### Preparation and Evaluation of Atenolol Floating Beads as a Controlled Delivery System Lena M. Thomas\* and Yehia I. Khalil\*,1

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### **Abstract**

This study aims to encapsulate atenolol within floating alginate-ethylcellulose beads as an oral controlled-release delivery system using aqueous colloidal polymer dispersion (ACPD) method. To optimize drug entrapment efficiency and dissolution behavior of the prepared beads, different parameters of drug: polymer ratio, polymer mixture ratio, and gelling agent concentration were involved. The prepared beads were investigated with respect to their buoyancy, encapsulation efficiency, and dissolution behavior in the media: 0.1 N HCl (pH 1.2), acetate buffer (pH 4.6) and phosphate buffer (pH 6.8). The release kinetics and mechanism of the drug from the prepared beads was investigated. All prepared atenolol beads remained floating on 0.1 N HCl (pH 1.2) medium over 24 hours. Besides, high yield beads of 73.07-84.31% was obtained. Encapsulation efficiencies were in the range of 33.10 % -79.04 %, and were found to increase as a function of increasing drug: polymer mixture ratio and the gelling agent concentrations. Moreover, atenolol release profile from the beads was affected by the pH of the dissolution medium. It was found to be slowest in 0.1 N HCl (pH 1.2) and fastest in phosphate buffer (pH 6.8). The obtained results suggest that atenolol could be formulated as a controlled release beads, using ethylcellulose and alginate as polymers, using ACPD method.

Keywords: Floating beads, Atenolol, Controlled Delivery System.

#### الخلاصة

تهدف هذه الدراسة لتغليف الاتينولول في كريات طافية من الأثيل سليلوز -الجينات الصوديوم كنظام تحرر مسيطر عليه باستعمال طريقة الانتشار المائي لتحسين كفاءة التحميل الدوائي و سلوك تحرر العقار من الكريات المحضرة، فان عدة عوامل مثل نسبة العقار المكوثرات، نسبة مزيج المكوثرات اضعة الى تركيز الملاة المهلمنة قد تضمنت في هذه الدراسة. لقد تم التحري عن الكريات المحضرة بالنسبة الى قابليتها على الطفو، كفاءة التحميل الدوائي وسلوك التحررالدوائي في الاوساط: 0.1مولاري لحامض الهيدرو جيني 4.6) ومطول الفوسفات المائي (الاس الهيدرو جيني 6.8)، كما تمت محاولة التوصل الى معرفة آلية التحرر الحركي الدواء من الكريات المحضرة القد وجد ان جميع الكريات المحضرة بقيت طافية في وسط حامضي 0.1 مولاري لحامض الهيدرو كلوريك (الاس الهيدرو جيني 2.1) لفترة زادت عن 24 ساعة المحضرة بقيت طافية في وسط حامضي 1.0 مولاري لحامض الهيدرو كلوريك (الاس الهيدرو جيني 1.0 لفترة زادت عن 24 ساعة المحفرة الى ان تلك لكريات كانت بكمية ناتج نهائي يتراوح بين 73.07-83 % وبقابلية تحميل دوائي بنسبة 79.04 داريات الحين المحفرة المهلمنة قد وجد ان الشكل البياني لتحرر كما وجد ان قابلية التحميل الدوائي وان ابطأ تحرر يتم في وسط الاتينولول من كريات الجينات الصوديوم الاثيل سليلوز تتأثر بالاس الهيدرو جيني لوسط التحرر الدوائي وان ابطأ تحرر يتم في وسط ان النتائج المستحصلة من الدراسة تقترح بان الاتينولول يمكن تصبيغه على شكل كريات محورة التحرر باستعمال الاثيل سليلوز والجينات الصوديوم كمكوثرات باستعمال طريقة الانتشار المائي.

### Introduction

Atenolol is a polar cardioselective βblocker, widely used alone or in combination with other drugs for treatment of various cardiovascular conditions. (1) It is slightly soluble in water with reported half-life of 6-7 hours.<sup>(2)</sup> It is considered a drug with low jejunal permeability and a low extent of therefore it has an oral absorption, bioavailability of about 46-62% (3). Thus, it seems that an increase in gastric residence time may increase the extent of absorption and bioavailability of the drug. (4) Sodium alginate (Na-Alg) is a water-soluble salt of the naturally occurring polysaccharide alginic acid, and has received much attention in pharmaceutical preparations, particularly due to its role as a

vehicle for controlled drug delivery. (5, 6) Ethylcellulose (EC) is an inert, hydrophobic, organosoluble polymer and has been extensively used as a pharmaceutical vehicle in many drug delivery systems including microcapsules and microspheres to control the dissolution rate of drugs from their preparations. (7, 8) Spherical gel beads of calcium alginate can be formed immediately when sodium alginate solution is added dropwise into a calcium chloride solution. The formed beads are able to entrap drug(s) in eggbox gel matrix, and thus act as a vehicle for the controlled release of many orally administered drugs. (9,10)

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Received: 27/11/2010 Accepted: 23/4/2011 Such beads have also been used in the design of floating systems in order to prolong gastric retention time <sup>(11,12)</sup> The floating and sustained drug release properties of calcium alginate beads were found to be enhanced by the addition of ethylcellulose. (13) This work aims to formulate a promised controlled-release atenolol beads that are capable of floating on gastric juice to prolong gastric residence time, thereby extend the time of drug release and then enhance its oral bioavailability, using aqueous colloid polymer dispersion method.

### **Materials and Methods**

### Materials

Atenolol powder (gift from Samarra Drug Industry), sodium alginate (low viscosity grade; 5.5 cp in 1% solution at 25 °C; Himedia lab, India), ethylcellulose (BDH chemicals Ltd. Poole, England), anhydrous calcium chloride (Gainland chemical Co. UK). All other reagents were of analytical grade.

### Methods

Beads were prepared according to the method described by Bodmeier et al. (14) In this method, atenolol powder (weight corresponds to drug:polymer mixture ratio, table 1) was dispersed in a previously prepared aqueous

solution of sodium alginate (prepared by dissolving sodium alginate in hot (40 °C) water) and mixed homogeneously. An aqueous dispersion of ethylcellulose was added to this mixture and stirred well. After a good mixing, the bubble-free dispersion was dropped from a 10 mL syringe barrel (without needle) into a manually shaken beaker containing an aqueous calcium chloride solution at room temperature. The falling distance was 3.5-5 cm. The droplets instantaneously formed gelled spheres by ionotropic gelation of alginate with Ca<sup>+2</sup> ions. The formed beads were separated after 3-5 minutes and washed twice with distilled water as they were filtered over Buchner funnel under vacuum. The beads were spread on a filter paper positioned in a petri-dish and left to dry overnight in an oven (Mammert, Germany) at 40 °C.

Nine formulas were prepared by this method, the composition of each formula are given in table 1:

- Formulas 1-4 to investigate the effect of drug: polymer mixture ratio.
- Formulas 4-7 to investigate the effect of sodium alginate: ethylcellulose ratio, and.
- Formulas 4, 8 and 9 to investigate the effect of the concentration of gelling agent (CaCl<sub>2</sub>) used.

Table 1: The Effect of Different Variables on Floating Beads of Atenolol Using Aqueous Colloidal Polymer Dispersion Method.

	Drug:	A te no lo l	(Polymer Mixture)	Gelling		apsulation eld		Drug loa	Encapsu-		
Formula Code	polymer Ratio (% w/w)	(Core) (gm)	Sodium alginate: Ethylcellulose ratio (gm)	Agent (CaCl <sub>2</sub> ) % w/v	Theor- etical (gm)	Actual (gm)	% Yie ld	Theo- retical	Actual	la tio n Efficie ncy (% EE)	
1	1:0.5 (66.6:33.	(8)	1:15 (0.25: 3.75)	1	12	9.45	78.75	66.66	49.40	74.18	
2	1:1 (50:50)	(4)	1:15 (0.25:3.75)	1	8	6.132	76.65	50	34.56	69.125	
3	1:2 (33.3:66. 6)	(2)	1:15 (0.25 : 3.75)	1	6	4.579	76.31	33.3	22.55	67.73	
4	1:3 (25:75)	(2)	1:15 (0.375 : 5.625)	1	8	6.018	75.22	25	16.65	66.60	
5	1:3 (25:75)	(2)	1:7.5 (0.70:5.30)	1	8	5.846	73.07	25	8.275	33.10	
6	1:3 (25:75)	(2)	1:22.5 (0.255:5.745)	1	8	6.00	75.00	25	12.65	50.60	
7	1:3 (25:75)	(2)	1:30 (0.1935 : 5.8065)	1	8	6.05	75.71	25	17.98	71.95	
8	1:3 (25:75)	(2)	1:15 (0.375 : 5.625)	3	8	6.279	78.48	25	18.12	72.49	
9	1:3 (25:75)	(2)	1:15 (0.375 : 5.625)	5	8	6.745	84.31	25	19.76	79.05	

Evaluation of the Prepared Beads Encapsulation Efficiency and Yield Percent Beads recovered after being dried were weighed and the yield was calculated as a percentage of the total weights of starting material (polymer and drug) added during preparation and the actual weight of beads obtained. Thus, the yield percent was calculated using the following equation (15):

Yield (%) = 
$$\frac{\text{Actual weight of beads}}{\text{Theoretical weight of beads}} \times 100$$

To determine the encapsulation efficiency of the beads, 50 mg beads were crushed using a porcelain mortar and a pestle, and dispersed in 50 mL me thanol. The dispersion was sonicated for 15 minutes and then the dispersion was filtered. A 1 mL sample was taken, diluted to 10 mL with methanol, and drug content assayed using a UV-visible spectrophotometer (Carry UV, Varian, Australia) at  $\lambda_{max}$  of 275 nm.The drug entrapment efficiency of prepared beads was determined by using the following equation  $^{(15)}$ :

#### In-vitro Buoyancy Test

The floating ability and duration of the prepared beads were determined in USP paddle type dissolution apparatus (Copley Scientific LTD, England). A weight of beads equivalent to 100 mg of atenolol were dispersed over 900 mL of 0.1 N HCl (pH 1.2). The paddle speed was maintained at 50 pm, and the temperature of the medium maintained at  $37\pm0.5$  °C. Buoyancy was observed visually. Beads were considered to be buoyant only when all of them are floated. (12)44

### Dissolution Studies

Dissolution studies of atenolol beads were performed using USP paddle type dissolution apparatus (Copley Scientific LTD, England) at a rotation speed of 50 rpm. For all dissolution studies, beads (equivalent to 100 mg atenolol) were dispersed separately over 900 mL of dissolution medium maintained at 37±0.5°C.For all formulas, dissolution studies were carried out using 0.1 N HCl (pH 1.2) to simulate gastric pH. Furthermore, to predict drug release behavior from beads in different pH media, dissolution media of acetate buffer (pH 4.6) and phosphate buffer (pH 6.8) were used to simulate the pHs pertaining to proximal and middle small intestine (duodenum and jejunum), and distal small intestine (ileum), respectively. (16, 17) The effect of pH on drug release behavior from the prepared beads was studied only for formulas

1-4.Ten milliliter samples were withdrawn at specific time intervals and replaced by the same volume of fresh media. The withdrawn sample was filtered with a millipore filter (pore size 0.45  $\mu$ m). The amount of atenolol released in all studied media was analyzed by a UV-visible spectrophotometer (Carry UV, Varian, Australia) at  $\lambda_{max}$  of 273 nm.

### Analysis of Drug Release Mechanism

To establish the release kinetics and mechanism of drug release from the floating beads in different media, data obtained in the first 120 minutes of the in vitro release studies in 0.1 N HCl (pH 1.2) and acetate buffer (pH 4.6) were fitted to into zero-order, first-order, Higuchi, and Baker-Lonsdale models. (18) Meanwhile, the release profile of atenolol in phosphate buffer (pH 6.8), which is estimated in the first 60 minutes was analyzed by Hopfenberg model in addition to the above mentioned models. The dissolution data were also fitted to the well-known exponential equation (Korsmeyer-Peppas equation), which is often used to describe the drug release behavior from polymeric systems when the mechanism is not well-known or when more than one type of release phenomena is involved. The value of the release exponent (n)Korsmeyer-Peppas equation determined and is used to indicate different release mechanisms. When n takes a value of 0.43, the drug diffuses through and is released from the polymer following Fickian diffusion mechanism. A value of 0.43 < n < 0.85represents a non-Fickian (anomalous) transport; a value of n equal to 0.85 indicates case-II transport, and a value of n above 0.85 indicates super case-II transport. (19) The best fit model was selected as the one with the highest values of regression coefficient  $(\mathbb{R}^2)$ .

### Statistical Analysis

The statistical analysis of results was performed by one way analysis of variance test using Microsoft Excel Program. Differences were considered to be statistically significant at  $p < 0.05\,.$ 

### **Results and Discussion**

### Encapsulation Efficiency and Yield Percent

The yield percent and encapsulation efficiency of atenolol-loaded alginate ethylcellulose beads prepared with different drug: polymer mixture ratios, using different formulation variables are listed in table 1.

The effect of drug: polymer mixture ratio

Increasing drug: polymer mixture ratio resulted in a significantly (p< 0.05) higher percentage yield and encapsulation efficiency as shown in table 1 (formulas 1-4). The higher encapsulation efficiency obtained may be attributed to the event of more available drug amounts to be encapsulated. Similar results were observed with mefenamic acid (20) and indomethacin beads. (21)

## The effect of different ratios of polymer mixture (sodium alginate: ethylcellulose ratio)

Table 1 shows that the percentage yield and encapsulation efficiency was significantly increased (p < 0.05) by varying sodium alginate: ethylcellulose ratio from 1:7.5 to 1:22.5 (formulas 4-6). This indicates that at higher amounts of ethylcellulose use, and due to greater hydrophobic barrier effect, higher encapsulation efficiency was obtained due to retardation of drug migration and loss to the external aqueous phases. Similar results were observed with floating cimetidine microspheres prepared by hydroxypropylmethyl cellulose and ethylcellulose as polymers. (22) However, further reduction in sodium alginate: ethylcellulose ratio to 1:30 (formula 7) produced significantly lower (p < 0.05) percent yield and encapsulation efficiency. Such an effect may be explained by the fact that at lower sodium alginate ratios, the drug particles were not encapsulated completely due to less available active calcium-binding sites in the polymeric chains and, consequently, a lower degree of cross-linking with gelling agent and formation of lower strength matrix structure. (23)

## The effect of gelling agent (CaCl<sub>2</sub>) concentration

It is observed that increasing  $CaCl_2$  concentration significantly (P < 0.05) increased the drug percentage yield and encapsulation efficiency (table 1, formulas 4, 8 and 9). This may be due to better cross-linking reaction of sodium alginate present in the bead structure with the more abundant presence of calcium ions, thus a better barrier entrapping the drug inside the polymeric matrix structure of the beads is provided. Similar results were observed with calcium alginate nicardipine microcapsules.  $^{(24)}$ 

### In-vitro Buoyancy Test

The prepared beads showed excellent floating characters. The beads remained on top of 0.1 N HCl (pH 1.2) for duration time over 24 hr; besides, buoyancy was not affected by the changes of the formulation variables during

the overall study. Meanwhile, no change was observed on the whole integrity of floated beads concerning color and shape during the period of buoyancy test. The floating ability of the prepared beads is because of the use of low density materials which produced an inherently low density beads that float immediately following contact with 0.1 N HCl (pH 1.2). Similar results were observed with alginate-ethylcellulose beads of metronidazole. (13)

### Dissolution studies

### The effect of drug: polymer mixture ratio

The behavior of drug release from beads having different drug: polymer mixture ratios (1:0.5, 1:1, 1:2, and 1:3) was studied in different dissolution media (0.1 N HCl (pH 1.2), acetate buffer (pH 4.6) and phosphate buffer (pH 6.8)), using an exact weight of beads equivalent to 100 mg of atenolol. The obtained release profiles are represented in figures 1, 2 and 3 respectively. For the drug release profile in acidic pH media (figures 1 and 2), a significant reduction (p <0.05) in drug release rate was observed by decreasing drug: polymer mixture ratio. The time to 50 % drug released showed a significant reduction (p < 0.05) equivalent to 3 and 5 fold from 15 to 50 minutes and from 18 to 90 minutes for 1:0.5 and 1:3 drug: polymer mixture ratio at pH (1.2) and pH (4.6), respectively. The higher drug release rates observed in the 2:1 drug: polymer mixture ratio could be attributed to inability to form a homogenous dispersion at the first step, and because of the fact that at this ratio the amount of polymer might be insufficient to coat all the drug particles present, such that unbound drug particles were randomly present in or on the surface of the beads, resulting in higher drug release rates. (24) Similar findings were observed with ethylcellulose coated diclofenac sodium microcapsules. (25) The most retardant drug release effect observed with 1:3 ratio as compared to lower ratios indicates that the release rate is controlled by wall thickness: an increase in polymer ratio will increase the coat thickness surrounding the drug particles, thereby increasing the distance travelled by the drug through the coat causing a greater impedance to drug release. (26) This finding is in accordance with the results found with coated ethylcellulose isoprinosine microcapsules. (27) For the drug release profile in pH 6.8 (figure 3), varying the drug: polymer mixture ratio had a non-significant (p > 0.05) effect on drug release, and drug release profile was in an order opposite to what was observed with that for release in acidic pH.

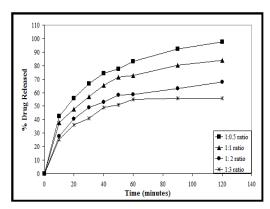


Figure 1: The release of atenolol from beads with different drug: polymer mixture ratio in 0.1 N HCl (pH 1.2) at  $37 \,^{\circ}$ C.

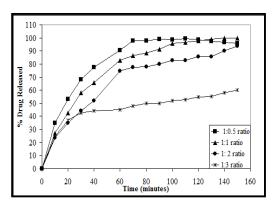


Figure 2: The release of atenolol from beads with different drug: polymer mixture ratio in acetate buffer (pH 4.6) at 37 °C.

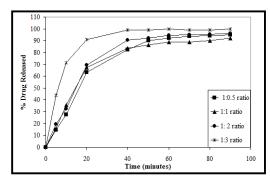


Figure 3: The release of atenolol from beads with different drug: polymer ratio in phosphate buffer (pH 6.8) at 37 °C.

## The effect of varying the pH of dissolution media

Atenolol, being a weakly basic drug with a pka value of 9.6 (28) is expected to possess higher solubility and therefore a faster drug

release rates at acidic pHs than at basic pHs. However, as it is evident from drug release profile in figure 4, it was seen that the drug release in acidic media (0.1 N HCl (pH 1.2) and acetate buffer (pH 4.6)) is relatively slow and equivalent to each other within the initial 2 hours compared to fast and complete drug release in phosphate buffer (pH 6.8) within 30-60 minutes. It is reported that alginate matrices demonstrate a pH-dependent hydration, swelling and erosion behavior, resulting in pHdependent drug release mechanisms. (29) Visual observation of atenolol beads during dissolution studies revealed that those hydrated in acidic pH showed no visible evidence of erosion and reserved their shape and structural integrity. Such structural stability in acidic pH may be attributed to the stability of alginate at lower pHs and the conversion of Ca-alginate to the insoluble but swelling alginic acid. (30) Thus, a greatly retarded and limited release of atenolol from alginate-ethylcellulose matrices was observed during dissolution into an acid environment. In contrast, for dissolution in phosphate buffer (pH 6.8), contrary to what was observed in acidic media, rapid erosion and disintegration of the beads have occurred. and this greatly contributed in facilitating atenolol release rate. Such bead disintegration occurs because of the exchange process of the calcium ions of the alginate beads with Na+ salt of the phosphate buffer, resulting in formation of monovalent sodium salts of alginates, which unlike the divalent Ca2+ salts alginates, are water soluble. (10) conclusion, atenolol release behavior from alginate-ethylcellulose beads was affected by the pH of the dissolution medium. Such behavior is consistent with that observed with nicardipine (31) and mefenamic acid beads. (20)

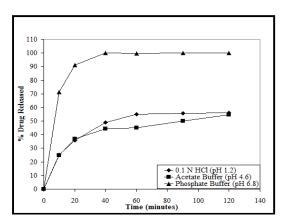


Figure 4: The release of atenolol from beads with (1:3) drug: polymer mixture ratio in different pH media at 37 °C.

# The effect of different ratios of polymer mixture (sodium alginate: ethylcellulose ratio)

To study the effect of different sodium alginate: ethylcellulose ratios on atenolol release, formulas 4-7 were subjected to in vitro drug release studies in 0.1 N HCl (pH 1.2). The drug release profiles of these formulations are shown in figure 5. The results indicated that the drug release rate varied depending on the ethylcellulose content and decreased significantly (p < 0.05) as the ratio of sodium alginate: ethylcellulose was decreased from 1:7.5 (formula F5) to 1:15 (formula F4). Such observation indicates that ethylcellulose, when used at higher amounts, is able to retard the release of drug from the beads due to the formation of a less permeable matrix. (32) Besides, the presence of lower amounts of sodium alginate produced a highly porous matrix structure having a low gel strength, this will result in rapid diffusion of the drug from the matrix. (33) Similar results were observed with floating metronidazole alginate beads containing ethylcellulose. (13)

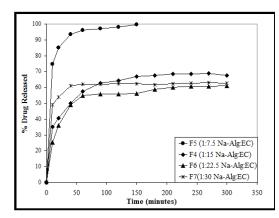


Figure 5: The effect different ratios of polymer mixture (sodium alginate: ethylcellulose ratio) on the release of atenolol in 0.1 N HCl (pH 1.2) at 37  $^{\circ}$ C.

### The effect of gelling agent (CaCl<sub>2</sub>) concentration

To study the effect of gelling agent (CaCl<sub>2</sub>) concentration on atenolol release, beads were formulated with three different concentrations of CaCl<sub>2</sub>: 1%, 3% and 5% (w/v) (formulas 4, 8 and 9). The release profiles for these formulations are shown in figure 6. From the obtained results, it appears that increasing the concentration of CaCl<sub>2</sub> produced a nonsignificant (p> 0.05) effect on dissolution behavior. This may be attributed to the possible saturation of calcium binding sites in the guluronic acid chains of sodium alginate

with the use of a 1 % (w/v)  $CaCl_2$  solution which prevented further calcium ion entrapment and hence crosslinking was not altered with the higher concentrations of  $CaCl_2$  solutions. (34) Similar results were obtained with furosemide-loaded calcium alginate beads. (35)

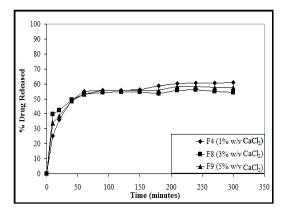


Figure 6: The effect of calcium chloride concentration on the release of atendol in 0.1 N HCl (pH 1.2) at 37 °C.

### Evaluation of Release Kinetics

In order to obtain meaningful information for atenolol release kinetics and mechanism from formulated beads, drug-release data were fitted into various drug-release kinetic models mentioned above, and the goodness of fit of the release data was assessed. Tables 2-4 summarize the values of regression coefficient (R<sup>2</sup>), kinetic constant (K) and release exponent (n) for the different release kinetic models in 0.1 N HCl (pH 1.2), acetate buffer (pH 4.6) and phosphate buffer (pH 6.8), respectively. In this study, as illustrated in table 2, atenolol release in 0.1 N HCl (pH 1.2) from different bead formulations showed a good fit into Korsmeyer-Peppas model. An exception is formula 1, which showed better fitting to Baker Lonsdale model. The release in all the prepared formulas is expected to occur by Fickian diffusion mechanism since the value of release exponent (n) was in the range of (0.1-0.43); this hypothesis is further supported by visual observations that beads neither changed their shape nor disintegrated during dissolution process. For release in acetate buffer (pH 4.6), as in the case of release in 0.1 N HCl (pH 1.2), the beads preserved their shape during dissolution studies. It was observed that the drug release data of formulas having different polymer mixture ratios intermediate to the equations of Higuchi, Baker-Lonsdale and Korsmeyer-Peppas (table 3). For formulas 1-3, since higher values of regression coefficient were obtained during

data fitting to Korsmeyer-Peppas equation and the value of release exponent (n) were in the range of 0.585-0.656, an anomalous transport mechanism of drug release where both diffusion through swellable and non swellable polymer is expected to occur, rather than drug release behavior totally based on diffusion, which generally is the case in Higuchi's and Baker-Lonsdale's models. On the other hand, for formula 4, release data fitted best to Higuchi model indicating that drug release occurs by Fickian diffusion mechanism. This conclusion is further supported by the value of release exponent (n = 0.272) obtained from fitting to Korsmeyer-Peppas equation.In case of drug release in phosphate buffer (pH 6.8), simulating the drug kinetics of formulas having different drug: polymer mixture ratios (formula 1-4) with different models, it is observed that release fitted intermediate with drug Hopfenberg and Korsmeyer-Peppas models while regression coefficients were slightly

higher with the latter model (table 4). The value of diffusional exponent (n) for formulas 1-3 was in the range of 0.921-1.068, meaning that a super case II transport mechanism is involved, which is related to polymer relaxation and erosion mechanism. A value of (n=0.525) for formula 4 indicates a non-Fickian (anomalous) transport mechanism which is an indication of diffusion/polymer relaxation controlled drug release. These mathematical finding, supported by observations obtained during dissolution experiments showing disintegration of the bead matrix structure, proposes a mixed drug release mechanism in phosphate buffer, partially involving swelling of sodium alginate in the bead structure, bead matrix disintegration and drug diffusion out of the beads. Similar drug release behavior was observed for furosemide (37) and tiaramide (38) loaded alginate beads during their dissolution in phosphate buffer.

Table 2: The release mechanism of atenolol from prepared beads by ACPD method using different drug: polymer ratios in 0.1 N HCl (pH 1.2)\*.

Formula Code	Zero Order		First Order		Higuchi		Baker- Lonsdale		Korsmeyer and Peppas					
	R2	K <sub>0</sub>	R <sup>3</sup>	K	R <sup>3</sup>	KH	R2	KBL	R <sup>2</sup>	KEP	n	Interpretation		
	0.872	0.464	0.782	0.007	0.962	7.021	0.998	0.003	0.994	2.900	0.375	Fickian Diffusion		
2	0.835	0.397	0.756	0.007	0.938	6.056	0.953	0.002	0.992	2.729	0.388	Fickian Diffusion		
3	0.781	0.311	0.675	0.006	0.900	4.799	0.912	0.001	0.975	2.395	0.425	Fickian Diffusion		
Ä	0.684	0.249	0.616	0.006	0.827	3,935	0.760	0.001	0.990	2.254	0.430	Fickian Diffusion		
5	0.674	0.141	0.645	0.002	0.807	2.410	0.869	0.002	0.909	4.126	0.100	Fickian Diffusion		
6	0.268	0.896	0.855	0.005	0.967	3.963	0.945	0.001	0.989	2.953	0.260	Fickian Diffusion		
7	0.683	0.105	0.625	0.0019	0.775	1.655	0.658	0.0003	0.889	3.689	0.100	Fickian Diffusion		
8	0.790	0.136	0.772	0.003	0.895	2.058	0,817	0.0003	0.952	3.354	0.142	Fickian Diffusion		
9	0.798	0.199	0.765	0.004	0.905	3.024	0.844	0.001	0.960	3.021	0.221	Fickian Diffusion		

\*Kinetic constant (k), correlation coefficient (R<sup>2</sup>), diffusional exponent (n). Shaded and bold font areas: optimum values of correlation coefficient. Bold underlined areas: second best fit values of correlation coefficient.

Table 3: The release mechanism of attenolol from prepared beads by ACPD method using different drug: polymer ratios in acetate buffer (pH 4.6)\*.

Formula Code	Zero Order		First Order		Higuchi		Baker- Lonsdale		Korsmeyer and Peppas					
	R <sup>2</sup>	K <sub>0</sub>	R <sup>2</sup>	Kı	R <sup>2</sup>	K <sub>H</sub>	R <sup>2</sup>	K <sub>BL</sub>	R <sup>2</sup>	K <sub>KP</sub>	n	Interpretation		
1	0.794	0.529	0.713	0.008	0.996	55.208	0.675	0.003	0.998	2.213	0.585	Anomalous transport		
2	0.889	0.606	0.784	0.010	0.992	60.565	0.993	0.004	0.996	1.791	0.656	Anomalous transport		
3	0.885	0.558	0.812	0.011	0.968	55.238	0.953	0.002	0.993	1.670	0.631	Anomalous transport		
4	0.813	0.206	0.715	0.005	0.958	21.192	0.915	0.0004	0.913	2.719	0.272	Fickian Diffusion		

<sup>\*</sup>Kinetic constant (k), correlation coefficient (R<sup>2</sup>), diffusional exponent (n). Shaded and bold font areas: optimum values of correlation coefficient. Bold underlined areas: second best fit values of correlation coefficient.

Table 4:The release mechanism of atenolol from prepared beads by ACPD method using different drug: polymer ratios in phosphate buffer (pH 6.8)\*.

Formula	Zero	Order	First	Order	Hig	uchi		ker- sdale	Hopfe	enberg		Korsme	yer and Peppas	
Code	R <sup>2</sup>	K <sub>0</sub>	R <sup>2</sup>	Kı	R <sup>2</sup>	K <sub>H</sub>	R <sup>2</sup>	K <sub>BL</sub>	R <sup>2</sup>	K <sub>HB</sub>	R <sup>2</sup>	K <sub>KP</sub>	n	Interpretation
1	0.840	1.246	0.710	0.019	0.923	13.192	0.921	0.005	0.982	4.489	0.994	1.085	1.054	Super Case- II transport
2	0.892	1.404	0.777	0.030	0.955	14.678	0.980	0.006	<u>0.991</u>	4.099	0.994	0.918	1.068	Super Case- II transport
3	0.860	1.361	0.771	0.026	0.934	14.327	0.966	0.006	0.972	4.133	0.987	1.442	0.921	Super Case- II transport
4	0.704	0.838	0.632	0.012	0.758	7.123	0.920	0.008	0.929	5.938	0.966	2.979	0.525	Anomalous transport

<sup>\*</sup>Kinetic constant (k), correlation coefficient (R<sup>2</sup>), diffusional exponent (n). Shaded and bold font areas: optimum values of correlation coefficient. Bold underlined areas: second best fit values of correlation coefficient.

### Conclusions

Atenolol was successfully formulated as floating alginate-EC beads by ACPD method. The drug: polymer mixture ratio, sodium alginate: ethylcellulose polymers ratio and CaCl<sub>2</sub> concentration are significant formulation factors which affected drug encapsulation efficiency. The release profile of atenolol from the alginate-EC beads increased as a function of drug: polymer mixture ratio. It is possible to achieve slow atenolol release rates from the alginate-EC beads by reducing drug: polymer mixture ratio or by increasing the amount of ethylcellulose used in the polymeric mixture. On the other hand, atenolol release from the prepared beads was found to be pH-dependant. It was slowe in acidic media. In view of the prolonged buoyancy of beads in the acidic environment, accompanied by slow drug release, entrapment of atenolol in these beads may provide a satisfactory oral controlled release drug delivery system. Having a prolonged release behavior and maximum percentage encapsulation efficiency, formula 9 was selected as optimized formulation, keeping in view the fact that the higher the encapsulation efficiency, the lower will be the dose size.

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