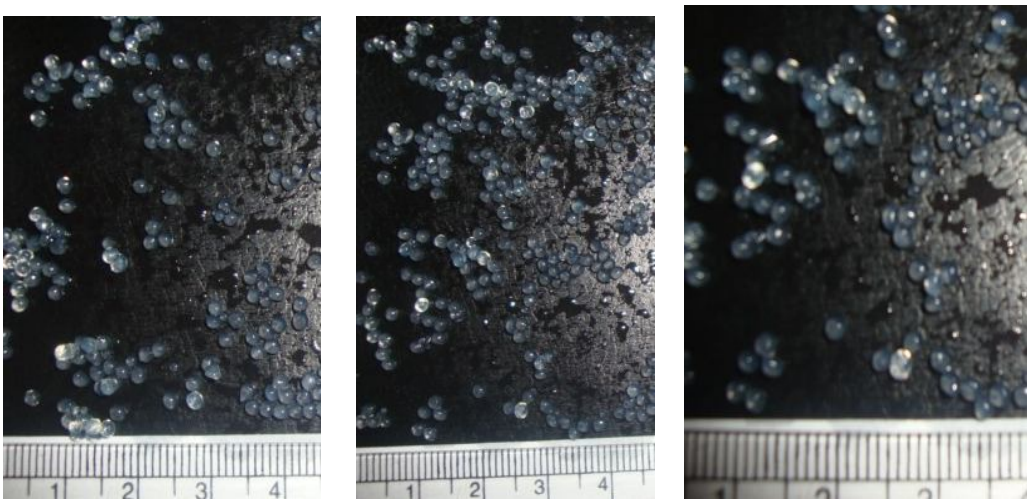
The crosslinking time was shown to be an important factor in preparation of beads. Increasing the crosslinking time was shown to decrease the drug entrapment efficiency, since prolonged exposure in the curing medium caused greater loss of drug through crosslinked alginate microsphere (Kassem *et al.*, 2012). Accordingly, the crosslinking time was kept constant (15 minutes) in all formulations. This was done to exclude any source of variability due to any variation in crosslinking time. The stirring rate during crosslinking is believed to be a determining factor that affects the bead size and the yield with very high stirring rate being responsible for reduction in the yield (Al-kassas *et al*., 2007). Accordingly, the stirring rate was kept at 400 rpm and was maintained with all formulation. This ensures that any variation in the bead size or morphology will be due to the variation in the composition.

The prepared beads were compared with respect to their morphology, size and entrapment efficiency of drug. The morphology of the prepared beads is shown in Figures and measured parameters are presented in Table 2. The standard alginate beads which were prepared in absence of any polymer (F1) were spherical and semitransparent in appearance (Figure 1). The particle size of these beads was 2000 µm and the beads were homogenous as reflected from the very low standard deviation values. The homogeneity of the beads is expected as the alginate solution was dropped on the calcium chloride solution at fixed rate with the droplet size being constant. Similar data was recorded using the same formulation (Arica *et al*., 2002; Chan *et al.,* 2009). Incorporation of PVP as a viscosity modifier in the crosslinking solution produced spherical beads which were semitransparent with marginal increase in the bead size compared with the standard beads (Figure 1 and Table 2). PVP is known to block the pores of alginate beads suggesting that most of the polymer will be intercalated within these pores with minute amounts being adsorbed on the surface of the beads. This may explain the recorded marginal increase in the bead size after incorporation of PVP in the crosslinking solution (Narra *et al*., 2012). Incorporation of CMC in the alginate solution resulted in relatively opaque beads with the beads loosing their spherical appearance with significant increase in the bead size compared with the standard bead or those prepared in presence of PVP as a viscosity modifier (Figure 2 and Table 2). The loss in the spherical nature of the beads can be explained on the bases that addition of CMC resulted in significant increase in the viscosity of alginate solution with the results that the falling droplets became non-spherical. This effect was associated with increased droplet size with subsequent increase in the bead size after crosslinking. The opacity of the beads can be explained on the base of the crosslinking effect of calcium on CMC with the later being expected to precipitate in presence of calcium. Similar increase in bead size was recorded after incorporation of CMC in the working solution and was explained on the base of increased viscosity (Saleem *et al*., 2012). Replacing CMC with HPMC E5 produced beads which retained their spherical appearance and were less opaque compared with those prepared in presence of CMC. The size of the beads was significantly smaller than that of the beads containing CMC but was relatively larger than that of the standard beads or the corresponding beads which were prepared in presence of PVP only (F2), (Figure 3 and Table 2). Considering the low viscosity of the tested HPMC E5, the recorded difference between HPMC based beads and CMC based beads confirm the previous explanation which suggested that the thickening effect of CMC was responsible for the increased particle size of CMC based beads. With respect to the absence of opacity in case of HPMC, it can be due to the lack of interaction between calcium ions and HPMC. It should be noted that, the presence of very high concentration of HPMC (30%) in alginate solution was previously shown to produce irregular structure due to the high content of HPMC in the blend which hindered the effective physical crosslinking. This can result in a situation where part of the material is washed out from the beads with subsequent collapse of the structure (Karewicz *et al*., 2010). This phenomenon was not recorded in the current study as the tested HPMC grade was of low viscosity with the maximum concentration being maintained at 2%.

Entrapment efficiency and drug content

The ability of beads to entrap the drug is the determining factor for selection of the method of preparation and composition of the beads. Accordingly, the effect of bead composition on the entrapment efficiency and drug content was investigated. Table 2 presents the results of entrapment efficiency and drug content in the beads. The standard beads which utilized sodium alginate as the bead former with calcium chloride as the crosslinking agent in absence of any viscosity modifier was able to entrap 23% of the drug.

The drug content of the solid beads was only 2% w/w. The low entrapment efficiency is expected taking into consideration the hydrophilic nature of the drug. This can lead to high potential for escaping from the beads before complete crosslinking. Incorporation of PVP in the crosslinking solution increased the entrapment efficiency of the drug to reach 25.66% with the drug content reaching 2.4% w/w on using 2% PVP in the crosslinking solution. Further increase in the concentration of PVP did not lead to significant increase in the drug loading (Table 2). Accordingly, 2% PVP was utilized in further optimization of drug content. The recorded improvement in the drug loading in presence of PVP can be explained on the bases that PVP is capable of closing the surface pores in the beads with the result that the loss of drug being reduced during the crosslinking step. Similar finding was recorded and was explained on the same base (Narra *et al*., 2012).



F9 F10 F11

Fig. 3: Photographs of sodium alginate beads in presence hydroxypropyl methylcellulose as hydrophilic polymer. Formulation details are in Table 1.

The study was extended to incorporate CMC with sodium alginate as a secondary bead former. This was conducted using calcium chloride/PVP solution for crosslinking. The presence of CMC resulted in significant increase in the entrapment efficiency and drug content. This was particularly evident in formulation containing 2% CMC. Preparing the same formulation in absence of PVP reduced the entrapment efficiency (Table 2). This suggests possible synergistic effect for PVP with CMC. The recorded improvement in the drug loading in presence of CMC can be explained on the bases that the presence of CMC enhanced the crosslinking efficiency as it can be precipitated with calcium which adds strength to the polymer chain crosslinking. Similar finding was recorded for the same polymer (Kassem *et al*., 2012). Reduction in drug loading in case of high concentration of CMC can be explained on the difficulty of obtaining proper spherical beads at high polymer concentration (Jelvehgari *et al.*, 2014). This explains the need for optimum concentration of CMC. Replacing CMC with HPMC resulted in a significant increase in the drug loading with the entrapment efficiency reaching 53.73 and the drug content being 4.54 %w/w in case of formulation containing 2% HPMC (Table 2). The recorded increase in the drug loading in presence of HPMC was previously explained on the base of formation of a more dense matrix structure (Goudanavar *et al*., 2010). Similar effect was recorded for hydroxyl propyl cellulose (Karewicz *et al*., 2010).

Drug release

The best formulation from each category was selected for release studies. The selected formulations included the prototype formulation which comprised sodium alginate with calcium chloride being the crosslinking solution (F1), the formulation utilizing 2% w/v PVP as viscosity modifier (F2), the formulation containing alginate with 2% CMC in the syringe and PVP and calcium chloride in the crosslinking solution (F6), the formulation containing alginate with 2% CMC in the syringe and calcium chloride in the crosslinking solution (F8) and the formulation containing alginate with HPMC in the syringe and PVP with calcium chloride in the crosslinking solution (F11). The release profile was performed both in the acidic and intestinal environments. The release profiles are shown in Figure 4 and the calculated release efficiency values are presented in Table 2. The amount of the drug released from the beads in the acidic environment (stomach conditions) was below the limit of quantification of the assay with the maximum recorded absorbance being around 0.14. Taking into consideration the fact that the limit of quantification of the assay was 8 µg/ml, it can be concluded that the amount of drug released from the beads is lower than 10% of the loaded drug in acid phase. In contrast the unprocessed drug powder was completely dissolved with the first hour. This is expected due to the poor solubility of calcium alginate beads in which the presence of calcium resulted in high degree of crosslinking in the acidic environment of the stomach (El Maghraby *et al*., 2012). Moving to the intestinal phase, the unprocessed drug powder librated more than 88% of the drug within 15 minutes with rest of the drug being dissolved after 30 minutes (Figure 4). Considering the beads the release in the intestinal phase depended on the composition of the beads. The prototype beads librated more than 70% of their contents in the first 15 minutes in the intestinal pH. The release efficiency was 91% (Table 2). Comparing the recorded release pattern of the drug from alginate beads in the intestinal phase with that recorded in the acid phase, it is clear that the former exhibited faster release compared with that recorded in the acidic environment. This can be explained on the bases of deprotonation of the alginate with subsequent disintegration of the beads (Narra *et al*., 2012, El Maghraby *et al*., 2012). To improve the ability of beads to retain drug, various hydrophilic polymers were included as a viscosity modifier. Incorporation of 2% w/v PVP in the crosslinking solution (F2) resulted reduced the drug release rate compared with the PVP-free formulation. This formulation librated 61% of its contents in the first 15 minutes in the intestinal phase with rest of the drug being librated slowly during the course of the study

(Figure 4). The release efficiency was significantly reduced compared with F1 (Table 2). The recorded reduction in drug release in presence of PVP can be explained on the bases that PVP can block the surface pores of the beads and can form a 'pseudo-gel layer' surrounding the bead. This layer can hinder drug release from the surface of the beads (Narra *et al.*, 2012). Another possible explanation for the recorded effect of PVP can be due to the formation intermolecular hydrogen-bonding between C=O groups of PVP, and –OH groups of alginate in alginate-PVP K 30 microbeads (Nayak *et al*., 2011). Incorporation of CMC with the alginate solution in presence of PVP/calcium chloride (F6) resulted in a significant reduction in the drug release rate with the formulation librating only 30.5% in the first 15 minutes with the rest of drug undergoing slow release throughout the course of the study (Figure 4). The release efficiency of the drug from this formulation was 69.65% (Table 2). This value was significantly lower than that recorded in absence of CMC ($P < 0.05$). The presence of CMC in the beads added to the network structure of the beads and inforced the degree of crosslinking due to its interaction with calcium ions. This produces tight packing which disintegrate and dissociate slowly with subsequent slow release even in the intestinal phase (Jelvehgari *et al*., 2014)

Formulating CMC/alginate based beads in absence of PVP (F8) resulted in slow release profile of drug but the release rate was relatively faster than that of F6 (Figure 4). This formulation liberated 40.43% in the first 15 minutes with the release efficiency being 75.9% (Table 2). These results reflect a synergism between the effect of CMC and that of PVP.

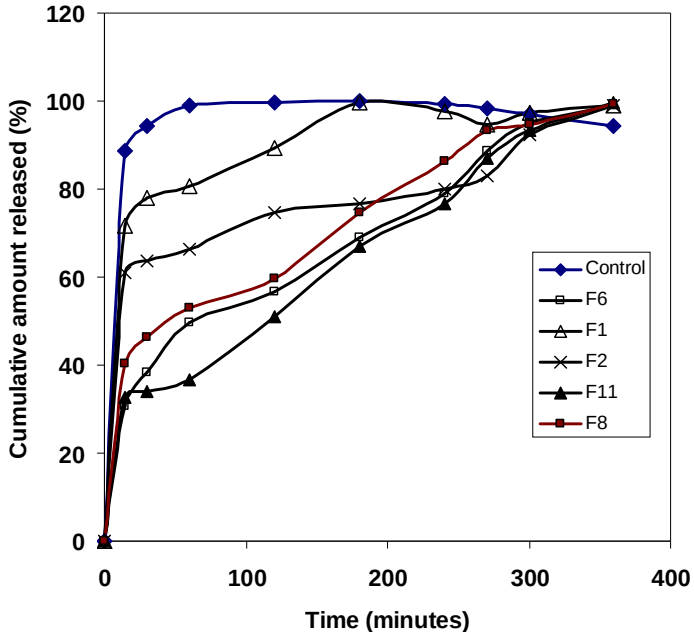


Fig. 4: Release of ambroxol hydrochloride from beads having different composition.

Incorporation of HPMC with alginate in the syringe and PVP/calcium chloride in the crosslinking solution (F11) produced beads capable of retaining the drug in the intestinal pH. These beads showed relatively slower drug release pattern with the release efficiency reaching 65.9% (Figure 4 and Table 2). The reduction in the release rate in presence of HPMC can be explained on the bases of reduction of the porosity of the formulation in presence of HPMC. This polymer can form viscous microenvironment upon hydration with subsequent reduction in the release rate (Chowdary *et al*., 2009).

It is interesting to note that there was an inverse relationship between the entrapment efficiency and the release efficiency (Table 2). This indicates that the formulation showing high ability to retain the drug during the crosslinking step will have the same tendency to retain the drug during the release phase.

CONCLUSION

The specifications of alginate beads depend on the composition of the beads. Addition of viscosity modifiers increases the drug entrapment efficiency into these beads. PVP showed high potential for this due to filling of the surface pores of the beads with subsequent inhibition of drug loss during crosslinking. This effect was further enhanced after addition of either CMC or HPMC with those polymers improving the ability of the beads to control the rate of drug release both in the stomach and intestinal conditions.

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