An investigation into the drug release from ibuprofen matrix tablets with ethylcellulose and some poly-acrylate polymers

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Abstract: This study was performed to achieve sustained-release Ibuprofen matrix tablets with a zero-order release kinetic while most of the previous formulations have shown Higuchi release kinetic. Considering the results from previous studies, ethyl cellulose, Carbopol 934P, Carbopol 974P, and Pemulen TR-1 were used at different amounts for preparation of the tablets by direct compression. The release profiles were studied in a two-stage release test using non-linear regression analysis. Carbopols 934P and 974P could not sustain the release adequately while Pemulen TR-1 had too strong sustaining effect. Therefore, combination formulations were considered and studied. The release profiles of ethyl cellulose formulation and the combination formulation consisting Carbopol 934P and Pemulen TR-1 best fitted in Higuchi model, although the zero-order model was not completely rejected. However, the kinetic model of release from the combination formulation consisting Carbopol 974P and Pemulen TR-1 changed to zero-order indicating the most constant release rate among formulations. This was speculated to be due to some erosion of the gel, as well as some interaction of the hydrophobic chain of Pemulen TR-1 with Ibuprofen. Therefore, this formulation is suggested for directly compressed sustained-release matrix tablets of Ibuprofen with a more constant release rate.

Keywords: Ibuprofen, sustained-release tablet, ethyl cellulose, carbopol, pemulen.

INTRODUCTION

Ibuprofen is the oldest member of the propionic acid subgroup of the large family of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), which is still widely used, all over the world. Among the major adverse effects of Ibuprofen are gastrointestinal disturbance and ulceration. A good approach to reduce these unwanted effects is preparation of sustained-release formulations which reduce the exposure time of the gastrointestinal tract (GIT) to drug. Sustained-release formulations of Ibuprofen could increase the efficacy by providing a more constant plasma concentration, and improve the patient compliance due to the less frequent administration, as well as the reduction in local disturbing effect of the drug on GIT.

Among the different polymers used for prolonging drug release from tablets, ethyl cellulose (EC) is a common and widely used polymer for formulation of matrix-type sustained-release tablets for various drugs (Khan and Zhu, 1998a; Makhija and Vavia, 2002; Pather *et al*., 1998; Shaikh *et al*., 1987; Tabandeh *et al*., 2003; Upadrashta *et al*., 1993). Carbopols, which are high molecular weight polymers of acrylic acid chemically cross-linked with polyalkenyl alcohols or divinyl glycol, have also been investigated and some carbopols have been suggested as good candidates for formulating sustained-release matrix tablets (Bravo *et al*., 2004; Emami *et al*., 2004; Khan and Jiabi, 1998b; Khan and Jiabi, 1999; Rao *et al*., 2001; Tapia-Albarran and Villafuerte, 2004; Vaithiyalingam *et al*., 2002). Matrix sustained-release tablets of Ibuprofen have been formulated by direct-compression, hot-melt and wet granulation methods using ethyl cellulose and other cellulosic polymers (Khan and Zhu, 1998; Kiortsis *et al*., 2005; Nerurkar *et al*., 2005; Shaikh *et al*., 1987; Shoaib *et al*., 2006), eudragits (Kidokoro *et al*., 2001; Palmieri *et al*., 1999; Patel *et al*., 2011), and some of the carbopol polymers (Khan and Jiabi, 1998b; Khan and Jiabi, 1999; Rao *et al*., 2001).

Different studies have suggested different kinetic models for release from matrices made of these polymers. These different results could be due to differences in type and amount of the polymer and excipients, as well as the nature of the drug itself. In most studies, matrix tablets containing ethyl cellulose have been reported to show a Higuchi release profile for Ibuprofen and some other drugs (Neau *et al*., 1999; Shaikh *et al*., 1987), while in a few other studies release profiles resembling the zero-order model have also been reported for ethyl cellulose-based matrix tablets usually due to some erosion of the matrices (Pather *et al*., 1998; Tabandeh *et al*., 2003). Carbopol-containing matrices have been reported to exhibit a zero-order drug release in some previous studies (Durrani *et al*., 1994; Huang and Schwartz, 1995), while Higuchi release (Perez-Marcos *et al*., 1991) and combinational model (Khan and Jiabi, 1999; Meshali *et al*., 1996) have also been reported. Pemulen TR-1 is a newer polymer from the carbopol family that has been reported to strongly sustain the release, which makes it improper when used individually (Mortazavi and

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Aboofazeli, 2003). Another study has also reported a very slow release with a near zero-order release kinetic for diazepam from matrix tablets of this polymer (Wahlgren *et al*., 2009).

The ideal release profile for a sustained-release tablet is a zero-order model which has a more constant release rate; although most of the products in market and previous formulations do not fit in this category. Therefore, this study aims at achieving a zero-order kinetic of Ibuprofen release through formulation of matrix tablets by the scientifically and economically better method of direct compression. Considering the goals of producing adequate sustaining effect on release as well as imparting a zero-order release kinetic, Ethyl cellulose (EC), Carbopol 974P, Carbopol 934P and Pemulen TR-1 were used as the release controlling polymers in this study. The release profiles were studied by using the release graphs and non-linear regression analysis performed by the GraphPad Prism 5 software.

MATERIALS AND METHODS

Materials

Ibuprofen (Boots Lab., U.K) and Ethyl cellulose powder with viscosity grade of 100 cps (Aldrich Chem. Co. Ltd., U.K) were gifted by Hakim Pharmaceutical Manufacturing Company, Tehran, Iran. Microcrystalline cellulose (Avicel PH102) was gifted by Akbarieh Co. Ltd. (Distributor of FMC Corporation, Tehran, Iran). Carbopol 974P, Carbopol 934P-NF and Pemulen TR-1-NF were obtained from B.F.Goodrich, U.K All other reagents used, were of analytical grade obtained from Merck Chemical Company, Germany.

Preparation of Ibuprofen matrix tablets by direct compression:

Based on preliminary studies, the optimum amounts of magnesium stearate (passed through a 100-mesh sieve) as lubricant and colloidal silicone dioxide as glidant was selected. All formulations contained 400 mg of Ibuprofen, the fixed optimum percentages of magnesium stearate (0.5%) and colloidal silicon dioxide (0.5%), along with ethyl cellulose or various poly-acrylate polymers including Carbopol 974P, Carbopol 934P, and Pemulen TR-1. The remaining parts of the tablets were filled with microcrystalline cellulose (Avicel PH102) as filler to a final weight of 600 mg (table 1). All materials were weighed accurately and passed through a 60-mesh sieve (except magnesium stearate which was passed through a 100-mesh sieve). The ingredients except magnesium stearate were placed in a cubic mixer (Erweka, Germany) and mixed for five minutes. Then, magnesium stearate was added and mixed for another two minutes.

All formulations were compressed into normal convex 12-mm diameter tablets, using a single-punch tablet machine (Erweka, Germany). The compression force was adjusted for each formulation to produce tablets with maximum possible crushing strength values. Since carbopols were not individually able to produce an appropriate sustained release pattern in low amounts, some combination formulations were also prepared and tested.

Determination of crushing strength and friability of the tablets:

Ten tablets from each formulation were tested for diametrical crushing strength, using an Erweka TBH 28 hardness tester. The crushing strength (hardness) values were determined and reported as mean ± SD (Standard Deviation). The percent friability of tablets was also determined using an Erweka TA Roche-type friabilator at a speed of 25 rpm for 4 minutes.

Assay

The amounts of Ibuprofen in tablets of each formulation were determined based on the method described under ibuprofen monograph with the implementation of the necessary alteration (European Pharmacopoeia, 2007). Briefly, twenty tablets from each formulation were randomly selected, weighted and grinded. Appropriate amount of this powder equivalent to 400 mg of Ibuprofen was extracted with 60 ml of chloroform for 15 minutes, and then filtered through sintered glass filter under vacuum. The filter system used in this study was found to produce no interference with the UV absorption of Ibuprofen. The remaining materials on the filter were washed twice with 20 ml of chloroform, and then dried. The remainder was dissolved in 50 ml of methanol, and 0.4 ml of phenolphtalein was added. This solution was then titrated by 0.1 M sodium hydroxide solution until a red color was obtained. Each ml of the titrant solution was equivalent to 20.63 mg of Ibuprofen.

Screening dissolution test

A screening dissolution test was performed on six tablets from each formulation accepted by the friability and crushing strength (hardness) tests. This test was conducted based on the USP monograph of Ibuprofen tablet (United States Pharmacopeia, 2008). For this purpose, the USP dissolution apparatus 1 (rotating basket Erweka DT6R Dissolution Tester) was used at a speed of 50 rpm and containing 900 ml of the phosphate buffer (pH=7.2) as the dissolution medium at 37±0.5°C. Samples were taken hourly until twelve hours to ensure adequate release in a reasonable time for the sustained-release tablet. The samples were then filtered through sintered glass filter. The amounts of Ibuprofen released from various tablet formulations were determined using a UV-Visible spectrophotometer at 221 nm. All experiments were performed in triplicate.

Drug release study

Tablet formulations found to be acceptable according to the screening test, underwent a two-stage drug release

test. The test was performed using the USP dissolution apparatus 1 (rotating basket Erweka DT6R Dissolution Tester) at a speed of 50 rpm and containing 900 ml of 0.1 N hydrochloric acid solution (pH=1.2) for the first two hours, followed by a phosphate buffer medium (pH=6.8) for the next ten hours. During the first stage, 5-ml samples were taken after 15, 30, 60 and 120 minutes. After filtration (using a sintered glass filter), the absorbance values were determined using a UV-Visible spectrophotometer at 221 nm. During the second stage, 5-ml samples were taken at one-hour intervals (up to ten hours after the beginning of the second stage), and the amounts of dissolved Ibuprofen were determined spectrophotometrically at 266 nm, using filtered portions of the samples. All experiments were performed in triplicate (United States Pharmacopeia, 2008; European Pharmacopoeia, 2007).

The cumulative percentages of the drug released at various time intervals were obtained by calculating the mean release of six tablets from each formulation, and a plot of drug release against time was used to study the drug release profile. The release profiles were then fitted into the Higuchi, zero-order and first-order kinetic models using non-linear regression analysis performed by the GraphPad Prism 5 software (GraphPad Software, Inc., USA).

RESULTS

The compositions of the three accepted formulations are shown in table 1. The results of hardness, friability, and screening dissolution tests for these formulations are presented in table 2. Table 3 shows the results of assay tests and the cumulative percentages of drug release after 12 hours from the selected formulations. Figs. 1 to 3 show the drug release profiles for the three selected formulations.

Apparently, the first stage release was negligible due to the acidic nature of Ibuprofen, and the main release occurred during the second stage. Therefore, the regression coefficients for three different kinetic models (Higuchi, zero-order, and first-order) were calculated for the whole graphs, as well as the second stages as the main drug release periods. These coefficients have been shown in table 4.

By considering the graph of release up to 80% of the whole drug, "r" values were calculated for the Higuchi and zero-order models, which are shown in table 5.

DISCUSSION

In tablet technology direct compression is the most attractive method from both scientific and economic

Table 1: Ingredients of formulations

Formulation	Pemulen TR-1	Carbopol 934 P	Carbopol 974 P	Ethylcellulose 100cps	Avicel PH102	Colloidal Silicon Dioxide	Mg Stearate	Ibuprofen	Tablet Weight
EC	--------	----------	----------	20%	12%	0.5%	0.5%	400 mg	600 mg
C974/Pem	1%	----------	9%	----------	22%	0.5%	0.5%	400 mg	600 mg
C934/Pem	2.5%	10%	--------	----------	19.5%	0.5%	0.5%	400 mg	600 mg

EC: Formulation containing 20% of ethylcellulose
C974/Pem: Formulation containing 9% of Carbopol 974P and 1% of Pemulen TR-1
C934/Pem: Formulation containing 10% of Carbopol 934P and 2.5% of Pemulen TR-1

Table 2: Results of hardness, friability, and screening dissolution tests

Formulation	Hardness (N), n =10	Friability (%)	Screening dissolution test (12 hrs. in Phosphate buffer), n=3
EC	128.5± 10.8	0.12	108.6± 1.2
C974/Pem	49.0± 6.4	0.55	101.1± 1.3
C934/Pem	50.0± 4.9	0.27	94.2± 1.5

Table 3: Results of assay and drug release tests

Formulation	Assay (%), n =3	Drug Release (12 hrs. in two-stage test), n =3
EC	101.9± 1.2	89.9± 1.0
C974/Pem	97.8± 2.8	99.3± 2.1
C934/Pem	99.4± 1.9	92.2± 1.9

Table 4: Regression coefficients for different kinetic models of release from the matrix tablets

Formulation	R (Higuchi)	R (Zero-order)	R (First-order)
EC (whole period)	0.9715	0.9446	0.8483
EC (2nd stage)	0.9869	0.9725	0.9548
C974/Pem (whole period)	0.9806	0.9637	0.8398
C974/Pem (2nd stage)	0.9972	0.9924	0.9656
C934/Pem (whole period)	0.9750	0.9490	0.8298
C934/Pem (2nd stage)	0.9891	0.9755	0.9458

points of view. Therefore, sustained-release Ibuprofen matrix tablets in this study were all designed for direct compression method.

Table 5: Regression coefficients for different kinetic models of the second stage release up to 80% release

Formulation	R (Higuchi model)	R (Zero-order model)
EC	0.9470	0.9374
C974/Pem	0.9685	0.9701
C934/Pem	0.9360	0.9344

As it is observed in figs. 1 to 3, the release profiles for all three formulations obviously consist of two stages: the acidic (pH=1.2), and the buffer medium (pH=6.8). Apparently, the first stage release was negligible due to the acidic nature of Ibuprofen, and the main release occurred during the second stage. Therefore, the regression coefficients for three different kinetic models (Higuchi, zero-order, and first-order) have been calculated for the whole graphs, as well as the second stages as the main drug release periods. These coefficients have been shown in table 4. The equations related to these models are as follows:

Zero-order model: $Q_t = Q_0 + K_0 t$ (1)
Where Q_t is the amount of drug dissolved in time t, Q_0 is the initial amount of drug in solution which is mostly zero and subsequently the term is omitted, and K_0 is the zero-order release constant.

First-order model: $\ln C = \ln C_0 - Kt$ (2)
Where C_0 is the initial concentration of the drug, K is the first order release constant, and t is the time.

Higuchi model: $Q_t = K_H t^{0.5}$ (3)
Where Q_t is the amount of drug released in time t, and K_H is the release rate constant for the Higuchi model.

Ethyl cellulose is a hydrophobic inert polymer having good compression capacity, and slow erosion which could help linearize the release profile. It has been widely used for preparation of sustained-release matrix tablets of various water-soluble and insoluble drugs (Khan and Zhu, 1998a; Makhija and Vavia, 2002; Neau *et al*., 1999; Pather *et al*., 1998; Shaikh *et al*., 1987; Tabandeh *et al*., 2003; Upadrashta *et al*., 1993). It could be a very good candidate for preparation of Ibuprofen sustained-release matrix tablets by direct compression. Although Ibuprofen had a poor flowability and compactability, ethyl cellulose could impart the appropriate properties to formulations, due to its own good flowability and compactability. Previous studies have reported different percentages of ethyl cellulose (EC) in matrix tablets producing desirable release rate of different drugs (Pather *et al*., 1998; Tabandeh *et al*., 2003). Within the range of 10-30% (w/w) used in this study, 20% was the lowest amount of ethyl cellulose which provided good quality. These tablets had a maximum hardness value of 128.5±10.8 N and 0.12%

percent friability, with the amount of the released drug after twelve hours in phosphate buffer being 108.6±1.2% (Table 2). The acceptable minimum release from the plain Ibuprofen tablets according to its monograph in USP is 80% (USP-NF, 1995). Therefore, this was considered as the minimum acceptable percentage of dissolution after twelve hours for the sustained-release Ibuprofen tablets. The formulation successfully passed this screening dissolution test and proceeded to the two-stage drug release test. In the two-stage drug release test, it released 89.9±0.9% of the drug content after twelve hours. The assay result was also 101.9±1.2% which was acceptable (Table 3). The release pattern could be observed in fig. 1. Non-linear regression analysis showed "r" values of 0.9446, 0.8483, and 0.9715 for zero-order, first-order, and Higuchi models, respectively (table 4). Of course, the first stage release was negligible, as shown in fig. 1. This could be due to the weak acidic nature of Ibuprofen, which favors the unionized form of the Ibuprofen in the acidic medium having a lower solubility. In the second stage, the "r" values were calculated as 0.9725, 0.9548, and 0.9869 for zero-order, first-order, and Higuchi models, respectively (table 4). Therefore, the "r" values for the second stage release suggest the Higuchi model as the best fitted model. Some previous works have also reported Higuchi model release for ethyl cellulose matrices (Lopes *et al*., 2006; Shaikh *et al*., 1987). By considering the graph of release up to 80% of the whole drug, "r" values of 0.9470 and 0.9374 were calculated for the Higuchi and zero-order models respectively (table 5), which also confirms the Higuchi model as the best fitted model and the release is therefore mostly diffusion-controlled. However, the difference is not so much to completely reject the zero-order model. Ethyl cellulose has a tendency to erode slowly, which could become more prominent by presence of the erosion-promoting ingredients (Pather *et al*., 1998). The erosion of the tablet could gradually reduce the distance between the diffusion boundary and the drug molecules to be diffused, thus attenuating the characteristic decrease of release rate in Higuchi model. This could cause a shift from Higuchi release towards zero-order release, which causes the "r" value for the zero-order model to be relatively high in our study. Also, in some other works on ethyl cellulose as the matrix former, combination kinetics has been reported (Pather *et al*., 1998; Tabandeh *et al*., 2003).

In a previous study on HPMC polymers as the matrix polymers, the exact chemical structure and heterogeneity of the polymers have been reported to have strong influence on the degree of erosion in matrices and the contribution of erosion to the release mechanism (Viriden *et al*., 2010; Viriden *et al*., 2011). In our study, the degree of matrix erosion is so low that diffusion of the low-soluble ibuprofen through the matrix is the predominant mechanism of release.

Carbopol polymers are water-insoluble polymers having good compressibility with plastic deformation being their consolidation mechanism. This makes them suitable for direct compression method (Bulletin 17: Controlled release tablet and capsules, 2002, Noveon Specialty Chemicals, USA). Carbopols 974P and 934P do not produce gel in acidic medium, because of the chains being coiled by hydrogen bonds between the unionized carboxylic groups. By increasing the pH of the medium, due to the repulsion between ionized carboxylic groups, the coiled branches of polymer molecule get a more opened configuration and by being hydrated with water molecules produce a gel through which the drug could be slowly diffused. However, this swelling is different from what is observed in swelling of linear hydrophylic

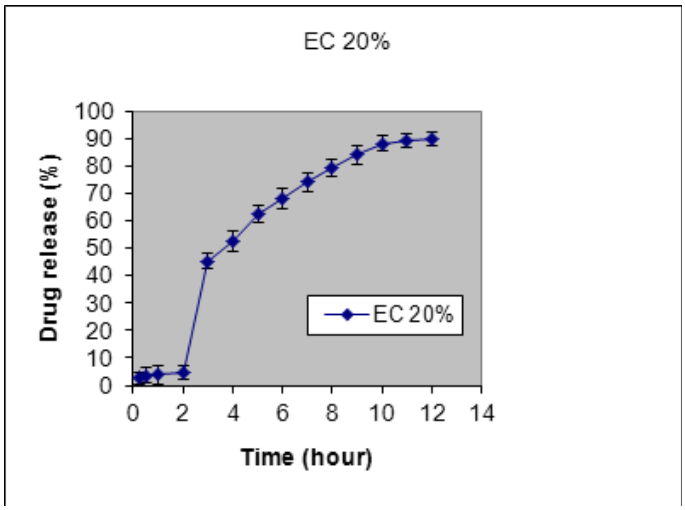

Fig. 1: Ibuprofen release from the 20% EC-containing matrix tablets (n= 6, mean ± SD)

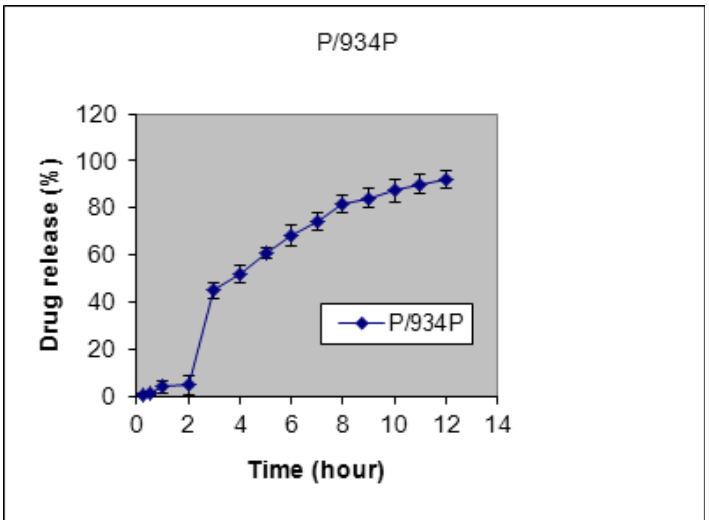

Fig. 2: Ibuprofen release from the Pemulen/C934P-containing matrix tablets (n=6, mean ± SD)

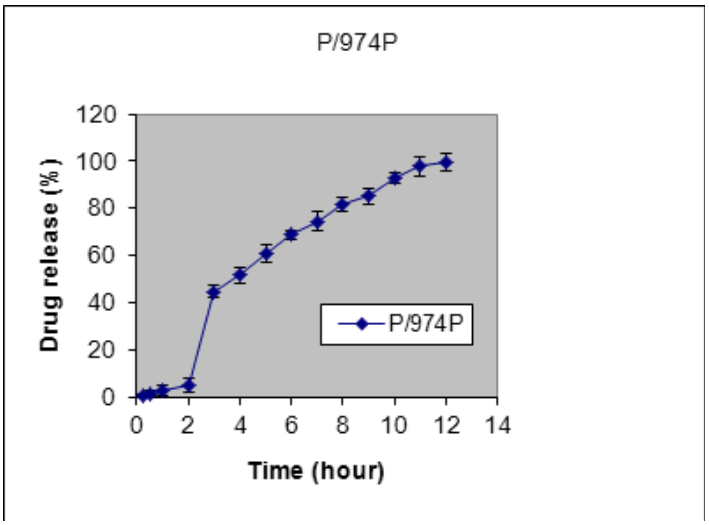

Fig. 3: Ibuprofen release from the Pemulen/C974P-containing matrix tablets (n= 6, mean ± SD)

polymers. In this case, microgels made up of many polymer particles are formed, in which the drug is dispersed (Bulletin 17: Controlled release tablet and capsules, 2002, Noveon Specialty Chemicals, USA).

In our study, neither Carbopol 974P nor Carbopol 934P could sustain the Ibuprofen release adequately even at amounts of up to 20% w/w of the formulation. This could be due to the fact that the polymer is so tightly cross-linked that it inhibits the drug from penetrating into the gel at high amounts. Therefore, the drug molecules would remain in the interstitial spaces between the gel domains and released relatively rapid. In addition, since they are polymerized in ethyl acetate, they are neutralized with 1-3% potassium (Bulletin 17: Controlled release tablet and capsules, 2002, Noveon Specialty Chemicals, USA). The presence of this monovalent cation in carbopols has a shielding effect on negative charges of the polymer chains, which could reduce the swelling of polymer resulting in faster drug release. At higher concentrations, these polymers have been reported to cause slower release profiles and linearization of the release process from matrix tablets (Khan and Jiabi, 1999; Rao *et al*., 2001; Seng *et al*., 1985 and Durrani *et al*., 1994). This could be due to more swelling and subsequent reduction in regions of low microviscosity or channels between the microgel regions for diffusion of the drug, which could even change the prominent mechanism and kinetic of release (Khan and Jiabi, 1999). However, the high amount of Ibuprofen in sustained-release tablets (at least 400mg) did not allow high percentage (more than 20% w/w) of the polymers in this study.

Pemulen TR-1 is a copolymer of acrylic acid and hydrophobic long chain (C10-C30) alkyl acrylates, cross-linked with allylpentaerythritol (Bulletin 17: Controlled release tablet and capsules, 2002, Noveon Specialty Chemicals, USA). Formulations with this polymer sustained the release rate extensively even at low concentrations, which was in accordance with the previously reported results for propranolol HCl (Mortazavi and Aboofazeli, 2003) and diazepam (Wahlgren *et al*., 2009). This could be due to the long chain alkyl acrylates in polymer molecules which deprive the chain from some of the carboxylic groups present in non-modified carbopols. This modification in structure could decrease the water absorption and gel forming capacity, and reduce the cohesive forces between polymer chains leading to less rigid microgel regions and smaller channels of low microviscosity. In addition, an interaction between the hydrophobic long chain alkyl acrylates in Pemulen TR-1 with the ibuprofen molecule could also contribute to this effect, similar to what has previously been suggested for Pemulen and diazepam (Wahlgren *et al*., 2009).

Considering the inadequate sustaining effect of carbopols 974P and 934P and the strong sustaining effect of Pemulen TR-1 on Ibuprofen release rate, combination formulations of each of the carbopols 974P and 934P along with Pemulen TR-1 were prepared and evaluated for a proper release profile. Among the combination formulations with Carbopol 934P, the one with 10% w/w of Carbopol 934P and 2.5% w/w of Pemulen TR-1 (Table 1) showed a maximum hardness of 50.0±4.9 N and had a percent friability of 0.27% (table 2). It released 94.2±1.5% of the drug content after twelve hours in phosphate buffer medium (table 2). According to the previously mentioned minimum acceptable amount, it successfully passed the screening dissolution test and proceeded to the two-stage drug release test. The formulation showed an assay result of 99.4±1.9%, and released 92.2±1.9% of its drug content after twelve hours in the two-stage drug release test (table 3). The release pattern could be observed in fig. 2. Non-linear regression analysis showed "r" values of 0.9490, 0.8298, and 0.9750 for zero-order, first-order, and Higuchi models respectively (table 4). Although in the first stage (acidic medium) the polymer could not swell and sustain the release, the release is negligible due to the weak acidic nature of Ibuprofen, which favors its unionized form having a lower solubility. For the second stage, the "r" values were calculated as 0.9755, 0.9458, and 0.9891 for zero-order, first-order, and Higuchi models respectively (table 4). Therefore, the Higuchi model is suggested as the best fitted model. By considering the graph of release up to 80% of the whole drug, "r" values of 0.9344 and 0.9360 were calculated for the zero-order and Higuchi models respectively (table 5). These results also suggest the Higuchi model as the best fitted model, although due to the little difference in "r" values, the zero-order model is not completely rejected. It has been suggested that after polymer hydration and gel formation, the osmotic pressure from within the gel regions sloughs off discrete pieces of the formed gel and breaks up the structure (Bulletin 17: Controlled release tablet and capsules, 2002. Noveon Specialty Chemicals, USA). This erosion could attenuate the characteristic decrease of the release rate in Higuchi model to some extent and result in a combination release profile, as previously reported for Carbopol 934P matrix tablets containing theophylline (Meshali, 1996). Therefore, the release seems to be controlled mainly by diffusion of the drug as well as some erosion of the matrix. In our study, a fast initial dissolution is also observed. This is speculated to be due to the fast dissolution of surface drug, as well as the fast penetration of water into matrix pores and subsequent diffusion of the drug before completion of the gel formation process.

Among the combination formulations of Carbopol 974P, the one with 9% w/w of Carbopol 974P and 1% w/w of Pemulen TR-1 (table 1) showed proper hardness (49.0±6.4 N) and percent friability (0.55%) values (table 2). It released 101.1±1.3% of drug content after twelve hours in phosphate buffer medium (table 2) and proceeded to the two-stage drug release test. The formulation showed an assay result of 97.8±2.8%, and released 99.3±2.1% of its drug content after twelve hours in the two-stage drug release test (table 3). The release pattern could be observed in fig. 3. Non-linear regression analysis showed "r" values of 0.9637, 0.8398, and 0.9806 for the zero-order, first-order, and Higuchi model, respectively (table 4). For the second stage, the "r" values were calculated as 0.9924, 0.9656, and 0.9972 for zero-order, first-order, and Higuchi models, respectively (table 4). By considering the graph of release up to 80% of the whole drug, "r" values of 0.9701 and 0.9685 were calculated for the zero-order and Higuchi models respectively (table 5). This suggests zero-order as the best fitted model, although not completely rejecting the Higuchi model. The contribution of matrix erosion as previously mentioned, incorporates a zero-order component into the release pattern, as in a previous study a mixed Higuchi and zero-order kinetic model has been reported for matrix tablets of Theophyline containing Carbopol 974P (Meshali *et al*., 1996). However, another study has reported a complete domination of zero-order kinetics over Fickian diffusion model for the release of diazepam from matrix tablets containing either Carbopol 981F or Pemulen TR-1 (Wahlgren *et al*., 2009). In addition to erosion, an interaction between Pemulen TR-1 chains with Ibuprofen molecule could also contribute to the domination of zero-order release kinetic in this formulation, as has previously been suggested for Pemulen and diazepam (Wahlgren *et al*., 2009). A fast initial dissolution was also observed similar to the

combination formulation with Carbopol 934P and Pemulen TR-1.

CONCLUSION

Ethyl cellulose could make sustained-release matrix Ibuprofen tablets with an amount of 20 percent in formulation and a release profile fitted best in Higuchi model. Carbopols 934P and 974P could not sustain the release adequately at amounts up to 20% w/w of formulation, while Pemulen TR-1 had a too strong sustaining effect. However, combination formulations of each carbopol with Pemulen showed promising results. The combination formulation of Carbopol 934P with Pemulen TR-1 showed a Higuchi model release, with minor contribution of zero-order kinetic. However, the best release profile was observed in the combination formulation consisting 9% w/w of Carbopol 974P and 1% w/w of Pemulen TR-1 which fitted best in zero-order model. This is speculated to be due to the polymer chain relaxation of Carbopol 974P, as well as the interaction between Ibuprofen molecule and hydrophobic Pemulen TR-1, which could play a barrier role in release process. Therefore, this formulation is suggested for preparation of directly compressed sustained-release matrix tablets of Ibuprofen.

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