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The Influence of the Copolymer Composition on the Diltiazem Hydrochloride Release From a Series of pH-sensitive Poly[(*N*-isopropylacrylamide)-*co*-(methacrylic acid)] Hydrogels

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ABSTRACT

A series of poly[(*N*-isopropylacrylamide)-*co*-(methacrylic acid)] (P[(*N*-iPAAm)-*co*-(MAA)]) hydrogels was investigated to determine the composition that exhibits a better pH-modulated release of diltiazem hydrochloride (DIL.HCl). For this purpose hydrogel slabs were loaded with DIL.HCl by the immersion method, and its release under acidic medium (0.1N HCl, pH 1.2) and in phosphate buffer pH 7.2, using *United States Pharmacopeia (USP)* 24 Apparatus 1, was investigated. According to the results from the slabs, copolymers with 85% mol *N*-iPAAm content were selected to prepare tablets with different particle size. The effect of pH and particle size changes on DIL.HCl release from these last hydrogel tablets was investigated by a stepwise pH variation of the dissolution medium. The amount of DIL.HCl released from high *N*-iPAAm content copolymer slabs under acidic pH medium was not only very low but it was also released at a slow rate. In the 85% *N*-iPAAm tablets, significant differences between and within release profiles were found as a function of particle size and pH, respectively. A relationship between particle size and release rate has been found. The lower DIL.HCl release at acidic pH from enriched *N*-iPAAm copolymers is interpreted by a cooperative thermal- and pH-collapse. Although for the whole range of copolymer composition a dependence of the equilibrium of swelling on the pH was found, DIL.HCl release experiments indicated that hydrogels with 85% mol *N*-iPAAm are the more adequate to be used for modulated drug delivery systems. Additionally, the particle size of the tablet can be used to tailor the release rate.

KEYWORDS: diltiazem hydrochloride, N-isoprylacrylamide, methacrylic acid, hydrogel, pH-modulated release.

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INTRODUCTION

Drug delivery systems from swellable matrices for oral administration are usually prepared as tablets by the compression molding of hydrophilic microparticulate powders.[1] Various commercial products are now available and usually consist of a mixture of drug, glassy polymer(s), and desirable excipients[2] compressed into a tablet.[3-4] When timed-release tablets are orally administered, the drug is going to be transferred into a physiological medium with a series of changing pHs, that is, from the highly acidic conditions of the stomach (pH = 1.2) to the slightly basic enteric conditions (pH = 6.8-7.4) then to drop in the colon to pH 5.5-6.8.[5] Therefore, the dissolution behavior must be studied in order to determine how the pH can affect its release characteristics and kinetics.

Stimuli-responsive hydrogels have been revealed as a route to obtain novel drug delivery systems by using their ability to swell or collapse in response to external factors such as pH, temperature, ionic strength, electrical field, or chemical substances.[6-12] However, in spite of the interest and the expectation that hydrogels have promoted, the mechanisms of drug release from swellable matrix tablets continue to be a matter of debate.[10,13-15] This is owing to the many factors that the process involves; among them are the rate and swelling degree of the hydrogel, the drug/polymer interaction, the drug solubility in the physiological medium, as well as the diffusion of the drug throughout the polymeric swollen matrix.

In the recent past poly[(*N*-isopropylacrylamide)-*co*-(methacrylic acid)] (P[(*N*-iPAAm)-*co*-(MAA)]) copolymers have been studied under different aspects by different authors.[10,16-26] These copolymers possess a wide range of swelling characteristics depending on composition and previous swelling history,[24-26] which potentially allow hydrogels to be obtained for specific uses. Because of the *N*-iPAAm moiety, these copolymers are able to respond to temperature changes, while the ionizable carboxyl group provides pH sensitivity. These copolymers have been used, for instance,

Table 1. Composition of Cross-Linked Samples Determined by Elemental Analysis*

	0.25% wt Cross-Linking Agent	
Sample	**P(*N*-iPAAm) (% mol)**	**P(MAA) (% mol)**
P(*N*-iPAAm)	100	0
P[(*N*-iPAAm)-*co*-(MAA)] (85/15)	82.6	17.4
P[(*N*-iPAAm)-*co*-(MAA)](70/30)	66.7	33.3
P](*N*-iPAAm)-*co*-(MAA)](50/50)	50.5	49.5
P[(*N*-iPAAm)-*co*-(MAA)](30/70)	32.4	67.6
P[(*N*-iPAAm)-*co*-(MAA)](15/85)	15.4	84.6
P(MAA)	0	100

*P(*N*-iPAAm) indicates poly[(*N*-isopropylacrylamide); P(MAA), poly(methacrylic acid); and P[(*N*-iPAAm)-*co*-(MAA)], poly[(*N*-isopropylacrylamide)-*co*-(methacrylic acid)].

for modulated delivery of antithrombotic[16,18] and thrombolitic agents,[16] as a novel separation carrier in fluorescence immunoassays,[19] and in a glucose-sensitive polymeric composite membrane for modulated permeation of insulin.[20]

Diltiazem hydrochloride (DIL.HCl), an antihypertensive drug that has been used recently as a model drug by several authors,[2,27-30] was chosen as a model active pharmaceutical material because of its good solubility in water and buffered solutions. The main goal of this contribution was to elucidate the influence of the copolymer composition on the DIL.HCl delivery from cross-linked P[(*N*-iPAAm)-*co*-(MAA)] copolymer hydrogels. On one hand, all the copolymer compositions exhibit potential pH sensitivity and in addition, some of them present thermal sensitivity. On the other hand, DIL.HCl is more soluble at acidic pH. Taking into account all of these factors, this study investigates which range of composition is more adequate for a pH-modulated delivery. Using these selected copolymers, the possibility of making tablets with different particle size to tailor the release rate is also evaluated.

Materials and Methods

Materials

DIL.HCl was obtained from Éthypharm Laboratories (Le Grand Quevilly, France). The following materials were also used: *N*-isopropylacrylamide (*N*-iPAAm) (Acros Organics, Fairlawn, NJ) 99%, methacrylic acid (MAA) 98%, tetraethylene glycol dimethyl acrylate (TEGDMA), ammonium persulfate (APS), *N,N,N,'N,'*-tetramethylethylenediamine (TEMED), potassium dihydrogen phosphate (Fluka-Chemie AG, Buchs, Switzerland), trisodium phosphate monohydrate, disodium hydrogen phosphate anhydride, *ortho*-phosphoric acid, hydrochloric acid, sodium chloride, ethanol, and methanol (Panreac Momplet and Esteban, SA, Barcelona, Spain). All products were used as received, except *N*-iPAAm, which was purified by recrystallization from a mixture of n-hexane/toluene (90/10, vol/vol) at room temperature, and MAA, which was vacuum distilled at 50°C/667 Pa. Deionized water from a Millipore Milli-U10 water purification facility (Millipore, Billerica, MA) was used where appropriate.

Synthesis of Homopolymers and Copolymer Hydrogels

P[(*N*-iPAAm)-*co*-(MAA)] hydrogels were synthesized by free radical polymerization in solution using a mixture of water and ethanol (50/50 wt%) as solvent and initial *N*-iPAAm/MAA comonomers molar ratios of 100, 85, 70, 50, 30, 15, and 0 in *N*-iPAAm monomer content. Then, 0.25% wt of TEGDMA cross-linking agent was used. APS (0.5 wt%) activated by TEMED (0.5 wt%) was used as initiator system. Some other details have been given.[24,25] Copolymer composition (Table 1) was determined by elemental analysis performed using a CHN EA 1108-elemental analyzer (Carlo Erba Instruments, Milano, Italy). Because the previous swelling history was shown to have strong influence on the swelling behavior,[26] samples from synthesis were soaked under acidic medium (pH 1.2) and dried in a vacuum oven at 60°C for 24 hours in order to obtain homogeneous samples with a controlled morphology history.

Equilibrium Swelling Experiments

To carry out swelling experiments, uniform discs were punched out of the hydrogel sample by using a stainless steel cork borer following the procedure described in a previous paper.[25] Analysis of the equilibrium and dynamic swelling characteristics of all hydrogels was performed at 37.0°C ± 0.1°C. For the swelling experiments, buffer solutions were prepared by mixing known amounts of *ortho*-phosphoric acid, disodium hydrogen phosphate, and potassium dihydrogen phosphate in order to vary the pH, and the ionic strength was kept constant at 0.1 M by using NaCl. Xerogel disks were left to swell in buffer solutions at pH = 2, 4, 7, 8, and 9 to achieve the equilibrium. Since the equilibrium depends on many factors, such as, copolymer composition, temperature,

pH, etc, it was considered to be achieved after 3 days for all cases. The normalized equilibrium swelling Q_∞ is given by $Q_\infty = (m_\infty - m_0) / m_0$, where m_0 is the initial weight of the dried disk (xerogel); namely, the weight at $t = 0$ and m_∞ is the weight after water uptake equilibrium is reached.

Loading of Drug Into P[(N-iPAAm)-co-(MAA)] Copolymers

In the past, 2 methods have been used for loading of hydrogels as drug carriers.[31] In the first method, the hydrogel comonomers and cross-linker agent are premixed with drug and polymerized, thus trapping the drug within the matrix. In the second method, a presynthesized dry hydrogel is loaded by swelling to equilibrium in a suitable drug solution. The drug-loaded hydrogel is then dried and appropriate release devices are prepared for drug release studies. The second method presents some obvious advantages over the first. In the first method polymerization may affect the drug release characteristics because secondary reactions among the drug and active monomers may take place during polymerization. Therefore, DIL.HCl was loaded into each hydrogel slab by the swelling-loading technique. Drug release behavior was studied as a function of copolymer composition using slabs, thus allowing an adequate copolymer composition to be chosen for tabletting as final dosage forms.

Slabs

Uniform discs of 1-cm diameter and 1-mm thickness were prepared by punching out of the hydrogel sheet sample using a stainless steel cork borer following the procedure described above for swelling experiments. The dried collapsed slabs (pH 1.2) were loaded by immersion in a solution of the drug in methanol during 24 hours with a pre-established drug concentration to obtain loads of the drug within the 30% wt/wt drug/polymer ratio. After equilibrium was attained, fully swelled hydrogels removed from the remaining drug solution were blotted with filter paper to eliminate the surface drug solution and slowly freeze dried. Finally, traces of methanol were removed using a high vacuum hot plate at 40°C for 24 hours.

Tablets

Slabs after a DIL.HCl loading of 30% wt/wt, as described in the above paragraph, were dried and then ground using an M 20 IKA universal mill (IKA Werke GmbH Staufen, Germany) and, finally, vacuum dried again for a period of 12 hours. Dried samples were submitted to particle sieving. Eight fractions ranging from 0.09 to 5 mm in diameter were obtained. Each one of the fractions was compressed using a rotary tabletting machine (J. Bonals, Barcelona, Spain) equipped with concave-faced punches of 7-mm diameter in order to manufacture tablets weighing 100 mg with a 30-mg DIL.HCl content. To minimize processing variables, all tablets were produced under identical conditions (1 unit in the J. Bonals' machine scale). For comparison purposes, in the limit of high particle size, a slab was prepared having 8-mm diameter and 3-mm thickness, which has been also assayed.

Dissolution Assays

In vitro dissolution tests were performed in the Apparatus 1, a rotating mesh basket in a hemispherical vessel, described in the *United States Pharmacopeia (USP)*,[32] at 37°C and stirred at 100 rpm. Samples were submitted at a prefixed scheduled time and then filtered. The drug released was determined by measuring its concentration by UV visible spectrophotometry at 236 nm. Two experimental pH conditions were considered for the dissolution medium: 2 constant pHs and a stepwise variation of pH.

Constant pH on Slabs

Preliminary studies have been done with homopolymer and copolymer slab samples under 2 media, at pH 1.2 (100 mL 0.1N HCl) and in a phosphate-buffered solution of pH 7.2 (250 mL 0.1 N HCl; 750 mL 0.2 N trisodium phosphate). Experiments were performed in triplicate.

Stepwise pH Variation on Tablets

In order to see how progressive changes of pH affect the DIL.HCl release profiles, a 5-step pH ramp (stepwise pH variation, or progressive gradient) was used. Such ramps have been used in previous studies.[33-36] This series of experiments has been done with tablets having a copolymer composition of 85% wt *N*-iPAAm. In order to determine how progressive changes of pH can affect the release profiles, a 5-step pH ramp program (stepwise pH variation) was used. The samples were submitted progressively to aqueous buffered solutions at pH 1.2 (1 hour); pH 2.5 (1 hour); pH 5.5 (2 hours); pH 6.6 (2 hours), and pH 7.2 (until release was completed). pH changes were attained by adding sequentially 250 mL 0.2 N trisodium phosphate-buffered aqueous solution to an initial 750-mL 0.1 N HCl aqueous solution. The experiment was performed in triplicate.

Disintegration Assay

The disintegration of tablets with 70% and 85% mol *N*-iPAAm has been studied at 37°C under a stepwise pH varia-

tion in a Pharma Test disintegration apparatus (Pharma Test Apparatebau GmbH, Hainburg, Germany).[32] The tablets were observed visually by means of an augmentation lens.

Results and Discussion

Equilibrium Swelling Experiments

Equilibrium swelling values, Q_∞, as a function of both pH and copolymer composition at 37°C are shown in Figure 1 as a 3-dimensional (3D) plot. P(*N*-iPAAm) homopolymer gel does not show any sign of swelling at this temperature because it is above its lower critical swelling temperature (LCST) of 32°C,[37] whereas P(MAA) exhibits pH dependence because of its ionizable COOH groups. A wide range of pH-dependent behavior is found for copolymers. The swelling ratio is much higher for copolymers slightly enriched in *N*-iPAAm at neutral and basic pHs. In this region, the 3D surface exhibits a Q_∞ maximum (see the response surface plot given in Figure 1). The swelling degree for all the copolymers decreases abruptly with decreasing pH, particularly for high *N*-iPAAm content copolymers. The pH sensitivity depends strongly on composition. It is obvious that the swelling behavior may affect the drug release, therefore the dissolution assays were performed within the whole composition range.

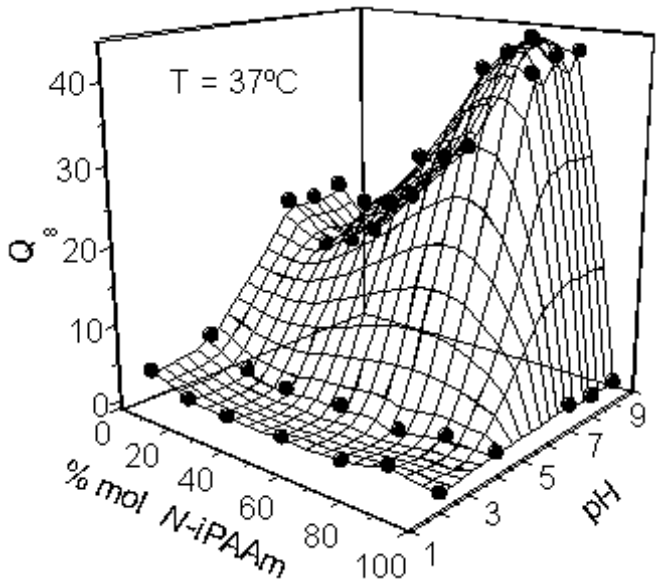

Figure 1. Equilibrium of swelling Q_∞ at 37ºC as a function of *N*-iPAAm molar percentage and pH.

Dissolution Assays From Slabs

Figure 2 shows the DIL.HCl released at 37°C and pH 7.2 as a function of the time from the whole range of copolymer composition. All of them have almost the same initial drug loading of 30% wt/wt. The slowest DIL.HCl release rate occurred from the P(*N*-iPAAm) homopolymer, which, after 25 hours, did not release the total amount of DIL.HCl. Regarding the rest of the polymers, the higher the *N*-iPAAm content, the faster the DIL.HCl release. The fastest drug release was exhibited by the 85% mol *N*-iPAAm copolymer, which after 5 hours reached equilibrium. This behavior could be explained by taking into account the swelling characteristics of the gels displayed in Figure 1. P(*N*-iPAAm) exhibits a sharp phase transition in water (LCST) at 32°C.[37] However, in its P[(*N*-iPAAm)-*co*-(MAA)] copolymers due to the addition of a more hydrophilic monomer MAA to *N*-iPAAm, which hinders the aggregation of the polymer chains and acts to expand the collapsed structure, the shrinkage at this temperature and pH is suppressed even in those cases in which only small amounts of MAA are present in the copolymer.[25] Copolymers presenting the highest equilibrium of swelling, also exhibited the fastest DIL.HCl release. In Figure 3, DIL.HCl release profiles are displayed for the same series of gels at 37°C and pH 1.2. It is notable that P(*N*-iPAAm), which does not show pH-sensitivity, exhibits a faster release rate of DIL.HCl than that from dissolution assays at pH 7.2, the probable reason being the higher DIL.HCl solubility at acidic pHs. The dependence of the release rate on composition is very tricky. In Figure 3, it can be observed that hydrogels containing 0%, 15%, 30%, and 50% mol *N*-iPAAm exhibit very similar release rates, and only differences in the final amount released are appreciated. In general, the release rate for this range of compositions is higher than the rate obtained at pH 7.2; it seems that at low pH, the release rate is more related to the high DIL.HCl solubility than to the pH dependence of the gels. However, a different trend can be observed for the 70% and 85% mol *N*-iPAAm copolymers, both presenting a sigmoidal release curve, which may indicate that in this case release is controlled by the hydrogel composition. This fact could be explained on the basis of a synergic effect between the thermal and pH collapse of the gels, which makes them more impermeable to water. From these experiments we concluded that copolymers having 70% and 85% mol could be suitable for developing modulated drug delivery systems because they release negligible amounts of the drug under the acidic pH of the stomach (in 2 hours, 4.5% and 1.5%, respectively), and at the higher pH of the intestinal track they release the whole amount of DIL.HCl within the first 8 hours. These 2 compositions were chosen for tabletting after previous grinding and sieving processes of slabs.

Disintegration Assays

Tablets consisting of 70% mol *N*-iPAAm exhibited the following pH dependence: at pH 1.2, they disintegrated within the first minute in primary opaque particles; no changes were observed until pH 6.6 was reached. At this pH, a swelling

front was observed, and its advance depended on particle size. Thus for tablets with 85% mol *N*-iPAAm, no disintegration was observed at pH 1.2. This effect was observed for poly[(*N*-isopropylacrylamide)-*co*-(acrylic acid)] microgels and was attributed to hydrophobic interaction between particles.[38] No changes were observed at either pH 2.5 or at 5.5. In the disintegration assays performed at pH 6.6, disintegration and swelling started, and its advance depended on particle size; at pH 7.2 the swelling was complete and the granule core disappeared. This second copolymer composition was chosen to develop pH-dependent tablets that can suppress drug release in the stomach and release the drug faster at the higher pH of the intestinal tract.

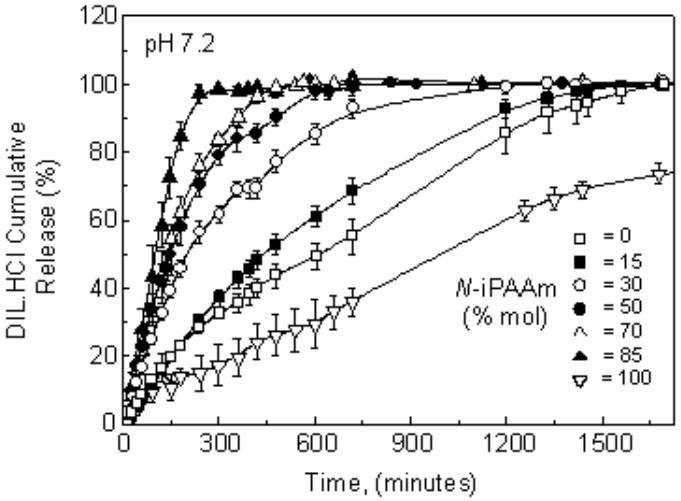

Figure 2. Release profiles of diltiazem hydrochloride from slabs of a series of P[(*N*-iPAAm)-*co*-(MAA)] copolymers containing a 30% wt/wt of drug loading, at pH 7.2 and 37°C.

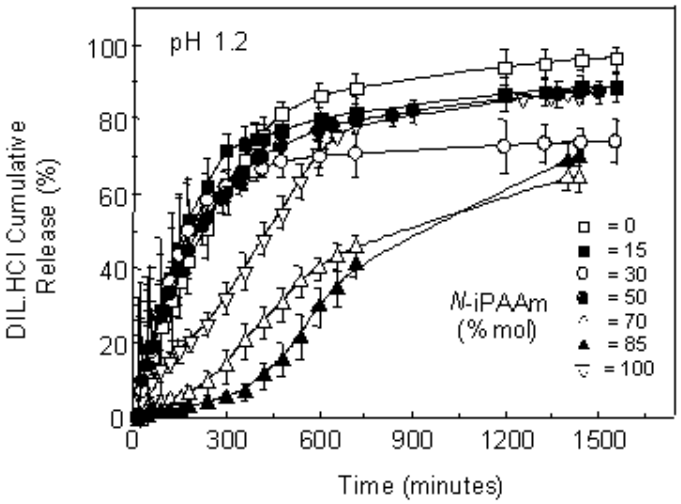

Figure 3. Release profiles of diltiazem hydrochloride from slabs of a series of P[(*N*-iPAAm)-*co*-(MAA)] copolymers containing a 30% wt/wt drug loading, at pH 1.2 and 37°C.

Dissolution Assays From Tablets

Figure 4 displays experimental release profiles from tablets of an 85% mol *N*-iPAAm content copolymer with 0.5% wt cross-linking agent containing a 30% wt/wt drug loaded at 37°C. A slab with dimensions similar to the tablets is included for comparison. The pH ramp goes from 1.2 to 7.2, and particle size varies from 0.09 to 5 mm.

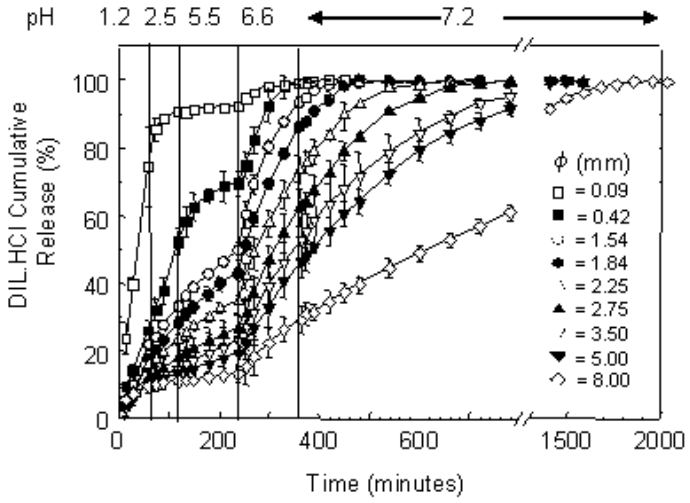

Figure 4. Influence of particle size and pH on the diltiazem hydrochloride release profiles from matrix tablets of an 85% mol *N*-iPAAm copolymer containing a 30% wt/wt drug loading at 37ºC. pH ramp as indicated on the top, particle size ranged from 0.09 to 5 mm. A slab with almost similar dimensions to tablets (8-mm diameter) is included for comparison purposes.

For the whole range of pH investigated, the drug release rate increased with decreasing particle size. However, there is a strong change in the release behavior for all particle size tablets at pH 6.6. Under more acidic media, the amount of DIL.HCl released increased when particle size decreased, but the shape of the curves indicates that not all the loaded drug would be delivered even for the smallest particle size tablets. In fact, a plateau corresponding to about 90% wt DIL.HCl released was reached for tablets of 0.09-mm diameter. After pH reached 6.6, a drastic change in the release behavior was observed; the release rate increased and the overall drug loaded was released after a time, depending on particle size. These results agree with swelling and disintegration assays. At acidic pH media, the swelling for this copolymer composition was almost negligible and tablets were not disintegrated. At higher pH, the tablets with this copolymer composition swelled and suffered disintegration, increasing the release amount and the release rate.

As a general rule, drug release behavior from swellable systems may be described by the power law expression, which describes the Fickian and non-Fickian release behavior of swelling-controlled release systems.[39-40] However, the release

process is controlled by the relationships between swelling/diffusion/dissolution mechanisms. We can consider that the swelling process is the limiting step under high pH medium because dissolution can be considered occurring instantaneously and the diffusion of DIL.HCl through the water-swelled gel is also a fast process. Otherwise, it has been experimentally observed that the DIL.HCl cumulative release M_t at pH ≥ 6.6 can be described according to a first order mechanism with an apparent rate constant k, by means of the following equation:

$$M_t = M_0 + M_\infty (1 - e^{-kt}) \quad (1)$$

where M_t is the amount of DIL.HCl released at time t; M_0 is the amount of DIL.HCl cumulative release up to pH 6.6; and M_∞ is the amount of DIL.HCl cumulative release when equilibrium is achieved.

Table 2. Kinetics Parameters Extracted From the Best Fit of the Experimental Diltiazem Hydrochloride Cumulative Release M_t Data to Equation 1 for Each Matrix Tablet of Particle Size ϕ, at pH ≥ 6.6*

ϕ (mm)	M_0	M_∞	k ·10² (min⁻¹)	R^2
0.09	92.48 (0.29)	7.71 (0.28)	2.26 (0.21)	0.9882
0.6	66.55 (1.31)	34.58 (1.29)	2.14 (0.2)	0.9883
1.54	47.91 (0.59)	52.85 (0.60)	1.60 (0.046)	0.9986
1.84	40.64 (1.03)	61.10 (1.08)	1.11 (0.050)	0.9962
2.25	33.49 (0.99)	69.08 (1.09)	0.73 (0.029)	0.9965
2.75	23.56 (1.27)	78.66 (1.39)	0.57 (0.024)	0.9948
3.5	21.02 (0.75)	80.72 (0.88)	0.42 (0.011)	0.9980
5	16.84 (0.87)	85.38 (1.08)	0.35 (0.011)	0.9973
8†	12.53 (1.16)	92.46 (1.79)	0.15 (0.009)	0.9946

*Determination coefficients, R^2, and standard errors (in brackets) are shown.

†A slab sample with dimensions similar to the tablets is included for comparison purposes.

Table 2 shows the releasing kinetics parameters and their standard errors extracted from the best fit of the experimental DIL.HCl cumulative release M_t to Equation 1. The fittings were performed for each tablet of particle size ϕ, at pH ≥ 6.6. As it can be seen, the high determination coefficients, R^2, and the low standard errors of regression parameters indicate the goodness of the fit, except for the tablets with the 2 smallest diameters. From the first and fourth columns in Table 2, we can see and conclude that the lower the particle diameter the higher the rate constant. Hence there exists an inverse proportionality between both parameters. If we assume that the particles are approximately spherical with a volume $V = (4/3)\pi r^3 = (4/3)\pi(\phi/2)^3$, then we may consider that $V \sim \phi^3$. The inverse relationship may be represented by a differential equation of the following type

$$\frac{dk}{d\phi} = \frac{A}{\phi^3} \quad (2)$$

which upon integration yields to

$$k = -\frac{C}{\phi^2} + B \quad (3)$$

where B could be interpreted as the limit of releasing rate constant. In Figure 5, values of the first order apparent release rate constant k have been plotted as a function of the inverse of the square of the average particle diameter $1/\phi^2$. The plot yields to the following regression parameters and their standard error: C = -3.4 10^{-2} (1.5 10^{-3}) min^{-1}; B = 1.3 10^{-3} (3.2 10^{-4}) min^{-1}. The goodness of the fit (R^2 = 0.9914) supports the assumption we have made to relate rate constant and particle size.

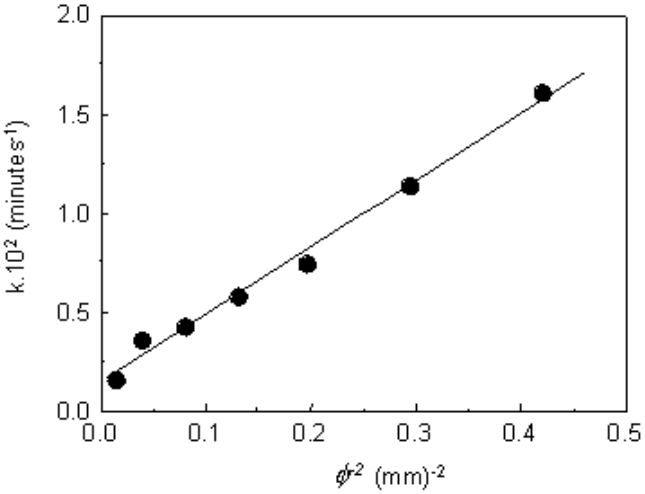

Figure 5. Dependence of the first order apparent release rate constant k on the square of the inverse particle size $1/\phi^2$.

CONCLUSION

The release of DIL.HCl from P[(*N*-iPAAm)-*co*-(MAA)] hydrogels depends strongly on copolymer composition. Enriched *N*-iPAAm hydrogel slabs would prevent DIL.HCl release in the stomach allowing drug release at the higher pH of the gastrointestinal tract. These facts indicate that enriched *N*-iPAAm hydrogels are suitable to be used as pH-modulated drug delivery systems. Controlling particle size in 85% mol *N*-iPAAm hydrogel tablets allows tailoring of the release rate of DIL.HCl. A relationship exists between release rate and particle diameter ϕ.

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