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Characterization of colon-specific azo polymers: A study of the swelling properties and the permeability of isolated polymer films

G. Van den Mooter [a,*], C. Samyn [b], R. Kinget [a]

[a] *Laboratorium voor Galenische en Klinische Farmacie, K.U. Leuven, B-3000 Leuven, Belgium*
[b] *Laboratorium voor Macromoleculaire en Fysisch-Organische Chemie, K.U. Leuven, Leuven, Belgium*

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Abstract

In order to prepare azo polymers for colonic targeting, copolymers of 2-hydroxyethyl methacrylate (HEMA) and methyl methacrylate (MMA), and terpolymers of HEMA, MMA, and methacrylic acid (MA) were synthesized in the presence of different azo compounds. In the present study, the azo polymers were characterized by swelling and permeability studies, performed on isolated films. It was shown that MMA is the swelling capacity and rate determining compound in the azo polymers investigated. Permeability experiments revealed that the diffusion of caffeine as well as the transmission of water vapour is proportional to the concentration of HEMA in the polymers. Hydrophilic plasticizers increase water vapour transmission and diffusion of caffeine through the films. By incorporation of MA into the azo polymers, pH dependency was introduced. The swelling behaviour and diffusion of caffeine are nearly constant over the pH range from 1 to 6. A sharp increase above pH 6, corresponding with the ionization of the carboxylic acid groups appears, with a maximum around pH 8.

Key words: Diffusion; Caffeine; Plasticizer; Permeability; Methacrylate polymer; Polymer swelling

1. Introduction

Pharmaceutical film coatings are widely used for the preparation of controlled release formulations.

Film forming materials can be either natural, semi-synthetic or synthetic polymers. Pharmaceutical films for the coating of dosage forms are xerogels, and different stages can be distinguished in the formation of a polymer film. Starting from a solution, where the polymer chains are isolated, the polymer concentration increases as the solvent evaporates, and finally, the isolated chains can penetrate each other, forming a polymer film (Osterwald, 1985).

The film forming process is controlled by cohesion forces between the polymer molecules and adhesion forces between the polymer molecules and the substrate, e.g., dosage forms.

* Corresponding author.

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The quality of a film is determined not only by the character and the properties of the polymer such as the molecular weight, the chemical structure and branching, but also by the interaction with the substrate and additives such as plasticizers and fillers. This makes the development of a film coating complex.

The film-controlled release of drugs is determined either by the dissolution properties of the film in the gastrointestinal tract or by its permeability to gastrointestinal fluids (Guo et al., 1991).

For the purpose of colon targeting, we developed different types of azo polymers suitable for the coating of oral dosage forms. Copolymers of 2-hydroxyethyl methacrylate (HEMA) and methyl methacrylate (MMA), and terpolymers of HEMA, MMA, and methacrylic acid (MA) were synthesized in the presence of different azo compounds (Table 1). The relative percentages of HEMA and MMA were varied to modify the degree of hydrophilicity and hence, the permeability of a given drug through the polymer membranes. As a consequence of the incorporation of MA, the azo polymers become pH-sensitive, and will show a higher degree of swelling, and a greater accessibility of the azo bonds for bacterial azo reductase in the neutral to slightly alkaline medium of the terminal ileum and large intestine.

Table 1
Composition of the azo polymers

Polymer	HEMA/MMA (w/w)	Azo agent
B0	[a]	B(MA)AB
B1	6:1	B(MA)AB
B2	5:1	B(MA)AB
B3	4:1	B(MA)AB
B4	3:1	B(MA)AB
S0	[a]	B(MOEOCA)AB
S1	6:1	B(MOEOCA)AB
S2	5:1	B(MOEOCA)AB
S3	4:1	B(MOEOCA)AB
S4	3:1	B(MOEOCA)AB
V0	[a]	DVAB
V1	6:1	DVAB
V2	5:1	DVAB
V3	4:1	DVAB
V4	3:1	DVAB
	HEMA/MMA/MA (w/w)	
P11	4:1:0.05	B(MOEOCA)AB
P12	9:2:0.10	B(MOEOCA)AB

DVAB, divinylazobenzene; B(MA)AB, *N,N'*-bis(methacryloylamino)azobenzene; B(MOEOCA)AB, *N,N'*-bis(methacryloyloxyethyloxycarbonylamino)azobenzene; HEMA, 2-hydroxyethyl methacrylate; MMA, methyl methacrylate; MA, methacrylic acid.

[a] No MMA was added.

Due to the presence of the azo bonds, the azo polymers are susceptible to degradation by gastrointestinal bacteria, based upon the reduction of the azo bond by bacterial azo reductase. The bacterial degradation of these and other azo polymers in vitro and in vivo has been reported elsewhere (Saffran et al., 1986; Brondsted and Kopecek, 1992; Van den Mooter et al., 1992, 1993) and it has been shown that the influence of hydrophilicity of the polymers on the degradation is very important. The site-specific degradation makes the azo polymers promising materials for the coating of oral dosage forms and to obtain colon-specific drug delivery.

The aim of the present study was to characterize the different azo polymers by studying their permeability and swelling characteristics using isolated films of the polymers. Permeability was investigated by water vapour transmission and diffusion of caffeine through the films. Since an excessively high permeability of a colon-specific coating will release a significant amount of drug before the colon is reached, there is a need to investigate the diffusion of dissolved molecules through the film under conditions comparable to the in vivo situation. On the other hand, a study of water vapour transmission yields valuable information on the protection against water uptake of a coated dosage form during storage.

Degradation of the azo polymers implies good accessibility of the azo bonds to bacterial azo reductase and this is related with the degree of swelling. Therefore, it is necessary to collect data on the relationship between the swelling characteristics of isolated films and their bacterial degradation.

2. Experimental

2.1. Materials

The azo polymers were synthesized as described previously (Van den Mooter et al., 1992, 1993). The composition of the azo polymers is given in Table 1.

Simulated gastric fluid and simulated intestinal fluid were prepared according to USP XXII.

All reagents for the preparation of the phosphate buffer solutions were of analytical grade (Merck, Darmstadt, Germany).

2.2. Preparation of isolated films

Polymer solutions containing 10% w/w of the azo polymers in ethanol were cast on a teflon-coated glass plate, using a film casting knife (Gardner Multicator type 411). To slow down solvent evaporation, the glass plate was covered with a funnel. After complete evaporation of the solvent, the films were removed from the glass plate, dried to constant weight, and stored in a desiccator until use. The thickness of the films was measured with a micrometer (Lorentzen and Wetters, Van der Heyden, Brussels, Belgium). In order to investigate the influence of hydrophilic plasticizers on the permeability of azo polymer films, the plasticizers were mixed together with the polymer solutions before casting.

The films prepared in this way are completely transparent.

2.3. Permeability study – diffusion of caffeine

Isolated films of the azo polymers were mounted between the donor and acceptor compartments of a diffusion cell. Three different experimental conditions were set up to examine the permeability of caffeine through pH-independent azo polymer films: the donor and acceptor compartment were both composed of (1) simulated gastric fluid (SGF); (2) simulated intestinal fluid (SIF); and (3) phosphate buffer (PB) (0.05 M) of pH 7.0. For polymers P11 and P12, the diffusion experiment was carried out in phosphate buffers covering the pH range from 3.0 to 8.5, and in 0.1 N HCl. The initial concentration of caffeine in the donor compartment was 0.0257 mol/l.

The amount of caffeine diffusing from the donor compartment through the polymer film into the acceptor compartment was spectrophotometrically determined at 272 nm.

In this diffusion experiment, pure polymer films as well as plasticized polymer films were used. The polymer films were plasticized either with propylene glycol (PG) and polyethylene glycol (PEG) 200 and 300 at a concentration of 20%, or PEG 400 used at concentrations ranging from 10 to 40%, all calculated on the basis of polymer weight.

The diffusion of caffeine through the isolated films can be described using the quasi-stationary state conditions as discussed by Flynn et al. (1974).

The rate of transfer of a diffusing substance through a membrane is expressed by Fick's first law:

$$dM/dt = -DS(dC/dx) \quad (1)$$

where dM/dt represents the rate of diffusion, D is the diffusion coefficient, S denotes the surface through which diffusion takes place, and dC/dx represents the concentration gradient. Since D is concentration dependent at higher solute concentration, only an average integral diffusion coefficient can be calculated in our experimental set up (Hwang and Kammermeyer, 1975).

When we assume that there is a linear fall of concentration within the film, the concentration gradient may be expressed as:

$$-dC/dx = (C_{m0} - C_{mh})/h \quad (2)$$

where C_{m0} and C_{mh} represent the surface concentration of the membrane at $x = 0$ and $x = h$, respectively. h denotes the film thickness.

From Eq. 1 and 2, we obtain:

$$dM/dt = DS(C_{m0} - C_{mh})/h \quad (3)$$

Eq. 3 presumes that the aqueous boundary layers on both sides of the membranes do not significantly affect the total transport process.

C_{m0} and C_{mh} can be related to concentrations

in the donor and acceptor compartment by incorporation of the partition coefficient K:

$$K = C_{m0}/C_d = C_{mh}/C_a \quad (4)$$

where C_d and C_a denote the respective solute concentrations in the donor and acceptor compartment at finite time.

The amount of diffusing substance in the membrane is negligibly small compared to that in the donor and acceptor compartment, so that:

$$C_d = (M_d - M)/V_d \quad (5)$$

and

$$C_a = (M_a + M)/V_a \quad (6)$$

where M_d and M_a are the respective amounts of diffusing substance in the donor and acceptor compartment when $t = 0$, M is the mass change, and V_d and V_a denote the volumes of the two compartments.

Eq. 3 can be written as follows:

$$\frac{dM}{dt} = \frac{DKS}{h}\left(\frac{M_d - M}{V_d} - \frac{M_a + M}{V_a}\right) \quad (7)$$

Integration of Eq. 7, and rearranging gives:

$$\frac{DKS}{h}t = \frac{V_d V_a}{V_d + V_a} \ln\left(\frac{M_d V_a - M_a V_d}{M_d V_a - M_a V_d - (V_d + V_a)M}\right) \quad (8)$$

Since $V_d = V_a = V$, and $M_a = 0$, Eq. 8 becomes:

$$\frac{2DKS}{hV}t = -\ln\left(\frac{M_d - 2M}{M_d}\right) \quad (9)$$

Since M_d/V is the solute concentration in the donor compartment at $t = 0$, and M/V denotes the solute concentration in the acceptor compartment at finite time, Eq. 9 becomes:

$$\frac{2DKS}{hV}t = -\ln\left(\frac{C_0 - 2C_a}{C_0}\right) \quad (10)$$

Since $(DK)/h = P$, P being the permeability coefficient, Eq. 10 becomes:

$$\frac{2PS}{V}t = -\ln\left(\frac{C_0 - 2C_a}{C_0}\right) \quad (11)$$

P can be calculated from a plot of $-\ln[(C_0 - 2C_a)/C_0]$ vs time. Note that D represents the average diffusion coefficient, and that the units of P are cm/s since h is included in the denominator.

2.4. Permeability study – water vapour transmission (WVT)

The study of WVT was carried out according to method B of ASTM designation E 96–66.

10 ml of demineralized water was put into a permeability cup (Payne permeability cup, Braive Instruments, Liège, Belgium), and the film was properly attached to the cup. The cup with the film was weighed and stored in a desiccator filled with silica gel. After 24, 48, 72, 96, and 120 h, the cup was reweighed to determine the permeated amount of water.

WVT was determined for plasticized and unplasticized films. The hydrophilic plasticizers used in the diffusion experiment were used at the same concentration as given before.

The results of the successive weighings were plotted against time. When a straight line fits the plot of the successive points, a nominally steady state exists, and the slope of the straight line is the rate of vapour transmission for the test area.

WVT standardized to a period of 24 h can be calculated using the following equation:

$$\mathrm{WVT} = g24/ta \quad (12)$$

where g is the weight loss, t denotes the time (in h) during which weight loss was followed and a represents the exposed area of film, which was 10 cm^2.

2.5. Swelling characteristics

Isolated films, approx. 1 cm in diameter, were prepared as described above. After evaporation of the solvent, the films were removed from the glass plate, dried for 14 days at 70°C in a vacuum oven, and stored in a desiccator until use.

The dry films were weighed and immersed in a buffer solution at 35°C for a specific period of time, after which they were removed from the

buffer solution, dried between filter paper and reweighed.

The swelling characteristics were investigated at pH 1.0 and 7.0, except for films of polymers P11 and P12. Since these polymers contain ionizable groups, it was interesting to investigate their swelling behaviour in the pH range from 1.0 to 8.0.

To quantify the swelling process, the swelling index, I_s (%), was calculated (Blanchon et al., 1991):

$$I_s(\%) = (W_s - W_d)/W_d \cdot 100 \quad (13)$$

where W_d is the weight of the dried polymer film and W_s denotes the weight after swelling.

To investigate the rate of swelling, we used the method of Schott (1992) which is an empirical approach to investigate the water uptake of polymer films. The rate of swelling at any given time t can be expressed as follows:

$$dW/dt = k(W_\infty - W_t) \quad (14)$$

where dW/dt is the rate of swelling, W_∞ denotes the maximum or equilibrium uptake of the swelling medium, W_t is the uptake at finite time, and k represents the proportionality constant between the rate of swelling and the unrealized swelling capacity.

Integration of Eq. 14 gives:

$$\ln(W_\infty/(W_\infty - W_t) = kt \quad (15)$$

From the definition of I_s, Eq. 15 can be transformed into the following equation:

$$\ln(I_{s_\infty}/(I_{s_\infty} - I_{s_t}) = k't \quad (16)$$

where I_{s_∞} represents the swelling index at the equilibrium uptake, I_{s_t} is the swelling index at finite time, and k' is the proportionality constant.

3. Results and discussion

3.1. Permeability experiments

3.1.1. Diffusion of caffeine

Fig. 1 shows a representative plot of the concentration of caffeine in the acceptor compartment, and $-\ln[(C_0 - 2C_a)/C_0]$ vs time. The data

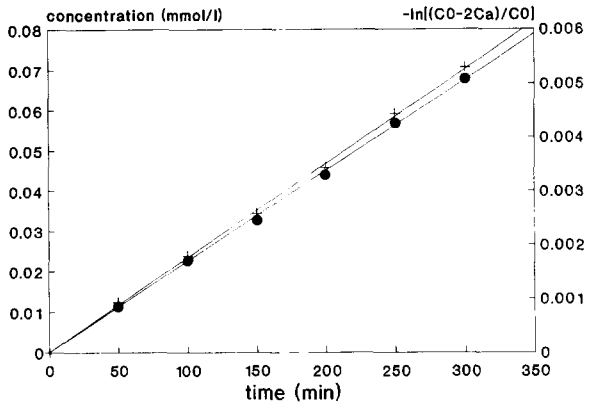

Fig. 1. Plot of the concentration in the acceptor compartment and $-\ln[(C_0 - 2C_a)/C_0]$ (•) vs time for polymer B1 plasticized with 20% w/w propylene glycol.

points were fitted using linear regression analysis. Correlation was in both cases > 0.99. Similar results were obtained with all the investigated polymers.

Table 2 shows the influence of the monomer composition on the diffusion of caffeine. The results demonstrate a large difference in permeability among the different polymers investigated. The permeability coefficient of caffeine increases significantly with increasing concentration of HEMA, which corresponds with increasing hydrophilicity of the polymers. No significant difference in permeability behaviour can be observed between different classes of azo polymers (B, S, and V) under the experimental conditions used. Since none of these polymers contain ionizable groups, the pH was not expected to influence the permeability of the films. This was confirmed by the data shown in Table 2.

From these data, one could conclude that polymer films showing the lowest permeability are the best coating materials with respect to premature release of the active agent in the small intestine. However, it has been shown previously (Van den Mooter et al., 1992, 1993) that only hydrophilic azo polymers are capable of being degraded by intestinal bacteria. Therefore, a balance must be found in the ratio between the amount of hydrophilic component which ensures good availability of the azo group for bacterial reduction, and the more hydrophobic component

Table 2
Influence of the polymer composition on the permeability coefficient of caffeine

Polymer	SGF	SIF	PB
B1	1.54	1.73	1.67
	(0.23)	(0.14)	(0.13)
B2	1.00	1.03	0.90
	(0.14)	(0.18)	(0.10)
B3	0.57	0.66	0.57
	(0.06)	(0.06)	(0.06)
B4	0.36	0.37	0.34
	(0.06)	(0.06)	(0.05)
B5	–	0.11	0.16
		(0.02)	(0.07)
S1	1.56	1.61	1.49
	(0.18)	(0.13)	(0.15)
S2	0.88	0.84	0.85
	(0.07)	(0.05)	(0.05)
S3	0.54	0.56	0.57
	(0.08)	(0.06)	(0.09)
S4	0.31	0.33	0.37
	(0.06)	(0.04)	(0.06)
V1	1.78	1.77	1.64
	(0.15)	(0.14)	(0.13)
V2	0.87	0.95	1.00
	(0.07)	(0.09)	(0.08)
V3	0.52	0.58	0.53
	(0.05)	(0.06)	(0.06)
V4	0.39	0.39	0.40
	(0.04)	(0.03)	(0.07)

Data are given with SD in parentheses. P is expressed in 10^{-5} cm/s.

which provides resistance to the gastrointestinal fluids.

To improve the quality of a film coating and to avoid film defects such as cracking, internal and external plasticizing techniques are available, and most often, external plasticizers are used for this purpose.

External plasticizing of the azo polymers could only be achieved with hydrophilic compounds such as PG and PEG, since the film forming polymers were not soluble or miscible with less hydrophilic plasticizers, e.g., diethyl phthalate, triacetine, castor oil, etc.

Data on the influence of hydrophilic plasticizers on the diffusion of caffeine through the azo polymer films are summarized in Table 3.

There was a small but significant increase in permeability when PEG 400 was used for B1. Raising the concentration of PEG 400 from 10% up to 40% did not affect the permeability. For polymers B2–B4, the permeability increased by 58, 73, and 109%, respectively, when 20% PEG 400 was added.

The strongly increased permeability for the less hydrophilic polymers might be explained by an increase in porosity of the film. PEG 400 is highly soluble in aqueous medium and is rapidly extracted from the film. As a consequence, small pores are created which caffeine molecules can permeate through. The same observations were reported for ethylcellulose films, plasticized with PEG (Donbrow and Friedman, 1975).

More hydrophilic polymers (B1) are less affected due to the higher swelling capacity of these materials. As a result of the swelling, the polymer chains are remote from each other and this, apparently, is more important than the pore-creating effect of PEG 400. However, this

Table 3
Influence of hydrophilic plasticizers on the permeability coefficient of caffeine

Polymer	Concentration of plasticizer	P
B1	10% PEG 400	2.21
		(0.18)
B1	20% PEG 400	2.19
		(0.21)
B1	30% PEG 400	2.49
		(0.26)
B1	40% PEG 400	2.27
		(0.17)
B1	20% PEG 200	2.22
		(0.16)
B1	20% PEG 300	2.57
		(0.20)
B1	20% PG	1.96
		(0.22)
B2	20% PEG 400	1.42
		(0.12)
B3	20% PEG 400	0.99
		(0.09)
B4	20% PEG 400	0.71
		(0.07)

This experiment was carried out in 0.05 M phosphate buffer, pH 7.0. Data are given with SD in parentheses. P is expressed in 10^{-5} cm/s.

pore-creating effect was evident during the first 15 min of the diffusion experiment. During this period, there was a steep increase in the concentration of caffeine in the acceptor compartment, followed by a uniform, linear increase for the rest of the experiment.

For polymers B2–B4, there was a linear increase in the concentration of caffeine from the beginning of the experiment.

No significant difference was observed between PEG 200, PEG 300, PEG 400, and PG, in the way these plasticizers increased the permeability of polymer B1.

The result of the diffusion experiment for polymer P12 is given in Fig. 2. The same profile was observed for polymer P11. An almost constant value in permeability from pH 1 to 6 is observed, followed by a steep increase and a maximum value around pH 8. The sharp increase at pH 6.5 is the result of the ionization of the carboxylic acid groups of MA.

The calculations of P for polymer P12 at pH 7, 7.5, 8, and 8.5 were based on the first 2 h of the diffusion experiment, since only in this period of time was a linear increase in the concentration of caffeine in the acceptor compartment found. Subsequently, the increase in concentration of caffeine was no longer linear due to the highly swollen state of the polymer film, and permeability was almost unlimited.

3.1.2. Water vapour transmission

It is apparent from Table 4 that the concentration of the casting solution has an influence on the water vapour transmission. The entanglement between the neighbouring chains will be more intensive when the polymer concentration is raised, resulting in films which are more tightly packed.

It is clear that permeation of water vapour is affected by the composition of the azo polymers. Water vapour transmission depends on the concentration of HEMA in the polymers, which corresponds with increased hydrophilicity.

The incorporation of carboxylic acid groups into the azo polymers seems to exert little influence, if any, on the permeation of water vapour. The values obtained for P11 and P12 are comparable with those of B3 and B2, respectively.

Hydrophilic plasticizers will increase the water

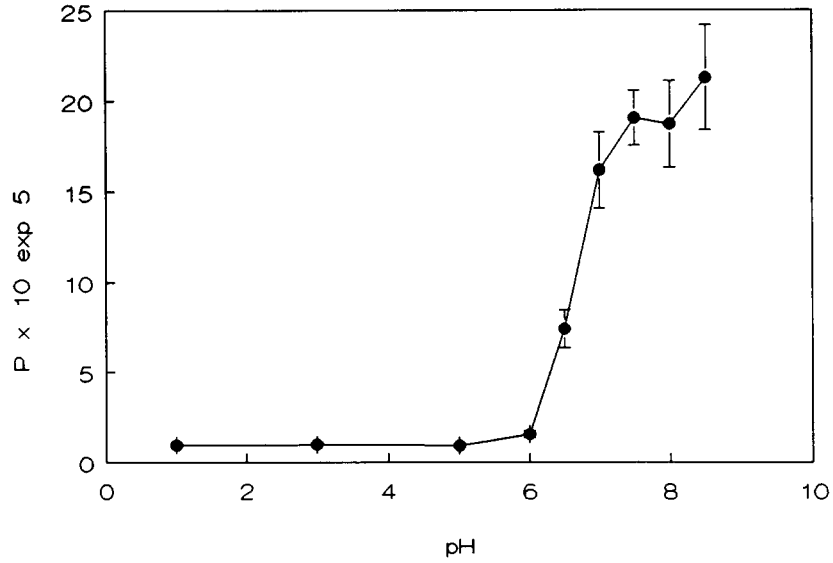

Fig. 2. pH dependence of the permeability coefficient (cm/s) of caffeine in a diffusion experiment with isolated films of polymer P12.

vapour transmission due to their excellent water solubility (Table 5). The addition of 10% of PEG 400 (calculated on the film forming material) results in a rise in water vapour transmission of approx. 30%, but a further increase of PEG 400 has, surprisingly, no effect.

3.2. Swelling characteristics

The results of the swelling experiments of non-ionizable azo copolymers are combined in

Table 4
Influence of the polymer composition and polymer concentration in the casting liquid on WVT

Polymer	Concentration (% w/w)	Film thickness (μm)	WVT (g/24 h per m^2)	g/t (g/h)
B1	4	44	763	0.0318
		36	781	0.0325
		32	782	0.0326
B1	7	38	650	0.0271
		42	642	0.0267
		41	647	0.0270
B1	10	36	522	0.0217
		36	519	0.0216
		42	508	0.0212
B2	10	38	496	0.0207
		41	482	0.0201
		46	480	0.0200
B3	10	27	476	0.0198
		34	470	0.0196
		38	468	0.0195
B4	10	31	460	0.0192
		28	462	0.0192
		37	457	0.0190
S1	10	38	512	0.0213
		44	499	0.0208
		40	504	0.0210
V1	10	46	497	0.0207
		32	510	0.0212
		34	510	0.0212
P11	10	33	470	0.0196
		33	462	0.0193
		37	471	0.0196
P12	10	38	477	0.0199
		41	472	0.0197
		33	481	0.0200

Table 5
Influence of the hydrophilic plasticizer on WVT of polymer B1

Plasticizer	Concentration	Film thickness (μm)	WVT (g/24 h per m^2)	g/t (g/h)
PEG 400	10%	41	690	0.0287
		38	701	0.0292
		33	710	0.0296
	20%	35	699	0.0291
		39	709	0.0295
		40	702	0.0292
	30%	49	688	0.0287
		38	720	0.0300
		37	714	0.0297
PEG 200	20%	33	701	0.0292
		37	689	0.0287
		43	680	0.0283
PEG 300	20%	38	704	0.0293
		34	710	0.0296
		29	721	0.0300
PG	20%	31	719	0.0300
		37	696	0.0290
		40	690	0.0288

The concentration of polymer in the casting liquid was 10% w/w.

Table 6. The equilibrium stage of swelling for all polymers is reached between 10 and 40 min residence time in the medium, depending on the composition of the polymers. As expected, polymers containing a higher concentration of HEMA reach the equilibrium degree of swelling faster and the swelling index (I_s (%)) is greater. There is a large difference between B0 and azo polymers containing MMA. From these results it is clear that MMA impedes the swelling of the polymers and therefore will reduce the availability of the azo bonds for reduction by intestinal bacteria. These results are in good agreement with degradation studies that we performed on these polymers (Van den Mooter et al., 1993). It was found that the concentration of MMA in the polymers was a degradation limiting factor.

The incorporation of different azo aromatic groups has no influence on their swelling behaviour. Hence, with respect to the availability of the azo bond, the three different types of azo polymers are equivalent.

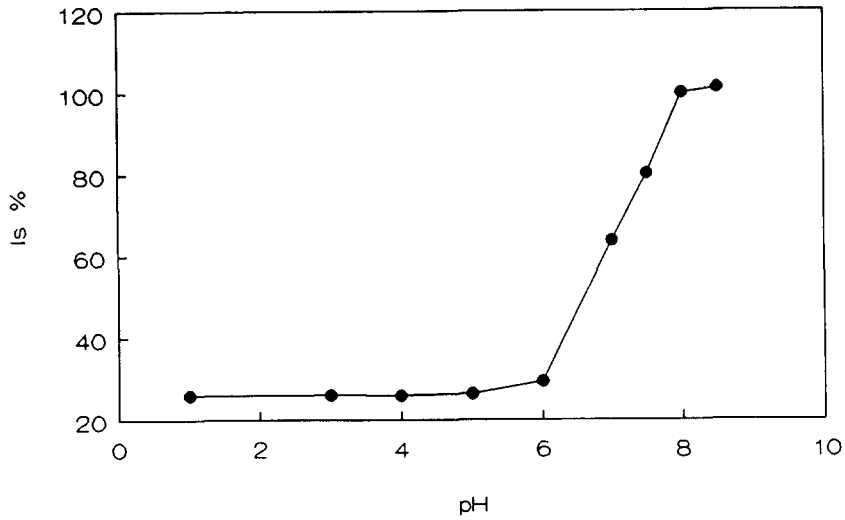

Fig. 3. pH dependence of the swelling index of polymer P12.

The absence of an ionizable group in the polymers explains why the swelling behaviour is independent of the pH. This means that in both gastric and intestinal juice, the polymers have the same degree of swelling. This is not advantageous since good availability of the azo bonds is only needed in the large intestine and a high degree of swelling of the film coating in the stomach or the small intestine could lead to premature release of the active ingredient due to diffusion through the coating.

Therefore, we developed pH-sensitive azo polymers having a degree of swelling that increases when passing from acidic to neutral or slightly alkaline pH, resulting in high accessibility of the azo bonds in the colon, without premature

Table 6
I_s (%) and k' of azo polymers at 35°C in 0.05 M phosphate buffer (pH 7)

t (min)	B0	B1		B2	B3	B4	B5	V1	S1
		pH 1 [a]	pH 7						
0	0	0	0	0	0	0	0	0	0
1	19.21	13.01	13.79	9.41	6.00	2.47	1.76	14.17	13.98
2	34.87	21.03	20.57	14.26	10.30	5.56	2.55	21.02	20.74
3	48.01	26.09	26.64	18.08	14.09	7.79	5.16	26.84	26.41
	(5.60)	(3.12)	(2.56)	(2.02)	(1.41)	(0.63)	(0.88)	(4.05)	(3.25)
4	53.07	29.56	28.92	21.38	17.38	11.74	6.14	29.14	28.86
5	55.00	31.72	30.82	25.11	20.82	14.32	7.94	31.34	31.61
6	55.96	32.32	32.11	26.91	22.39	17.02	9.02	32.61	32.54
7	56.12	33.07	33.78	29.00	25.17	19.21	10.31	34.44	33.94
	(4.32)	(2.22)	(2.65)	(1.54)	(1.78)	(1.89)	(2.32)	(2.41)	(2.65)
10	57.24	35.12	34.82	30.56	25.09	22.62	13.35	34.34	35.12
15	56.88	35.38	34.74	30.49	26.80	23.04	15.76	35.14	35.62
40	57.01	35.31	34.95	30.91	27.01	22.98	16.92	35.78	35.89
k'	0.674	0.422	0.416	0.333	0.295	0.220	0.134	0.401	0.397
r	0.996	0.996	0.997	0.993	0.995	0.981	0.993	0.997	0.998

SD is indicated in parentheses; k' is expressed in min^{-1}.
[a] Carried out in HCl (0.1 N).

release of the active agent. It has already been shown by Ulbrich and co-workers (1982) and Brondsted and Kopecek (1992) that enzymatic degradation of crosslinks in hydrogels depends largely on their equilibrium degree of swelling.

Fig. 3 depicts the progress of I_s (%) as a function of pH for polymer P12. The same profile was found for polymer P11. I_s (%) is nearly constant in the pH range from 1 to 6 but exhibits a sharp increase above pH 6, corresponding with the ionization of the carboxylic acid groups of MA. The same profile was also found for the diffusion of caffeine (Fig. 2), indicating that the results of both experiments were in good agreement. For polymer P11, I_s (%) increases by approx. 230% at pH 7.5; under the same conditions polymer P12 shows an increase in I_s (%) of approx. 300%. It is surprising that such a small amount of MA can affect the degree of swelling so much. Because of extensive swelling above pH 6, the equilibrium degree of swelling was reached after approx. 3 h for P11, and 4 h for P12.

Eq. 16 can be used to compare the swelling rate of the azo polymers and can be applied for periods longer than 80% of the time needed to reach the equilibrium degree of swelling. A linear relationship was found between $\ln(I_{s_\infty}/I_{s_\infty} - I_{s_t})$ and time (except for B4, $r > 0.99$). The increase in k' is proportional to the concentration of HEMA in the azo polymers for the concentration range investigated (Table 6). This result confirms that MMA is both the swelling rate and swelling capacity determining compound in the azo polymers investigated.

Eq. 16 cannot be applied to describe the swelling process of the pH-dependent azo polymers. The ionization of the carboxylic acid groups will result in a stress relaxation of the polymers as a result of hydratation of these functional groups. The discussion of this complicated process is beyond the scope of this paper.

4. Conclusion

The results of this study indicate that pH-sensitive azo polymers are more promising materials for colonic targeting than pH-insensitive azo polymers. Isolated films of the first exhibit minor swelling properties and a low permeability of caffeine below pH 7, but a high degree of swelling and a high permeability of caffeine above pH 7 as a result of the neutralization of the carboxylic acid groups of MA. Therefore, release of an active agent in the stomach or small intestine will not occur, and due to the high degree of swelling in the colonic environment, the azo bonds are more accessible for bacterial azo reductase.

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