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THE EFFECTS OF POLYMER TYPE AND RATIO ON THE EXTENDED RELEASE OF ATENOLOL FROM HYDROPHILIC MATRICES

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Abstract

In this study, the effects of type and ratio of the polymers [hydroxypropylmethylcellulose (Methocel® K100LV and K15M), methacrylic acid copolymer (Eudragit® L100)] and direct compression agents (Pharmatose DCL11®, Cellactose® 80, Microcel® PH101) on the extended release of atenolol from hydrophilic matrix tablets prepared by direct compression method were investigated. Spectrophotometric method used for the determination of atenolol in dissolution media was validated by calculating linearity and range, precision, accuracy and specificity values. The dissolution profiles showed that hydroxypropylmethylcellulose ratio and type play a significant role in drug release and direct compression agents (lactose or cellulose based) can be effective on drug release at the presence of low amounts of hydroxypropylmethylcellulose in the formulations. It is also observed that methacrylic acid copolymer could not effectively hinder the drug release in acidic medium and binary mixtures of polymers could lead to discontinuous drug release profiles. Results indicated that low viscosity grade hydroxypropylmethylcellulose can be preferred to obtain linear drug release profiles for a duration of eight hours with a lactose-based direct compression agent. Results of kinetic data indicated that atenolol release from the formulations generally fits best to the Korsmeyer-Peppas kinetic model and drug release mechanism shows non-Fickian transport mechanism according to the values of diffusion exponent.

Key Words: *Atenolol, HPMC, methacrylates, matrix tablet, direct compression, release kinetics*

Atenolol`ün Hidrofilik Matrislerden Uzatılmış Salımı Üzerine Polimer Tipi ve Oranının Etkileri

Bu çalışmada polimerler [hidroksipropilmetilselüloz (Methocel® K100LV ve K15M), metakrilik asit kopolimeri (Eudragit® L100)] ve doğrudan tabletleme ajanlarının (Pharmatose DCL11®, Cellactose® 80, Microcel® PH101) tip ve oranlarının atenolol'ün doğrudan basım yöntemi ile hazırlanan hidrofilik matris tabletlerinden uzatılmış salımı üzerindeki etkileri incelenmiştir. Atenolol'ün çözünme ortamlarındaki tayininde kullanılan spektrofotometrik analiz yöntemin validasyonu için, doğrusallık ve aralığı, kesinlik, doğruluk ve seçicilik değerleri hesaplanmıştır. Çözünme hızı profilleri, etkin madde salımı üzerinde hidroksipropilmetilselüloz oranı ve tipinin önemli rol oynadığını ve doğrudan tabletleme ajanlarının (laktoz veya selüloz kökenli) formülasyonlarda hidroksipropilmetilselüloz oranının düşük olması durumunda etkili olabileceğini göstermektedir. Metakrilik asit kopolimerinin asit ortamda etkin madde salımını etkili bir biçimde baskılayamadığı ve ikili polimer karışımlarının düzensiz etkin madde salım profillerine neden olabileceği de görülmektedir. Sonuçlar, düşük viskoziteli hidroksipropilmetilselülozun laktoz kökenli bir doğrudan tabletleme ajanı ile beraber, sekiz saatlik sürede doğrusal etkin madde salım profili elde etmek amacıyla tercih edilebileceğini göstermektedir. Kinetik veriler, formülasyonlardan atenolol salımının genellikle en iyi Korsmeyer-Peppas kinetik modeline uyduğunu ve difüzyon katsayısı değerlerine göre etkin madde salım mekanizmasının Fick'e uymayan taşınma durumuna uyduğunu belirtmektedir.

Anahtar Kelimeler: *Atenolol, HPMC, metakrilatlar, matris tablet, doğrudan basım, salım kinetikleri*

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INTRODUCTION

Atenolol, a β-blocker drug, is prescribed widely in diverse cardiovascular diseases, *eg*, hypertension, angina pectoris, arrhythmias, and myocardial infarction (1). The drug is also frequently indicated in the prophylactic treatment of migraine. There are only conventional tablets of atenolol in the market and administration of these tablets has been reported to exhibit fluctuations in the plasma drug levels, resulting either in manifestation of side effects or reduction in drug concentration at the receptor site (2-4). Accordingly, studies have been reported on regulation of drug release by formulating its diverse extended-release (ER) dosage forms such as coated beads, osmotic pumps and matrix tablets (3-5). Among these classes, matrix tablets composed of drug and the release retarding material (polymer) offers the simplest approach to design an ER system. Hydrophilic polymers like hydroxypropylmethylcelluloses (HPMCs) are commonly used in these systems as release retarding materials. Drug release from the HPMC-based matrix tablets can be modulated by several formulation variables such as HPMC concentration and viscosity grade, dosage size, excipient type and ratio (6,7). In these systems drug release profiles are strongly influenced by the viscosity of the gel layer which forms on the tablet surface as a result of hydration of the constituent polymer and the solubility of the excipient which is effective on the formation of the gel layer and the hydrosolubility of drug as well (8,9). Another release retarding material is the group of polymethacrylates which are generally used as film coating materials in ER dosage forms and also used in tablet formulations at 10-50 % ratios as they have good compactability properties. The solubility properties of methacrylic acid copolymers (MAC) are high in neutral and weak basic pH and they have no solubility in acidic pH which can hinder the release of drug in acidic medium (10, 11).

The objective of the present work was to prepare atenolol ER tablets by altering the type and the ratio of polymer and direct compression agent (DC-agent) in combination with different amounts of the drug.

EXPERIMENTAL

Materials

Atenolol (Abdi İbrahim, İstanbul, Turkey), hydroxypropylmethylcellulose (Methocel® K100LV and K15M with nominal viscosities of 98 mPa.s and 7382 mPa.s, respectively, Dow Chemical Co., Stade, Germany), α-lactose monohydrate-amorphous lactose mixture (Pharmatose® DCL11, DMV International, Veghel, The Netherlands), α-lactose monohydrate (25% mixture with cellulose powder: Cellactose® 80, Meggle GmbH, Wasserburg, Germany), microcrystalline cellulose (MCC) (Microcel® PH101, Blanver Farmaquimica Ltd, Sao Paulo, Brasil) and methacrylic acid copolymer-type A (Eudragit® L100, Röhm Pharma, Darmstadt, Germany) were used. All other chemicals used were of analytical grade.

Preparation of Tablets

Tablets were prepared, one by one, using direct compression method. Each of the tablet component (drug, polymer and DC-agent) were weighed separately and then blended on a glass plate by using a spatula to obtain a homogenous mixture (the composition of each formulation is presented in Table 1). The mixture with a total mass of 260 mg including 50 mg or 100 mg atenolol was manually fed into the die of a hydraulic press (Ayaşlı Üçler, Ankara, Turkey) equipped with flat-faced punches of 8 mm in diameter to produce tablets. The compression force was kept constant at 200 MPa for 10 seconds.

Table 1. Composition of the investigated matrix tablets (all quantities are given in mg).

Code	Atenolol	Methocel® K 100LV	Methocel® K 15M	Eudragit® L 100	Pharmatose® DCL11	Cellactose® 80	Microcel® PH100
F1	50	90	-	-	120	-	-
F2	50	90	-	-	-	120	-
F3	50	90	-	-	-	-	120
F4	50	-	-	90	120	-	-
F5	50	45	-	45	120	-	-
F6	50	45	45	-	120	-	-
F7	100	60	-	-	100	-	-
F8	100	60	-	-	-	100	-
F9	100	60	-	-	-	-	100
F10	100	30	-	30	100	-	-
F11	100	-	30	30	100	-	-
F12	100	30	30	-	100	-	-
F13	100	-	60	-	100	-	-
F14	100	80	-	-	80	-	-
F15	100	100	-	-	60	-	-
F16	100	120	-	-	40	-	-

Analytical Validation of the Quantification Method

Analytical validation of spectrophotometric method used for the quantification of atenolol in dissolution studies was done by investigating the linearity and range, accuracy and precision values in terms of repeatibility and intermediate precision according to ICH Guidelines Q2(R1) (12). Linearity and range was studied at six points in a concentration range of 0.005-0.2 mg/mL. Accuracy was tested by repeating six experiments for the same concentration point in the same day. Precision was tested as repeatibility and intermediate precision. Repeatibility was done on three different concentrations from the calibration curve performing three measurements for each concentration and intermediate precision was done by measuring the same samples on two consecutive days. Paired-Student's *t* test was used to compare the data for the intermediate precision with a confidence interval of 95%. Results were expressed as mean values ± SE (Standard Error) or RSD % (Relative Standard Deviation).

In Vitro Drug Release Studies

Drug release studies were carried out according to the method given for Delayed Release Articles in USP XXVII by using the USP paddle (Apparatus II) method with a dissolution tester (Aymes D96D, İstanbul, Turkey) at 50 rpm rate. pH 1.2 (0.1 N HCl) medium was used for first two hours and pH 6.8 phosphate buffer was used for the following six hours as the dissolution medium. The amount of atenolol was determined spectrophotometrically (UV-1601 Shimadzu

Spectrophotometer, Tokyo, Japan) at 274 nm. All the experiments were performed in triplicate. Drug release data of all the formulations were evaluated by mathematical models (Zero Order, First Order, Higuchi, Hixson-Crowell and Korsmeyer-Peppas) using SPSS 9.0 for Windows.

RESULTS AND DISCUSSION

Analytical validation of the spectrophotometric method used for the quantification of atenolol was investigated according to ICH guidelines. The low values of SE of slope (0.0129 for pH 1.2 and 0.0208 for pH 6.8) and good correlation coefficient values (1.000 for pH 1.2 and 0.999 for pH 6.8) establish the linearity of the method in 0.005-0.2 mg/mL concentration range. Accuracy and precision of the determination method was assessed by performing replicate analysis in the *in vitro* dissolution media. Accuracy results were 103.70 ± 1.63 RSD % and 102.87 ± 1.69 RSD % for pH 1.2 and pH 6.8, respectively. Significant difference was not found between the data for the intermediate precision study ($P>0.05$). These results indicate that precision and accuracy results are acceptable for the spectrophotometric method used in *in vitro* dissolution studies.

Rapidly hydrating Methocel® K series were used in this study, to prevent the probable dose dumping of highly soluble atenolol from hydrophilic matrix tablets. Drug release profiles from matrix tablets containing 50 mg or 100 mg atenolol are presented in Figure 1, Figure 2 and Figure 3, Figure 4 and Figure 5, respectively. Standard error bars were not shown on drug release profiles as they have very small values.

In Figure 1, effects of DC-agents with low viscosity grade HPMC on the release of atenolol (50 mg) from matrix tablets are presented. Although it was expected to obtain high drug release with soluble lactose rather than insoluble MCC (has also tablet binding property) (8,13), formulations gave almost the same release profiles of drug with three types of DC-agents containing different ratios of lactose and MCC (14). This can be attributed to the high amount of HPMC and low amount of atenolol in the formulations limiting the DC-agents to modulate the release of drug. However, drug release profile of F1 containing Pharmatose® DCL11 (100% lactose) was found to be more linear than the others among this group of formulations. According to the results obtained in this study and our previous studies (13,15), Pharmatose® DCL11 was decided to be used in consequent formulations.

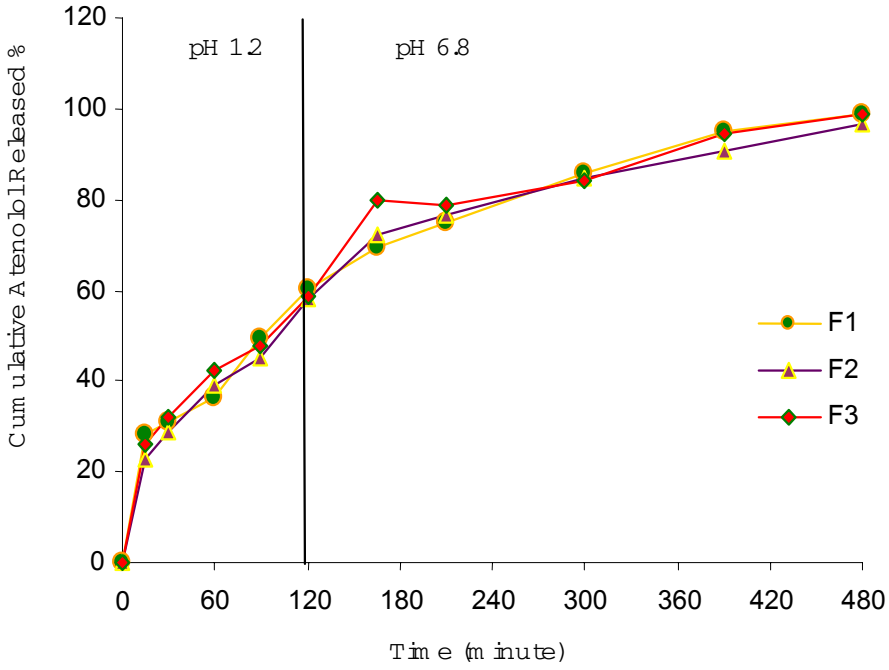

Figure 1. Dissolution profiles of atenolol from F1, F2 and F3 formulations.

Figure 2 shows the effects of different types of polymer with the lactose based DC-agent on the release of atenolol (50 mg) from the matrices. Eudragit® L100 which is a kind of MAC has no solubility in acidic medium and has high solubility in neutral and weak basic media. Therefore it was expected that the high drug release in acidic medium could be slowed down to obtain a more linear release profiles from the formulations containing Eudragit® L100. Comparing F4 and F5 containing MAC with F1, drug release was found to be faster from F4 and F5 formulations containing MAC compared to F1 formulation containing HPMC in acidic medium. However, F5 containing the mixture of MAC and low viscosity grade HPMC (1:1) gave a discontinuous drug release profile and, neither F4 nor F5 could extend the release of drug for the planned eight hours. F6 containing the mixture of low and high viscosity grade HPMCs (1:1) gave the lowest release of drug among this group of formulations.

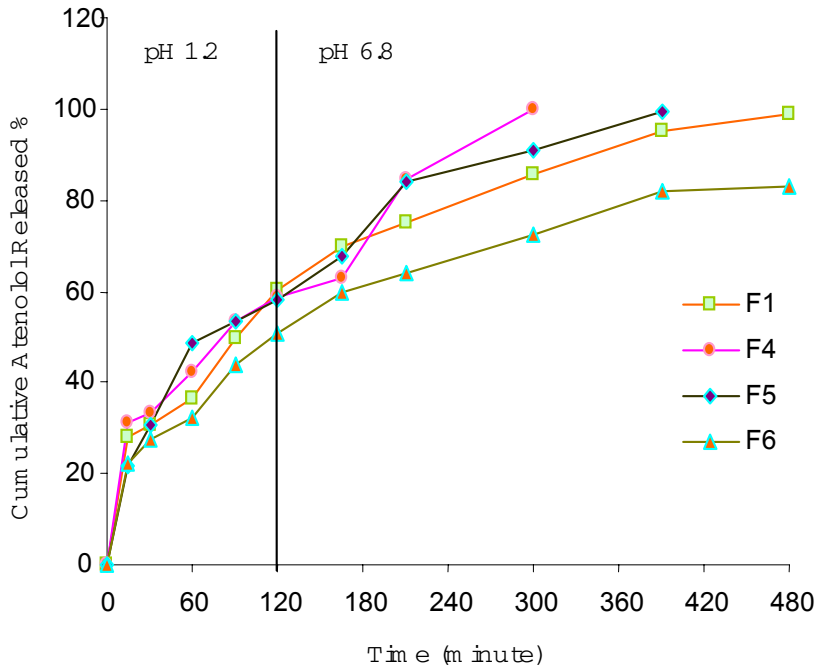

Figure 2. Dissolution profiles of atenolol from F1, F4, F5 and F6 formulations.

Release profiles of atenolol (100 mg) from the matrix tablets containing different DC-agents with low viscosity grade HPMC are presented in Figure 3. In this group of formulations, type of DC-agents was found to be effective on drug release profiles by increasing the amount of drug and decreasing the concentration of HPMC. As seen in Figure 3, increase in lactose content of formulations resulted in an increase in drug release from F7 and F8, respectively and, F9 containing only insoluble MCC showed the lowest release of drug (7,8,13). Among this group of formulations, the release profiles of F8 and F9 were non-linear while the profile of F7 was more linear. However, extension in the release of atenolol was not adequate from F7 in the test period of eight hours. Therefore, F7 formulation was decided to be modified by two alternative formulation parameters. In the first group, combination of MAC with low or high viscosity grade HPMC (F10 and F11, respectively), combination of low and high viscosity grade HPMC (F12) and high viscosity grade HPMC alone (F13) were used as the polymer material in the formulations. In the second group, the amount of Methocel® K100LV was increased while the amount of DC-agent was decreased to prepare this group of formulations (F14, F15 and F16) (Table 1).

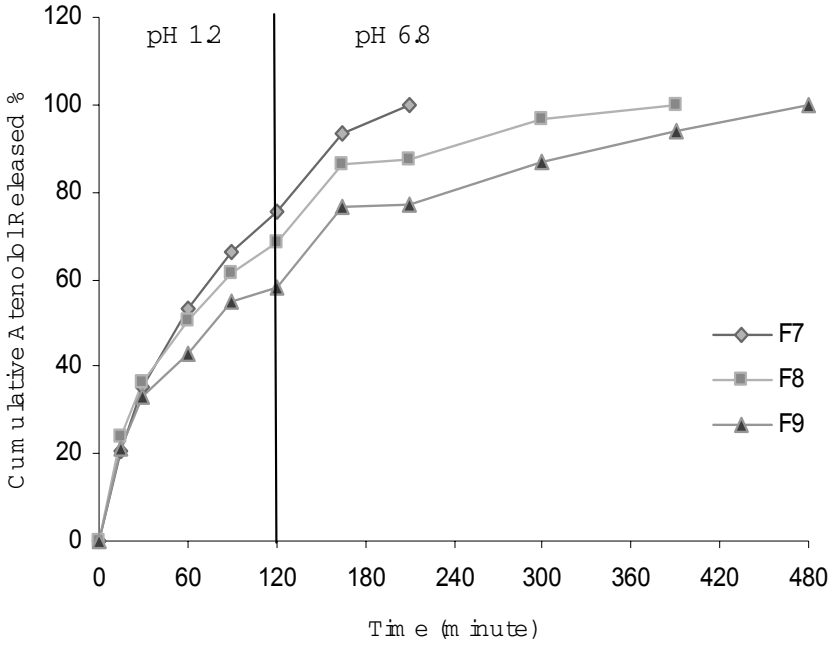

Figure 3. Dissolution profiles of atenolol from F7, F8 and F9 formulations.

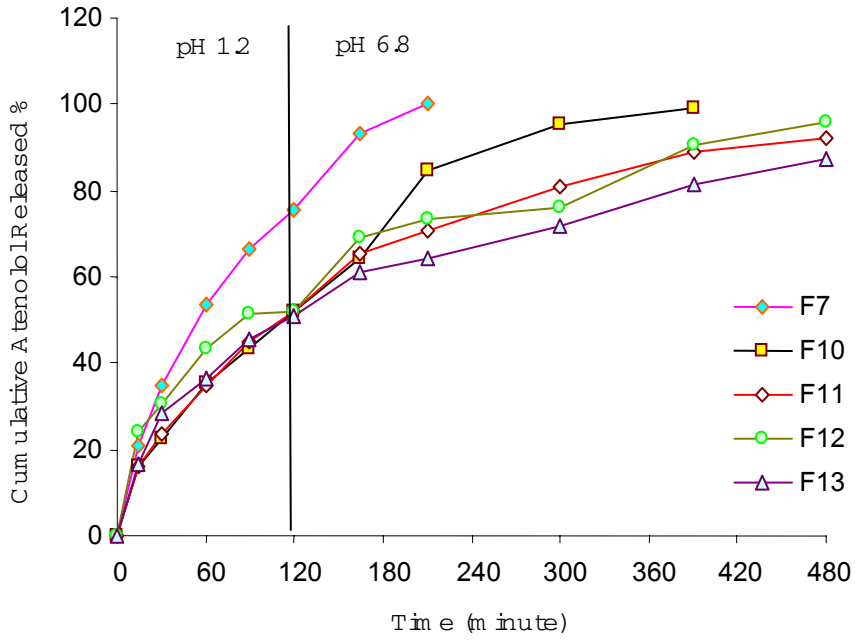

Figure 4. Dissolution profiles of atenolol from F7, F10, F11, F12 and F13 formulations.

Figure 4 shows the release profiles of atenolol (100 mg) from F10, F11, F12 and F13 compared to F7. Replacing half amount of low viscosity grade HPMC with MAC caused a significant decrease in the release of drug while replacing the low viscosity grade HPMC with the high viscosity (F11) also resulted in a decrease in the release of drug. Combination of low and high viscosity grade HPMC (F12) showed low and discontinuous drug release from the formulation. The lowest release of drug was obtained from F13 formulation where only high viscosity grade HPMC was used (7). In this group, the release from F7 and F10 was not low enough, while it was not high enough from F11, F12 and F13 to accomplish the release of drug along the eight hour period (8,13,15).

The release profiles of F14, F15 and F16 in comparison to F7 are presented in Figure 5. The second group modification resulted in a decrease in the release of drug for F14 and F15, as expected (7,8,13). In contrast, the modification resulted in a very high release of drug from the F14 formulation which gives different data from a similar study (7). An unexpected increase in the release of drug was obtained from F16 formulation when it was compared with F15.

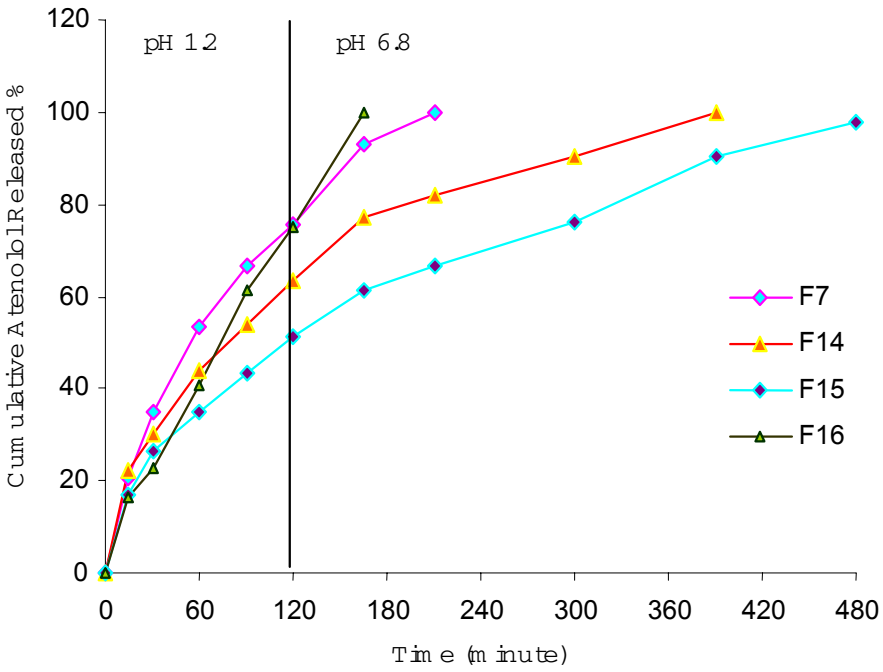

Figure 5. Dissolution profiles of atenolol from F7, F14, F15 and F16 formulations.

Among the formulations investigated, F1 containing 50 mg atenolol and F15 containing 100 mg atenolol prepared with low viscosity grade HPMC and lactose based DC-agent can be accepted as successful formulations depending on their drug release profiles (7,15).

As a general trend, the release profiles of atenolol showed that the release in pH 1.2 acidic medium was higher than that in pH 6.8 basic medium which can be attributed to an increase in the viscosity of gel layer at pH 6.8 (16,17). This indicates that, it is difficult to obtain Zero Order drug release kinetics with HPMC matrix tablets (7,13,15). Additionally, formulations

including methacrylic acid copolymer showed more linear drug release profiles compared to HPMC polymers.

Drug release data of all formulations were evaluated by various mathematical models (Zero Order, First Order, Higuchi, Hixson-Crowell and Korsmeyer-Peppas). The parameters of kinetic modelling are summarized in Table 2. According to the highest determination coefficient (r^2) and the lowest residual mean square values, atenolol release from the formulations generally fits best to the Korsmeyer-Peppas and First Order kinetic models. The results of diffusion exponent (n) indicated that the release of atenolol was generally controlled by non-Fickian transport mechanism which involves both diffusion and erosion mechanisms. However, formulations containing 50 mg atenolol (F1-F6) and binary mixtures of HPMCs (F6, F12) showed low values of n, while the formulations containing binary mixtures of HPMCs and Eudragit® L100 (F5, F10, F11) showed higher values of n. Among the formulations accepted as successful formulations, F1 containing 50 mg atenolol fits best to the First Order kinetic model and therefore showed a diffusion controlled drug release mechanism according to the value of n=0.359. F15 containing 100 mg atenolol fits best to the Korsmeyer-Peppas kinetic model and showed non-Fickian transport mechanism of drug according to the value of n=0.518. The results obtained are in accordance with some previous studies (7, 13,18,19).

CONCLUSION

In conclusion, the results of the present study indicate that the release of a hydrophilic drug from a matrix tablet formulation is primerly affected by the ratio and the type of the polymer and secondarily by the direct compression agent. However, high amount of hydroxypropylmethylcellulose polymer in the formulation can limit the effects of direct compression agents on the release of drug. Methacrylic acid copolymers can not effectively hinder the release of drug in acidic medium and the use of binary mixtures of polymers can result in discontinuous drug release profiles. It is inferred that the mechanism of drug release from hydrophilic matrix formulations is mainly diffusion controlled due to the low values of diffusion exponent obtained. It can be concluded that an extended release tablet formulation of a hydrophilic drug can be prepared by using a low viscosity grade hydroxypropylmethylcellulose and a lactose-based direct compression agent by direct compression method.

Table 2. Kinetic modelling data of formulations.

Kinetic Model		F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15	F16
Zero Order	**r^2**	0.8595	0.8574	0.8162	0.9229	0.8745	0.8467	0.9240	0.7914	0.8213	0.9156	0.8640	0.8399	0.8526	0.8518	0.9073	0.9948
	RMS	153.9	164.6	204.1	82.142	152.01	119.61	106.0	258.8	202.2	117.08	143.01	153.8	122.2	173.5	96.587	7.959
	k	0.1818	0.1863	0.1783	0.2939	0.2375	0.1523	0.4450	0.2305	0.1806	0.2601	0.1786	0.1682	0.1575	0.2305	0.1821	0.5924
	SE	0.0245	0.0253	0.0282	0.0321	0.0318	0.0216	0.0520	0.0415	0.0281	0.0279	0.02361	0.0245	0.0218	0.0339	0.0194	0.0192
First Order	**r^2**	0.9779	0.9874	0.9590	0.9000	0.9713	0.9702	0.9478	0.9699	0.9861	0.9123	0.9961	0.9640	0.9839	0.9932	0.9219	0.9796
	RMS	0.0205	0.0087	0.0748	0.04365	0.0252	0.0115	0.0517	0.0479	0.0119	0.1412	0.0030	0.0367	0.0072	0.0046	0.1127	0.0070
	k	0.0069	0.0060	0.0078	0.0078	0.0087	0.0036	0.0148	0.0117	0.0067	0.0114	0.0052	0.0059	0.0039	0.0076	0.0069	0.0112
	SE	0.0004	0.0002	0.0005	0.0011	0.0006	0.0000	0.0016	0.0008	0.0003	0.0013	0.0001	0.0004	0.0002	0.0002	0.0007	0.0008
Higuchi	**r^2**	0.9867	0.9674	0.9531	0.9232	0.9820	0.9811	0.9965	0.9775	0.9663	0.9771	0.9790	0.9780	0.9842	0.9802	0.9968	0.9683
	RMS	10.87	29.25	36.58	80.284	16.589	10.372	3.401	21.33	26.96	27.07	17.139	14.58	9.4490	16.56	2.571	44.47
	k	4.453	4.6210	4.2800	6.3190	5.3130	3.6420	7.3800	5.3780	4.3650	6.0080	4.4370	3.9940	3.8090	5.0550	4.457	9.788
	SE	0.183	0.3001	0.3356	0.7438	0.2721	0.1787	0.1958	0.3085	0.2881	0.3476	0.2297	0.2119	0.1706	0.2718	0.0890	0.8850
Hixson Crowell	**r^2**	0.9536	0.9249	0.9717	0.8768	0.9584	0.9647	0.9291	0.9887	0.9205	0.9797	0.9795	0.9775	0.9781	0.9392	0.9815	0.8426
	RMS	0.0885	0.1419	0.0336	0.2730	0.0884	0.0151	0.1846	0.0244	0.1441	0.0519	0.0160	0.0182	0.0107	0.1226	0.0197	0.5275
	k	0.0080	0.0079	0.0064	0.0133	0.0105	0.0038	0.0199	0.0108	0.0077	0.0117	0.0052	0.0053	0.0041	0.0101	0.0061	0.0265
	SE	0.0006	0.0061	0.0004	0.0020	0.0008	0.0003	0.0025	0.0004	0.0008	0.0007	0.0003	0.0003	0.0004	0.0010	0.0003	0.0057
Korsmeyer Peppas	**r2**	0.8909	0.8887	0.9886	0.9584	0.9768	0.9768	0.9983	0.9943	0.9860	0.9965	0.9991	0.9821	0.9850	0.9976	0.9949	0.9731
	RMS	0.0028	0.0039	0.0003	0.0010	0.0012	0.0009	0.0001	0.0002	0.0006	0.0002	0.0001	0.0005	0.0008	0.0001	0.0003	0.0028
	n	0.3586	0.4184	0.3887	0.3516	0.5219	0.4200	0.5615	0.4405	0.4861	0.6055	0.5824	0.4026	0.5177	0.5071	0.5182	0.7632
	SE	0.0725	0.0855	0.0241	0.0366	0.0465	0.0289	0.0166	0.0236	0.0335	0.0179	0.0090	0.0314	0.0320	0.0144	0.0186	0.0898

r^2 : Determination coefficient
RMS : Residual mean square
k : Dissolution rate constant
n : Diffusion exponent
SE : Standard error of k or n for model parameter

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