*International Journal of Pharmaceutics*, 97 (1993) 133–139



IJP 03115

# Azo polymers for colon-specific drug delivery. II: Influence of the type of azo polymer on the degradation by intestinal microflora

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(Received 8 July 1992)
(Modified version received 20 October 1992)
(Accepted 9 November 1992)

*Key words*: Colon targeting; Selective drug delivery; Azo polymer; Biodegradable coating; Permeability; Solution viscosity

**Summary**

Degradation by gastrointestinal microflora of different azo polymers was studied by performing permeability experiments on isolated films and solution viscosity measurements before and after incubation in Schaedler broth, inoculated with human feces. The investigated azo polymers were different in monomer composition (hydroxyethyl methacrylate/methyl methacrylate ratio) and azo aromatic group (divinylazobenzene, *N,N'*-bis(methacryloylamino)azobenzene and *N,N'*-bis(methacryloyloxyethyloxycarbonylamino)azobenzene). The degradation of the azo polymers was strongly affected by the hydrophilicity of the polymers. The chain length of the azo aromatic groups, built into the azo polymers, seems to be of little influence on the degradation rate of the polymers.

## Introduction

Oral, colon-specific drug delivery has attracted much interest recently. Delivery of drugs to the colon can be achieved in several ways. Four different types of delivery systems can be distinguished: prodrugs (Peppercorn and Goldman, 1972; Khan et al., 1983; Friend and Chang, 1984; Klotz, 1985; Friend and Tozer, 1992), pH-sensitive coatings (Lehmann, 1975), biodegradable hydrogels (Bronsted and Kopecek, 1991; Kopecek et al., 1992) and biodegradable coatings (Saffran, 1986).

Recently, new, pH-independent, biodegradable copolymers were developed in order to prepare biodegradable coatings (Van den Mooter et al., 1992). Selectivity and the unlimited amount of drug which can be administered are two major benefits of pH-independent, biodegradable coatings.

In this paper, our objective was to investigate the degradation of different types of azo polymers. The influence of the type of azo aromatic molecule, built in the azo polymers, and of the

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degree of hydrophilicity of the azo polymer, on the degradation by intestinal microflora are discussed. Three types of azo aromatic molecules were examined: divinylazobenzene, *N,N'*-bis-(methacryloylamino)azobenzene and *N,N'*-bis-(methacryloyloxyethyloxycarbonylamino)azobenzene. Degradation of the azo polymers was studied using solution viscosity and permeability of isolated polymer films.

## Materials and Methods

### *Materials*

HEMA and MMA (both Janssen Chimica, Beerse, Belgium) were purified by vacuum distillation. Azobisisobutyronitrile (AIBN) (Janssen Chimica, Beerse, Belgium) was recrystallized from methanol. Triethylamine, tetrahydrofuran and triphosgene (all Janssen Chimica, Beerse, Belgium) were used without further purification. Ethanol and methylene chloride were purified by distillation.

### *Instrumentation*

In vitro degradation tests were carried out in a Compact Anaerobic Workstation (DW Scientific, West Yorkshire, U.K.).

UV absorption measurements were carried out with a HP8452A diode array spectrophotometer equipped with a HP vectra 286/12 computer (Hewlett Packard Co., Santa Clara, CA, U.S.A.).

NMR spectra were recorded with a Varian EM 390 NMR spectrometer (Varian Assoc., CA, U.S.A.).

### *Synthesis of azo agents*

*N,N'-Bis(methacryloylamino)azobenzene (B(MA)AB)* B(MA)AB was synthesized as described elsewhere (Van den Mooter et al., 1992).

*Divinylazobenzene (DVAB)* DVAB was prepared according to the method of Kumar et al. (1985).

*Synthesis of N,N'-bis(methacryloyloxyethyloxycarbonylamino)azobenzene (B(MOEOCA)AB)* To a solution of 6.5 g (50 mmol) of 2-hydroxyethyl methacrylate, 5.7 g (19 mmol) of triphosgene and 10 mg of hydroquinone, dissolved in 100 ml of dry tetrahydrofuran, was added dropwise under stirring and cooling, 7.3 ml (55 mmol) of triethylamine. The reaction mixture was then left at room temperature for 1 week.

After 1 week, the mixture was intensively purged with a nitrogen stream to evaporate the excess of phosgene and filtered. Evaporation under diminished pressure (rotovapor) of the filtrate gave a viscous liquid, the chloroformate of 2-hydroxyethyl methacrylate.

4.81 g (25 mmol) of the chloroformate was dissolved in 50 ml of dry tetrahydrofuran. This solution was added dropwise under stirring and cooling to a solution of 2.12 g (10 mmol) of diaminoazobenzene in 50 ml of dry tetrahydrofuran to which 4.3 ml (30 mmol) of triethylamine was added. After addition of the chloroformate, the reaction mixture was left at room temperature for 2 days.

After 2 days, the mixture was filtered and the filtrate was evaporated under vacuum. The residue was dissolved in chloroform and washed three times with distilled water. The organic layer was dried over anhydrous sodium sulfate and evaporated under diminished pressure.

TLC analysis ($CHCl_3$–$CH_3CN$ 80:20) revealed a minor impurity. The reaction product was purified with column chromatography ($CHCl_3$–$CH_3CN$ 80:20) and recrystallized three times from ethanol. Yield: 1.3 g (25%); m.p. 178–179°C. $^1$H-NMR in dimethyl sulfoxide-$d_6$ ($\delta$ in ppm): $\delta$ 1.93 ($CH_3$, 6H); $\delta$ 4.43 ($-OCH_2CH_2O-$, 8H); $\delta$ 5.65 and 6.13 ($CH_2=$, 4H); $\delta$ 6.75 (NH, 2H); $\delta$ 7.80 (aromatic protons, 8H). UV (EtOH): $\lambda_{max}$ 366 nm.

### *Synthesis of azo polymers*

Copolymers of HEMA and MMA were prepared via a free radical mechanism using AIBN as initiator. All polymerizations were carried out at 60°C in a mixture of methanol and methylene chloride (50:50).

The ratio of HEMA to MMA was 6:1; 5:1 or 4:1, respectively. The overall concentration of monomers, in order to obtain soluble copolymers,

TABLE 1

*Composition of the azo polymers*

| Polymer | HEMA/MMA | Azo agent |
|---|---|---|
| B1 | 6:1 | B(MA)AB |
| B2 | 5:1 | B(MA)AB |
| B3 | 4:1 | B(MA)AB |
| S1 | 6:1 | B(MOEOCA)AB |
| S2 | 5:1 | B(MOEOCA)AB |
| S3 | 4:1 | B(MOEOCA)AB |
| V1 | 6:1 | DVAB |
| V2 | 5:1 | DVAB |
| V3 | 4:1 | DVAB |

was never higher than 7% w/w. The amount of azo agent, added to the reaction mixture, was 0.7 mol%, with respect to monomer concentration.

The azo polymers were isolated and purified by repeated precipitation in diethyl ether. The yield after 24 h of reaction was about 80%. The inherent viscosity in dimethylformamide at 24°C was 0.8 (0.2 g/dl). Table 1 gives the composition of the different azo polymers.

*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 at 35°C and stored in a desiccator for 2 weeks. The thickness of the films was measured with a micrometer (Lorentzen & Wetters, Van der Heyden, Brussel, Belgium), and varied between 35 and 44 $\mu$m.

*Bacterial degradation tests*

In order to quantify the degradation of the azo polymer films by gastrointestinal bacteria, intrinsic viscosity and permeability of isolated films was determined before and after incubation in Schaedler broth, inoculated with human feces. The control films were incubated in Schaedler broth only.

*Permeability measurements*

The permeability of isolated films was studied by determination of the diffusion of caffeine through the films. The films were mounted between the donor and acceptor compartment of a diffusion cell. The amount of caffeine diffusing from the donor to the acceptor compartment was spectrophotometrically determined at 272 nm.

Supposing that diffusion of caffeine through the polymer films takes place under steady state conditions, then:

$$C_2 = PSC_1 t / xV_2 \text{ (Peeters, 1990)}$$

where $C_2$ is the concentration of caffeine in the acceptor compartment, $C_1$ denotes the concentration of caffeine in the donor compartment, $S$ is the surface area of the polymer membrane, $x$ represents the thickness of the film, $V_2$ is the volume of the acceptor compartment, $P$ denotes the permeability constant and $t$ is the time.

$P$ can be calculated from the graph of $C_2$ as a function of time.

*Solution viscosity measurements* Intrinsic viscosities were determined using a Ubbelohde capillary viscometer at a constant temperature of 24°C.

After incubation, the azo polymer films were intensively rinsed with distilled water, dried to constant weight, dissolved in dimethylformamide and filtered through a glass filter (pore size 20–40 $\mu$m). The solution concentration was restricted to the range that gives relative viscosities ($\eta_{rel}$) between 1.1 and 1.5.

Efflux times of the polymer solutions were determined and the respective specific viscosities ($\eta_{sp}$) calculated. By converting $\eta_{sp}$ to reduced viscosity ($\eta_r$) and plotting these values against concentration, the intrinsic viscosities ($[\eta]$) were obtained by extrapolation to infinite dilution by means of Huggins' equation:

$$\eta_{sp}/C = [\eta] + k'[\eta]^2 C$$

where $C$ is the concentration of the polymer solution, expressed in g/dl, and $k'$ denotes a constant of a series of polymers of different molecular weights in a given solvent.

## Results and Discussion

*Permeability measurements*

The results of the permeability measurements are given in Tables 2–4.

All polymer films show a significant increase in $P$ after incubation, compared to the control films. The increase in $P$ is significantly different for polymers with high or low HEMA content; it is inversely proportional to the MMA content. No value for $P$ could be calculated after 24 and 48 h for films of polymers B1, S1 and V1 and after 48 h for films of polymers B2, S2 and V2. These films show a high amount of irregularly shaped holes after incubation. The appearance of holes in the polymer films can probably be explained as a consequence of azo reduction and splitting of the azo bond, followed by massive water uptake and extensive swelling of the neighbouring polymer chains, resulting in a local rupture of the film surface.

The influence of the different azo agents incorporated is not very large, but a significant difference in $P$, however, is observed for B3, S3 and V3. After 48 h, the value of $P$ for S3 is 2-fold greater than those of V3 and B3 ($35.61 \times 10^{-10}$ $cm^2/s$ vs $21.99 \times 10^{-10}$ and $17.22 \times 10^{-10}$ $cm^2/s$, respectively). Fig. 1 shows the structural formulae of the different incorporated azo agents. The distance between the azo group and the vinyl groups is larger for B(MOEOCA)AB than for B(MA)AB and DVAB. This could make the azo groups more readily accessible and explain why polymers with B(MOEOCA)AB are more sensitive to bacterial azo reduction.

In previously reported permeability experiments (Van den Mooter et al., 1992), the azo polymer films were incubated in a salt solution inoculated with human feces instead of the

TABLE 2

*Permeability of isolated films of polymers B before ( = P blanc) and after incubation ( = P test)*

| Polymer | Time (h) | $P$ blanc | $P$ test |
|---|---|---|---|
| B1 | 0 | 6.20 (±0.44) | 6.20 (±0.44) |
| | 12 | 5.94 (±0.52) | 34.35 (±11.10) |
| | 24 | 6.14 (±0.56) | – |
| | 48 | 6.31 (±0.42) | – |
| B2 | 0 | 3.64 (±0.31) | 3.64 (±0.31) |
| | 12 | 3.42 (±0.41) | 5.70 (±0.59) |
| | 24 | 3.44 (±0.29) | 34.91 (±7.02) |
| | 48 | 3.54 (±0.51) | – |
| B3 | 0 | 2.61 (±0.31) | 2.61 (±0.31) |
| | 12 | 2.37 (±0.47) | 3.61 (±0.21) |
| | 24 | 2.59 (±0.31) | 8.80 (±0.97) |
| | 48 | 2.49 (±0.32) | 17.22 (±3.12) |

$P$ is expressed in $10^{-10}$ $cm^2/s$. Data are given ± SD.

TABLE 3

*Permeability of isolated films of polymers S before ( = P blanc) and after incubation ( = P test)*

| Polymer | Time (h) | $P$ blanc | $P$ test |
|---|---|---|---|
| S1 | 0 | 5.41 (±0.61) | 5.41 (±0.61) |
| | 12 | 5.92 (±0.54) | 41.20 (±9.10) |
| | 24 | 5.43 (±0.72) | – |
| | 48 | 5.85 (±0.61) | – |
| S2 | 0 | 3.31 (±0.41) | 3.31 (±0.41) |
| | 12 | 3.22 (±0.39) | 7.41 (±0.54) |
| | 24 | 3.47 (±0.42) | 43.70 (±4.27) |
| | 48 | 3.41 (±0.36) | – |
| S3 | 0 | 2.56 (±0.31) | 2.56 (±0.31) |
| | 12 | 2.78 (±0.32) | 7.46 (±0.92) |
| | 24 | 2.47 (±0.46) | 12.86 (±1.41) |
| | 48 | 2.31 (±0.57) | 35.61 (±5.22) |

$P$ is expressed in $10^{-10}$ $cm^2/s$. Data are given ± SD.

TABLE 4

*Permeability of isolated films of polymers V before ( = P blanc) and after incubation ( = P test)*

| Polymer | Time (h) | $P$ blanc | $P$ test |
|---|---|---|---|
| V1 | 0 | 5.97 (±0.41) | 5.97 (±0.41) |
| | 12 | 6.21 (±0.38) | 33.16 (±8.12) |
| | 24 | 6.16 (±0.46) | – |
| | 48 | 6.25 (±0.38) | – |
| V2 | 0 | 3.38 (±0.30) | 3.38 (±0.30) |
| | 12 | 3.57 (±0.48) | 6.69 (±0.62) |
| | 24 | 3.52 (±0.51) | 37.51 (±4.51) |
| | 48 | 3.67 (±0.22) | – |
| V3 | 0 | 2.47 (±0.33) | 2.47 (±0.33) |
| | 12 | 2.31 (±0.28) | 4.26 (±0.77) |
| | 24 | 2.61 (±0.41) | 9.04 (±0.98) |
| | 48 | 2.51 (±0.37) | 21.99 (±3.12) |

$P$ is expressed in $10^{-10}$ $cm^2/s$. Data are given ± SD.

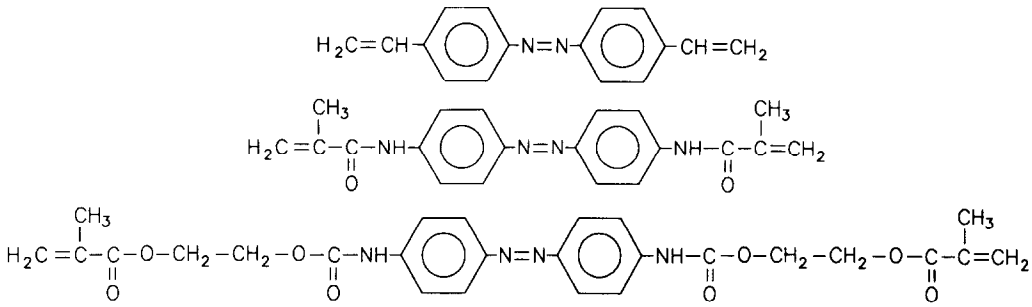

Fig. 1. Structural formulae of DVAB (a), B(MA)AB (b) and B (MOEOCA)AB (c).

Schaedler broth and resulted in lower values of $P$. This can be explained by the fact that Schaedler broth is a better growth medium for anaerobic bacteria then the salt solution.

*Solution viscosity measurements*

Intrinsic viscosity can be used to calculate molecular weights of polymers according to the equation of Mark-Houwink:

$$[\eta] = KM^a$$

in which $K$ and $a$ are constants characteristic of a particular polymer-solvent system. Although this empirical relation between viscosity and molecular weight is valid only for linear polymers, a change in intrinsic viscosity for branched polymers can be correlated with a change in molecular weight.

Since DVAB, B(MA)AB and B(MOEOCA)AB are covalently bound in the azo polymers, reduction followed by splitting of the azo bond by intestinal microflora must result in a decrease in the molecular weight of the polymer and therefore a diminution of viscosity.

The results of our experiments are summarized in Tables 5–7 and show the decay of intrinsic viscosity as a function of incubation time.

After 24 h incubation, intrinsic viscosity dropped by more than 30% of the initial value for B1, S1 and V1, almost 25% for B2, S2 and V2 and by about 15% for B3, S3 and V3, indicating a decrease in molecular weight of the azo polymers caused by bacterial degradation. Intrinsic viscosity decreases more rapidly for polymers with the highest content of HEMA. These results clearly indicate that the rate of azo reduction is directly proportional to the content of HEMA in the polymers.

In theory, the degradation of the azo polymers can continue until the molecular weight of the

TABLE 5

*Influence of incubation time on viscosity of polymer B*

| Polymer | Incubation time (h) | Conc. (g/dl) | $\eta_r$ | $\eta_{int}$ |
|---|---|---|---|---|
| B1 | 0 ( = blanc) | 0.150 | 0.889 | 0.838 |
| | | 0.202 | 0.915 | |
| | | 0.247 | 0.925 | |
| | 12 | 0.195 | 0.700 | 0.658 |
| | | 0.254 | 0.708 | |
| | | 0.306 | 0.723 | |
| | 24 | 0.189 | 0.596 | 0.564 |
| | | 0.239 | 0.610 | |
| | | 0.294 | 0.615 | |
| B2 | 0 ( = blanc) | 0.174 | 0.925 | 0.857 |
| | | 0.221 | 0.939 | |
| | | 0.271 | 0.964 | |
| | 12 | 0.190 | 0.808 | 0.754 |
| | | 0.255 | 0.829 | |
| | | 0.296 | 0.838 | |
| | 24 | 0.200 | 0.705 | 0.658 |
| | | 0.251 | 0.721 | |
| | | 0.304 | 0.730 | |
| B3 | 0 ( = blanc) | 0.180 | 0.932 | 0.864 |
| | | 0.262 | 0.959 | |
| | | 0.311 | 0.981 | |
| | 12 | 0.210 | 0.865 | 0.804 |
| | | 0.259 | 0.884 | |
| | | 0.296 | 0.890 | |
| | 24 | 0.225 | 0.808 | 0.750 |
| | | 0.261 | 0.819 | |
| | | 0.295 | 0.826 | |

polymers has reached the molecular weight of the chains between the azo bonds and this is limited by the concentration of azo aromatic groups in the azo polymers. Raising the concentration of azo bonds in the polymers should offer the possibility of degrading the polymers to lower molecular weight, but care must be taken to prevent chemical crosslinking. The addition of 0.7 mol% of azo aromatic compound is almost the limit to obtain soluble azo polymers.

Although the influence of the HEMA content (or degree of hydrophilicity) is more important, the influence of the different crosslinking agents on the degradation of the azo polymers cannot be completely ignored. The differences in intrinsic viscosity after 12 and 24 h incubation between B, S and V are only 3% at most, but it appears that

TABLE 6

*Influence of incubation time on viscosity of polymer S*

| Polymer | Incubation time (h) | Conc. (g/dl) | $\eta_r$ | $\eta_{int}$ |
|---|---|---|---|---|
| S1 | 0 ( = blanc) | 0.141 | 0.899 | 0.845 |
| | | 0.261 | 0.939 | |
| | | 0.303 | 0.962 | |
| | 12 | 0.165 | 0.686 | 0.651 |
| | | 0.236 | 0.700 | |
| | | 0.325 | 0.719 | |
| | 24 | 0.176 | 0.594 | 0.559 |
| | | 0.249 | 0.602 | |
| | | 0.314 | 0.620 | |
| S2 | 0 ( = blanc) | 0.151 | 0.934 | 0.872 |
| | | 0.205 | 0.948 | |
| | | 0.275 | 0.982 | |
| | 12 | 0.170 | 0.815 | 0.766 |
| | | 0.261 | 0.845 | |
| | | 0.316 | 0.857 | |
| | 24 | 0.200 | 0.712 | 0.663 |
| | | 0.265 | 0.723 | |
| | | 0.312 | 0.739 | |
| S3 | 0 ( = blanc) | 0.162 | 0.935 | 0.872 |
| | | 0.225 | 0.952 | |
| | | 0.300 | 0.986 | |
| | 12 | 0.180 | 0.853 | 0.803 |
| | | 0.250 | 0.877 | |
| | | 0.321 | 0.893 | |
| | 24 | 0.174 | 0.772 | 0.731 |
| | | 0.249 | 0.795 | |
| | | 0.305 | 0.803 | |

TABLE 7

*Influence of incubation time on viscosity of polymer V*

| Polymer | Incubation time (h) | Conc. (g/dl) | $\eta_r$ | $\eta_{int}$ |
|---|---|---|---|---|
| V1 | 0 ( = blanc) | 0.175 | 0.904 | 0.834 |
| | | 0.231 | 0.929 | |
| | | 0.285 | 0.947 | |
| | 12 | 0.164 | 0.700 | 0.662 |
| | | 0.254 | 0.715 | |
| | | 0.310 | 0.733 | |
| | 24 | 0.200 | 0.612 | 0.577 |
| | | 0.272 | 0.622 | |
| | | 0.315 | 0.632 | |
| V2 | 0 ( = blanc) | 0.185 | 0.915 | 0.846 |
| | | 0.279 | 0.955 | |
| | | 0.315 | 0.962 | |
| | 12 | 0.196 | 0.783 | 0.732 |
| | | 0.251 | 0.803 | |
| | | 0.305 | 0.812 | |
| | 24 | 0.200 | 0.676 | 0.632 |
| | | 0.259 | 0.692 | |
| | | 0.307 | 0.700 | |
| V3 | 0 ( = blanc) | 0.150 | 0.936 | 0.880 |
| | | 0.201 | 0.951 | |
| | | 0.249 | 0.972 | |
| | 12 | 0.202 | 0.870 | 0.812 |
| | | 0.274 | 0.888 | |
| | | 0.310 | 0.901 | |
| | 24 | 0.180 | 0.803 | 0.763 |
| | | 0.219 | 0.817 | |
| | | 0.304 | 0.833 | |

polymers containing B(MOEOCA)AB are slightly more susceptible to bacterial reduction.

The results mentioned above indicate that the influence of the chain length of the azo aromatic group in the azo polymers on the degradation rate is not very large. This is not surprising in view of the fact that the polymers are branched and not crosslinked. Kopecek et al. (1992) investigated hydrogels crosslinked with azo aromatic groups. They found that when hydrogels synthesized with the same composition of monomer mixture but different structure (chain length) of the crosslinking agent were compared, hydrogels containing the longer crosslinking agent degraded faster.

## Conclusion

Water-insoluble azo copolymers of HEMA and MMA can be degraded by intestinal bacteria. The influence of the monomer composition (hydrophilicity of the polymers) in the azo polymers is far more important than the structure of the crosslinking agent.

Decomposition of the azo polymers was described using permeability and solution viscosity experiments.

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