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The Impact of the Polymer Content on the Kinetics of Propranolol HCl from Buccal Adhesive Tablets

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Abstract

The relation between Higuchi rate constant (k) and amount of polymer (mg) in hydrophilic matrix tablets of propranolol HCl was evaluated. Each tablet composed of 80 mg propranolol, 80 mg Hydroxypropyl methyl cellulose (HPMC) K4M, Polycarbophil AA1, Carbopol 934P, and Lactose or Dicalcium phosphate with different ratios. After preparing several formulations the release profiles were evaluated. The dissolution data were fitted to Higuchi model. A new relationship between k and polymer content was found in hydrophilic matrices. The results showed the relationship between HPMC K4M (mg) and k in the presence of constant amount of polycarbophyl, this relationship showed no differences in reciprocal, logarithmic and content of polymer ($P > 0.05$). This relationship was observed between polycarbophyl content and k in the presence of constant amount of HPMC K4M ($P < 0.001$). In formulations with constant amount of lactose, these results showed that there is relation between logarithm of polycarbophyl amount in formulations and log k ($P < 0.05$), and this relationship was also obtained for HPMC K4M containing formulations in the presence of dicalcium phosphate ($P < 0.05$). In formulations which containing constant amount of Carbopol 934P, HPMC K4M content (mg) showed relationship with k ($P < 0.01$). In the presence of constant amounts of lactose, the logarithmic relationship was obtained with Carbopol 934P content ($P < 0.05$). In this study, the direct relationship between k and polymer content in some hydrophilic matrices was obtained.

Keywords: *Kinetic; Higuchi; HPMC K4M; Carbopol; Polycarbophyl*

Introduction

The hydrophilic matrices are one of the most used controlled delivery systems in the world, due to the simple technology and low cost. Its study is a difficult task due to its complex and disordered structure. These hydrophilic matrices are widely accepted because of their biopharmaceutical and pharmacokinetics advantages over conventional dosage forms [1]. A number of publications have reported studies about the mechanisms of drug release from hydrophilic matrices. Nevertheless, nowadays, the mechanisms of drug release from these systems continue to be a matter of debate [2]. Significant experimental and theoretical work has been performed to accurately model drug transport and reveal the mechanisms of drug release from these systems. Despite the complexity of the phenomena involved, two well known approaches are used extensively and successfully for the analysis of drug release data in these systems. The first approach relies on the famous Higuchi equation, which the fraction of drug released is proportional to the square root of time. The second approach relies on the semi-empirical, used extensively and successfully for the analysis of the first 60% of the release curves as Korsmeyer-peppas model [3,4].

Various attempts have been made to achieve the prolonged release of active agents; prominent amongst these is the enhanced retention of formulations at their intended site of action by means of bioadhesive formulations [5]. Recent years have seen an increasing interest in the development of novel mucoadhesive buccal dosage forms [6,7]. The buccal mucosa has been investigated for local and systemic delivery of therapeutic peptides and other drugs that are subjected to first pass metabolism or are unstable within the rest of the gastrointestinal tract [8-10]. Bioadhesive formulations use polymers as the adhesive component.

These formulations are often water soluble and when in a dry form attract water from the biological surface and this water transfer leads to a strong interaction. These polymers also form viscous liquids when hydrated with water that increases their retention time over mucosal surfaces and may lead to adhesive interactions. Bioadhesive polymers should possess certain physicochemical features including hydrophilicity, numerous hydrogen bond-forming groups, flexibility for interpenetration with mucus and epithelial tissue, and viscoelastic properties [11]. Mucoadhesive materials are hydrophilic macromolecules containing numerous hydrogen bond-forming groups [12]. Bioadhesive polymers such as sodium carboxymethyl cellulose, carbopol 934, polycarbophil (PAA), hydroxypropyl cellulose, hydroxypropyl methylcellulose (HPMC), carrageenan and poloxamer are suitable for use in buccal adhesive preparations. These polymers when hydrated with water can adhere to the oral mucosa and withstand salivation, tongue movements and swallowing for a significant period of time [13]. These polymers not only cause the adhesion effects, but also control the release rate of drug [14]. Polycarbophil and HPMC are suitable polymers for formulation the bioadhesive tablets. These polymers in addition of bioadhesion effects, decrease release rate and change kinetic of drug release from mucoadhesive tablets [15-17]. Propranolol is subjected to first pass effect; therefore, formulation of buccal-adhesive dosage form can circumvent this effect [6].

The kinetics of drug release from matrices were examined for both freely soluble and poorly water soluble drugs, and mathematical models have been developed for expression the mechanism of drug release. One of these models is Higuchi square root of time model [18]. Previous studies showed relationship between dissolution rate constant in Higuchi model (k) and polymer content. These studies showed a logarithmic relationship between k and polymer content or reciprocal relation between k and amount of polymer (mg) [19]. The objectives of this study were to examine the *in vitro* release characteristics of propranolol hydrochloride from different buccal adhesive tablets and evaluation the relationship between Higuchian release rate and polymer quantity in the presence of lactose and dicalcium phosphate as water soluble and insoluble fillers. In this research, a new relation between k and amount of polymer was evaluated for the first time.

Materials and Methods

Materials

Propranolol HCl was USP grade (Rouz Daru Co., Iran). Hydroxy propyl methyl cellulose K4M viscosity grade (Colorcon Co., UK), polycarbophil (Noveon AA1), and carbopol 934P (B.F. Goodrich, USA) were used as mucoadhesive polymers. Dicalcium phosphate and lactose (Merck, Germany) were used as required as fillers. Magnesium stearate (Merck, Germany) was used as lubricant.

Tableting

Formulation composition of different buccal adhesive tablets of propranolol hydrochloride has been shown in Table 1. Compaction was accomplished using direct compression (Korch single punch model 9219-77, Germany) of the blends that has been thoroughly mixed for 15 min using a cubic mixer (Erweka, Germany). The punch No.9 in diameter was used for Tableting. Formulations 1-11 composed of 80 mg of different ratios of HPMC K4M, Polycarbophyl (PAA1) and lactose and in formulations 12-16, Dicalcium phosphate (DCP) was used as filler. This composition in formulations 17-23 was 80 mg of drug and 80mg of different ratios of HPMC K4M, Carbopol 934P (Car. 934P) and lactose. All of formulations had magnesium stearate (1%) as lubricant.

Formulation Code	Formulation Composition (mg)						
	Drug	HPMC K4M	PAA1	Car. 934P	Lactose	DCP	Mg Stearate
F1	80	72	4	-	4	-	1.6
F2	80	68	4	-	8	-	1.6
F3	80	64	4	-	12	-	1.6
F4	80	56	4	-	20	-	1.6
F5	80	60	16	-	4	-	1.6
F6	80	60	12	-	8	-	1.6
F7	80	60	8	-	12	-	1.6
F8	80	60	4	-	16	-	1.6
F9	80	68	8	-	4	-	1.6
F10	80	64	12	-	4	-	1.6
F11	80	56	20	-	4	-	1.6
F12	80	72	4	-	-	4	1.6
F13	80	68	4	-	-	8	1.6
F14	80	64	4	-	-	12	1.6
F15	80	60	4	-	-	16	1.6
F16	80	56	4	-	-	20	1.6
F17	80	72	-	4	4	-	1.6
F18	80	68	-	4	8	-	1.6
F19	80	64	-	8	8	-	1.6
F20	80	56	-	8	16	-	1.6
F21	80	56	-	20	4	-	1.6
F22	80	56	-	16	8	-	1.6
F23	80	56	-	12	12	-	1.6

Table 1: *Formulation composition of different buccal adhesive tablets of propranolol HCl. HPMC K4M = Hydroxy Propyl Methyl Cellulose K4M, PAA1 = Polycarbophil, Noveon AA1, Car. 934P = Carbopol 934P, DCP = Dicalcium Phosphate.*

Evaluation of tablets

Tablet properties (crushing strength, mass variation, and friability) were determined by standard procedure [20]. The tensile strength (T) of tablet which is a measure of the stress necessary to cause diametric fracture of the compact was determined from the mean data obtained from the hardness test carried out on the tablets (n = 10) using the Erweka hardness tester (TBH 30 MD, Germany). The T values were computed from equation below [21]:

$$T = \frac{2P}{\pi Dt}$$

Where, P is the load applied on the tablet that causes diametric fracture of the tablet of diameter, D, and t is the tablet thickness (m).

Dissolution rate study

The dissolution rates were evaluated by apparatus type II of USP dissolution tester (Caleva 8ST, Germany). For study of drug release from only one side of tablets, the glass dies were used.

For this purpose every die filled with melted wax, and before solidification, the tablets put in semisolid wax, as only one side of them were in contact with dissolution medium. In this evaluation six tablets of each formulation which were placed in the die, and were at the bottom of the vessel with 900 ml of phosphate buffer with pH 6.8 evaluated at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7 and 8h after the beginning of dissolution test. Sample (10 ml) was taken and immediately replaced with an equivalent volume of dissolution medium. Samples were filtered and assayed at 288.8 nm by using UV spectrophotometer (Shimadzo 60A, Japan).

***In vitro* release data analysis**

The most widely model to describe drug release from matrices, derived from Higuchi for a planar matrix; however it is applicable for systems of different shapes also:

$$\frac{M_t}{M_\infty} = kt^{\frac{1}{2}}$$

Where $\frac{M_t}{M_\infty}$ is the fractional release of the drug, t is the release time, and k is a constant incorporating structural and geometric characteristic of the controlled release device [22,23].

Previous studies showed relationship between release rate and polymer quantity. Examination of some drugs showed that when the polymer fraction increases, the dissolution of the drug decreases. The generalized relationship for each of these lines can be expressed by the following relationship [24]:

$$k = M(\frac{1}{W}) + c \quad (2)$$

Where k is Higuchian release rate ($min^{-1/2}$), M is slope of the derived line, W is weight of HPMC (mg), and c is constant.

Other studies on different drugs showed a linear relationship existed between the logarithm of the tablet polymer content and the logarithm of the release rate in Higuchi model [25]:

$$\log k = M' \log W + c' \quad (3)$$

Where k and W is like equation 2, M' is the slope of line and c' is constant [19].

In this study a new equation was presented for relation between k and polymer content.

$$k = M''W + c'' \quad (4)$$

Where k and W is like equations 1 and 2, M″ is the slope of line and c″ is a constant.

Statistical analysis

Statistical analysis was carried out by using analysis of variance (ANOVA) with computer software SPSS 10. Tukey-Kramer multiple-comparison tests were used to compare group's data. P values ≤ 0.05 were considered significant.

Results

Tablet characteristics

Table 2 shows the characteristics of investigated tablets. These results show that all of formulations have the suitable friability and hardness. The content uniformity was in the Pharmacopeial criteria.

Formulation Code	Characteristics of Evaluated Tablets			
	Hardness* ($kg.cm^{-2}$) (n=10)	Friability* (%w/w) (n=10)	Tensile Strength* ($MN.m^{-2}$) (n=10)	Assay* (%) (n=20)
F1	8.9 ± 1.2	0.51 ± 0.05	5.24 ± 0.70	98.62 ± 1.51
F2	9.8 ± 0.7	0.31 ± 0.04	5.92 ± 0.11	96.37 ± 3.00
F3	11.7 ± 0.8	0.15 ± 0.06	7.19 ± 0.55	97.62 ± 3.62
F4	9.7 ± 0.7	0.25 ± 0.04	6.13 ± 0.44	98.62 ± 3.62
F5	9.6 ± 1.1	0.35 ± 0.07	5.66 ± 0.65	98.00 ± 4.00
F6	10.1 ± 0.8	0.28 ± 0.05	6.05 ± 0.48	100. 15 ± 3.12
F7	6.4 ± 0.5	0.71 ± 0.06	3.90 ± 0.30	97.37 ± 2.87
F8	10.2 ± 0.9	0.18 ± 0.02	6.32 ± 1.79	99.75 ± 3.87
F9	11.3 ± 0.8	0.32 ± 0.03	6.72 ± 0.68	100.50 ± 3.87
F10	14.1 ± 0.7	0.17 ± 0.02	8.17 ± 0.41	97.62 ± 4.50
F11	6.4 ± 0.7	0.68 ± 0.07	3.65 ± 0.39	100.12 ± 4.73
F12	5.6 ± 0.3	0.81 ± 0.08	3.33 ± 0.17	99.50 ± 2.62
F13	6.7 ± 0.4	0.72 ± 0.06	3.98 ± 0.24	100.12 ± 3.87
F14	10.7 ± 0.7	0.27 ± 0.03	6.47 ± 0.42	99.25 ± 4.12
F15	10.9 ± 0.6	0.20 ± 0.02	6.70 ± 0.37	99.62 ± 4.15
F16	9.6 ± 0.4	0.25 ± 0.03	6.01 ± 0.25	100.75 ± 1.87
F17	9.1 ± 0.5	0.29 ± 0.03	5.59 ± 0.31	98.37 ± 2.37
F18	8.6 ± 0.7	0.75 ± 0.06	5.15 ± 0.42	99.50 ± 4.37
F19	8.6 ± 0.5	0.68 ± 0.07	5.11 ± 0.29	100.12 ± 3.37
F20	9.6 ± 0.4	0.48 ± 0.05	5.80 ± 0.24	99.25 ± 2.75
F21	6.7 ± 0.5	0.81 ± 0.07	4.16 ± 0.31	98.25 ± 2.12
F22	8.7 ± 0.4	0.47 ± 0.05	5.49 ± 0.25	100.25 ± 3.87
F23	9.0 ± 0.8	0.35 ± 0.03	5.63 ± 0.50	101.12 ± 2.25

**Data are shown as mean±SD*

Table 2: *Characteristics of propranolol HCl prepared tablets.*

Formulations with different amount of HPMC K4M and constant quantity of PAA1 in the presence of lactose

The results of kinetic evaluation of drug release from formulations F1 -F4 (Figure 1) in Higuchi model have been presented in Table 3. The results showed relationship between reciprocal amounts, logarithm of polymer, and content of HPMC K4M (mg) and Higuchian release rate. The statistical analysis showed no significant differences between these equations (P>0.05):

$$k = 58.636\left(\frac{1}{W}\right) + 0.865 \quad r^2 = 0.988 \quad (5)$$

$$\log k = -0.518 \log W + 1.186 \quad r^2 = 0.985 \quad (6)$$

$$k = -0.015W + 2.724 \quad r^2 = 0.983 \quad (7)$$

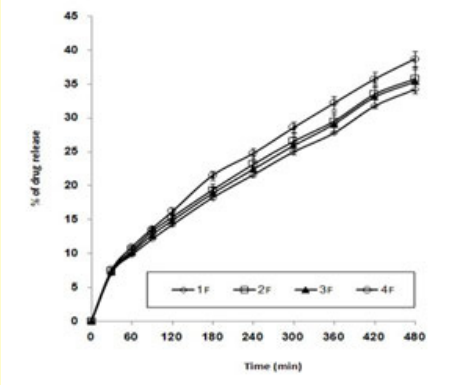

Figure 1: *Release profile of propranolol HCl from Formulations (F1-F4) with different amount of HPMC K4M and constant quantity of PAA1 in the presence of lactose (n = 4).*

Formulation with different amount of PAA1 and lactose in the presence of constant quantity of HPMC K4M

The results of kinetic evaluation of drug release from formulations F5-F8 (Figure 2) in Higuchi model have been presented in Table 3. The results showed a relation between Higuchi release rate and polycarbophil quantity in equation 10 ($P < 0.001$).

$$k = 3.916\left(\frac{1}{W}\right) + 0.952 \quad r^2 = 0.842 \quad (8)$$

$$\log k = -0.402 \log W + 0.535 \quad r^2 = 0.907 \quad (9)$$

$$k = -0.0692W + 2.155 \quad r^2 = 0.998 \quad (10)$$

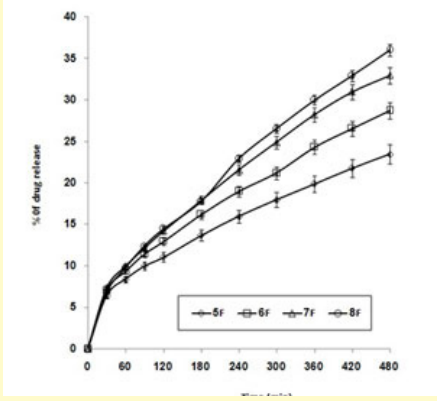

Figure 2: *Release profile of propranolol HCl from Formulations (F5-F8) with different amount of PAA1 and lactose in the presence of constant quantity of HPMC K4M (n = 4).*

Formulation with different amount of HPMC K4M and PAA1 in the presence of constant quantity of lactose

The results of kinetic evaluation of drug release from formulations F9, F10, F5, and F11 (Figure 3) in Higuchi model have been presented in Table 3. The results showed a relationship between logarithms of PAA1 with logarithm of Higuchian release rate in equation 13 ($P < 0.05$):

$$k = 7.18(\frac{1}{W}) + 0.634 \quad r^2 = 0.936 \quad (11)$$

$$\log k = -0.495 \log W + 0.632 \quad r^2 = 0.955 \quad (12)$$

$$k = -0.096W + 1.854 \quad r^2 = 0.949 \quad (13)$$

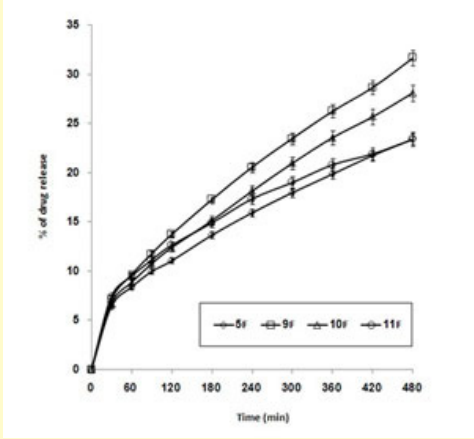

Figure 3: *Release profile of propranolol HCl from Formulations (F5, F9-F11) with different amount of HPMC K4M and PAA1 in the presence of constant quantity of lactose (n = 4).*

Formulation Code	Polymer Content (mg)			Kinetic Data in Higuchi Model		
	HPMC K4M	PAA1	Car. 934P	k ($min^{-1/2}$)	r^2	ss
F1	72	4	-	1.67	0.992	6.47
F2	68	4	-	1.74	0.995	4.54
F3	64	4	-	1.77	0.993	6.25
F4	56	4	-	1.91	0.996	4.10
F5	60	16	-	1.04	0.996	1.24
F6	60	12	-	1.33	0.994	2.88
F7	60	8	-	1.61	0.994	4.55
F8	60	4	-	1.87	0.994	5.20
F9	68	8	-	1.50	0.995	3.18
F10	64	12	-	1.32	0.993	3.56
F11	56	20	-	0.98	0.999	0.39

Formulation Code	Polymer Content (mg)			Kinetic Data in Higuchi Model		
	HPMC K4M	PAA1	Car. 934P	k ($min^{-1/2}$)	r^2	ss
F12	72	4	-	1.58	0.995	3.26
F13	68	4	-	1.60	0.996	2.97
F14	64	4	-	1.65	0.996	3.15
F15	60	4	-	1.74	0.996	3.73
F16	56	4	-	1.76	0.997	2.52
F17	72	-	4	1.64	0.994	4.56
F18	68	-	4	1.80	0.995	4.74
F19	64	-	8	1.89	0.994	6.60
F20	56	-	8	1.95	0.997	3.70
F21	56	-	20	1.04	0.997	0.86
F22	56	-	16	1.29	0.995	2.32
F23	56	-	12	1.49	0.996	2.81

Table 3: *Kinetic constants, determination coefficients, and sum of squares of deviations following fitting of dissolution data to Higuchi model (n = 6).*

k = Rate constant in Higuchi equilibrium, r^2 = Determination constant of fitting of data in Higuchi equilibrium, ss = Sum of squares of deviations, n = Number of samples

Formulations with different amount of HPMC K4M and constant quantity of PAA1 in the presence of DCP

The results of kinetic evaluation of drug release from formulations F12-F16 (Figure 4) in Higuchi model have been presented in Table 3. The results showed a relationship between logarithms of amount of HPMC K4M (mg) and logarithm of Higuchian release rate ($P < 0.05$):

$$K = 50.444\left(\frac{1}{W}\right) + 0.871 \quad r^2 = 0.951 \quad (14)$$

$$Log\, k = -0.477 \log W + 1.083 \quad r^2 = 0.973 \quad (15)$$

$$K = -0.0125W + 2.466 \quad r^2 = 0.949 \quad (16)$$

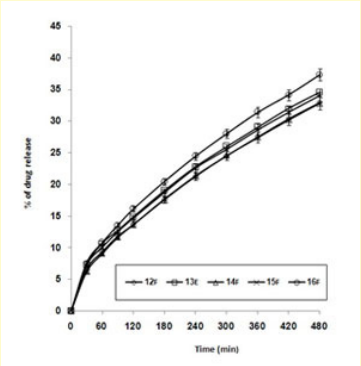

Figure 4: *Release profile of propranolol HCl from Formulations (F12-F16) with different amount of HPMC K4M and constant quantity of PAA1 in the presence of DCP (n = 4).*

Formulations with different amount of HPMC K4M in the presence of carbopol 934P and Lactose

The results of kinetic evaluation of drug release from formulations F17-F20 (Figure 5) in Higuchi model have been presented in Table 3. The results showed a relationship between amounts of Car.934P with of Higuchian release rate ($P < 0.01$):

$$k = 70.60(\frac{1}{W}) + 0.724 \quad r^2 = 0.802 \quad (17)$$

$$\log k = -0.632 \log W + 1.404 \quad r^2 = 0.813 \quad (18)$$

$$k = -0.018W + 3.01 \quad r^2 = 0.856 \quad (19)$$

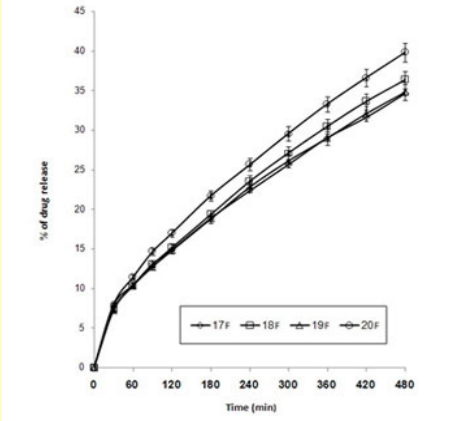

Figure 5: *Release profile of propranolol HCl from Formulations (F17-F20) with different amount of HPMC K4M in the presence of carbopol 934P and Lactose (n = 4).*

Formulations with different amount of carbopol 934P in the presence of HPMC K4M and Lactose

The results of kinetic evaluation of drug release from formulations F20-F23 (Figure 6) in Higuchi model have been presented in Table 3. The results showed a logarithmic relationship between amount of carbopol 934P (mg) and Higuchian release rate ($P < 0.05$):

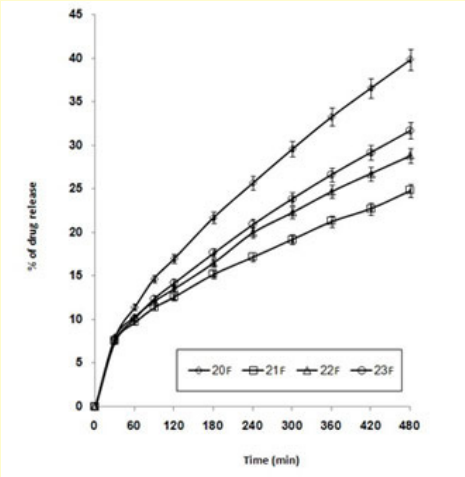

Figure 6: *Release profile of propranolol HCl from Formulations (F20-F23) with different amount of carbopol 934P in the presence of HPMC K4M and Lactose (n = 4).*

$$k = 11.64\left(\frac{1}{W}\right) + 0.509 \quad r^2 = 0.983 \quad (20)$$

$$\log k = -0.663 \log W + 0.8341 \quad r^2 = 0.988 \quad (21)$$

$$k = -0.073W + 2.47 \quad r^2 = 0.963 \quad (22)$$

Discussion

Controlled release by hydrophilic matrix remains a very versatile tool in the hands of the formulator and we can only look forward to greater formulation predictability as more and more fundamental studies become available. HPMC is a semisynthetic ether derivative of cellulose. It has been the dominant hydrophilic vehicle used in controlled release dosage forms because of its non-toxic nature, ease of compression, and accommodation to high levels of drug loading. It is desirable to predict the drug release from HPMC matrices with enough accuracy in the design of drug containing HPMC matrices [25]. Fu *et al.* proposed an empirical relationship between drug release rate and HPMC concentration [26].

The Higuchi model has been an invaluable framework over its 50-year history for developing large parts of modern drug delivery technology. It captures the essence of what governs drug release from a permeable matrix when the drug loading is well in excess of its solubility limit and allows prediction of release rates with good accuracy in most cases. It has endured because of its simplicity. Naturally, it embodies a number of assumptions and approximations, some of which are not so obvious [27]. Drug release rate (Higuchi-type release rate) was correlated with the reciprocal HPMC concentration in their empirical model. Shah *et al.* [28] reported a method for the prediction of the fraction drug release as a function of HPMC concentration and release time [28].

This research has elaborated a new relationship between release rate of drug and amount of mucoadhesive polymer in propranolol buccal adhesive tablets. Some studies had been shown a relationship between dissolution rate constant in Higuchi model (k) and reciprocal amount of polymer in hydrophilic matrices. Ford *et al.* [25] showed this relation is valid when applied to drugs of diverse aqueous solubility, provided that square time release kinetics are approximately followed [24]. The relation between log k and logarithm of polymer content had been obtained in hydrophilic matrices containing HPMC too. Ford *et al.* [25] studied hydrophilic matrices of Propranolol hydrochloride and aminophylline which prepared by several grades of HPMC. A straight line relationship was established between the logarithm of the tablet HPMC content and the logarithm of release rates ($mg.min^{-1/2}$), enabling release rates to be predicted for a variety of different drug substances [25]. In this research these equations and relation between k and amount of polymer was examined for dissolution data in propranolol buccal adhesive tablets.

In formulations F1-F4 with constant quantity of PAA1 in the presence of lactose, no significant differences were observed between three equations (equations 5-7). Evaluation of the equations 6 and 7 showed a similar relation too. In formulations F5-F8 with different amount of PAA1, the best fit was observed in new relationship equation between k and amount of PAA1. This different was very manifest. In formulations with different amount of HPMC K4M and PAA1 in the presence of lactose (Table 3) the logarithmic relationship was observed. In these formulations the relation between k and amount of polymer (equation 13) was significant. In formulations F12-F16 with different amount of HPMC K4M in presence of carbopol 934P, the relation between k and amount of HPMC K4M was observed too (equation 19). In other formulations, this new relationship was fitted too.

Within the context of hydrophilic polymeric matrices containing water-soluble drug, excipients should not be regarded as neutral or simple additives as they are certainly capable of altering water penetration, erosion and hence mechanism of release. The role of gel layer and its rate of growth are central and fundamental to define various fronts and understand the operating release mechanism [29].

Conclusion

It can be concluded from this study that the kind and ratio of bioadhesive polymers have synergistic effect on controlling release rate and kinetic of propranolol HCl from evaluated buccal adhesive tablets. This study showed that the direct relation between k and amount of polymer should consider for prediction and regulating of release rate in hydrophilic matrices.

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