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Poly(*N*-isopropylacrylamide) copolymers for constant temperature controlled drug delivery

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Abstract

In the course of the development of a new drug delivery concept, four thermosensitive copolymers of poly(*N*-isopropylacrylamide) (PNIPAAm), with phase transition temperature slightly higher than 37 °C, were synthesised and used as time-controlled drug delivery agents.

For this purpose, compression-coated tablets coated with the thermosensitive copolymers and containing Na_2SO_4 were prepared and in vitro dissolution tests were performed at constant physiological temperature, the lag time before drug release being controlled by the amount of Na_2SO_4 incorporated into the form. Due to the salting out effect, the lag time was increased by up to 80–90% for PNIPAAm-co-NVA and PNIPAAm-co-MVA coated tablets.

Keywords: Poly(*N*-isopropylacrylamide); Controlled drug release; Thermosensitive copolymers; Compression-coated tablets; Salting out effect

1. Introduction

Aqueous solutions of certain polymers, called thermosensitive polymers, exhibit an inverse dissolution behaviour, their phase diagram presenting a lower critical solution temperature (LCST) (Platé et al., 1999; Fujishige et al., 1989; Hahn et al., 1998; Idziak et al., 1999; Kubota et al., 1990; Wu and Zhou, 1997). The solutions are homogenous at low temperature and a phase separation, also called demixing, appears when the temperature exceeds a definite value. The LCST is the minimum of the isobaric phase diagram (temperature versus mole-fraction) (Durand and Hourdet, 2000), and in the cases to be treated in the following, the temperatures at which demixing occurs will be denoted "T_d". However, in those cases, LCST and T_d are generally very close because of the flatness of the lower segment of the phase diagram (Fujishige et al., 1989; Durand and Hourdet, 2000; Heskins and Guillet, 1968).

Among the existing thermosensitive polymers, poly (*N*-isopropylacrylamide) (PNIPAAm) has been widely studied (Kubota et al., 1990; Durand and Hourdet, 2000; Heskins and Guillet, 1968; Schild, 1992), mainly because of the sharpness of its phase transition, of the closeness of its LCST, about 32 °C, to the physiological temperature, and of the easiness to vary its LCST by copolymerisation (Xue and Champ, 2001; Feil et al., 1993; Eeckman et al., 2004, in press), addition of salts (Schild and Tirrell, 1990; Eeckman et al., 2001) or addition of surfactants (Eeckman et al., 2001; Schild and Tirrell, 1991) to the polymer solution.

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That kind of stimuli-responsive material is an attractive candidate to the development of new controlled-release systems, and has stirred up particular interest during the last 20 years (Okano et al., 1990; Kolchob et al., 1998; Yoshida et al., 1992; Zhang et al., 2002; Ichikawa and Fukumori, 2000; Brasel and Peppas, 1996).

In our laboratory, we have developed a new drug delivery concept making thermosensitive polymers suitable for an in vivo application, which might be a new approach to specific drug targeting into the GI tract, mainly for colonic drug delivery (Eeckman et al., 2002). Considering that it is unfeasible to change the temperature of the human body, the proposed concept offers the advantage of controlling drug delivery without having to vary the medium temperature as is currently done in some other reported works over in vitro studies (Okano et al., 1990; Kolchob et al., 1998; Yoshida et al., 1992; Zhang et al., 2002).

In a previous paper (Eeckman et al., 2002), the validity of that new delivery concept was established by associating PNIPAAm-homopolymer and salts in time-controlled-release oral dosage forms.

The mechanism of the drug release, previously explained in details (Eeckman et al., 2002) and relying on the sensibility of the demixing temperature of PNIPAAm to salts, can be explained as follows. When a salt-loaded PNIPAAm-coated tablet is dipped in water, at a temperature at which the thermosensitive polymer is soluble, a saline micro-environment with a locally lowered T_d is created in the surroundings of the polymer, making it insoluble or less soluble (this is the so-called salting out effect) (Eeckman et al., 2001) and thus preventing or delaying the release of the drug. The polymer solubilisation is depending on the persistence of the salted micro-environment. The salt concentration inside the soaked tablets will decrease by diffusion out of the form and the polymer will remain insoluble as long as the salt concentration is sufficiently high to maintain the demixing temperature of the polymer below the ambient temperature of the dissolution medium. The drug release lag time is thus depending on the salting out effect of the added salt.

When the salt concentration has become sufficiently low for T_d to become higher than the ambient temperature, the polymer will dissolve and drug release can occur.

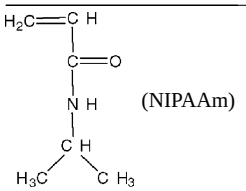
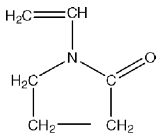
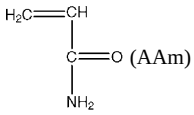
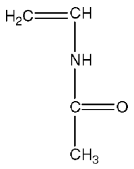
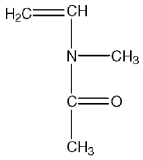
When compression-coated tablets are used, the tracing agent is contained in the core and release will occur after dissolution of the thick polymeric coating, implying a delay of the drug release and thus the appearance of a lag in the release curve.

It was shown (Eeckman et al., 2002) that the delay of the drug release can be controlled by selecting the type and amount of the salt incorporated in the dosage form.

The dissolution tests performed in that paper (Eeckman et al., 2002), where PNIPAAm was used as coating material, had obviously to take place at a temperature lower than T_d, i.e. lower than 32 °C, which of course cannot correspond to in vivo conditions. Consequently, when the delivery concept expounded above is to be used at physiological temperature, the thermosensitive polymer cannot be PNIPAAm anymore (considering its insolubility at that temperature), but instead a copolymer with phase transition temperature higher than 37 °C.

Since the LCST of PNIPAAm can be raised by copolymerisation with hydrophilic comonomers, recourse will be had, in accord with results addressed in

Table 1
Chemical structure of the monomers

Main monomer	Comonomers
 (NIPAAm)	 (VPL)
	 (AAm)
	 (NVA)
	 (MVA)

a forthcoming paper (Eeckman et al., 2004, in press), to acrylamide (AAm), *N*-methyl-*N*-vinylacetamide (MVA), *N*-vinylacetamide (NVA) and *N*-vinyl-2-pyrrolidinone (VPL) (Table 1).

2. Experimental methods

2.1. Materials

N-isopropylacrylamide (NIPAAm) monomers, and diethyl ether were purchased from Acros (Belgium). *N*,*N*′-azoisobutyronitrile (AIBN) was purchased from Fluka (Belgium). Acrylamide, *N*-methyl-*N*-vinylacetamide, *N*-vinylacetamide and *N*-vinyl-2-pyrrolidinone were purchased from Aldrich (Belgium). Unstabilised 1,4-dioxane and *N*-hexane were purchased from Lab-Scan (Belgium). Anhydrous theophylline (Certa, Belgium), microcrystalline cellulose (Avicel PH 102, FMC Corporation, Philadelphia, United States), lactose (Pharmatose 100 mesh, DMV Int., The Netherlands) and magnesium stearate (UCB, Belgium) were used respectively as model drug, binder, diluent, and lubricant. The other materials were of analytical reagent grade.

2.2. Copolymer preparation

N-isopropylacrylamide (NIPAAm) was purified by recrystalisation from *N*-hexane, the other materials were used as received.

PNIPAAm copolymers were prepared in 1,4-dioxane by free radical polymerisation. Using AIBN as an initiator (1 mol%), polymerisations were carried out for 5 h under nitrogen atmosphere and magnetic stirring at 70.0 ± 0.5 °C (67 °C for MVA). Prior to polymerisation, the monomers solutions (1 mol l^{-1}) were bubbled with nitrogen for 20 min in order to remove the remaining oxygen.

According to Eeckman et al. (2004, in press), the comonomers percentages incorporated in the reaction media, in order to obtain appropriate T_d values, were the following: 31.2, 11.8, 12.9 and 27.6 mol% for PNIPAAm-co-VPL, PNIPAAm-co-AAm, PNIPAAm-co-NVA and PNIPAAm-co-MVA, respectively. The comonomer conversion factor, determined by NMR ^{1}H were 12.8, 11.4, 9.1 and 10.6 mol%, respectively (Eeckman et al., 2004, in press).

After polymerisation, the obtained polymers were precipitated in diethyl ether by adding the polymeric solutions to an excess volume of diethyl ether (5:1) at room temperature, under agitation. The suspensions were filtered and washed with diethyl ether, and the polymers were dried in a vacuum oven at 60 °C.

Afterwards, they were subjected to an additional purification process. For this purpose they were dissolved in water (280 g/l) at room temperature and precipitated by heating the solutions at 42.0 ± 0.5 °C. At this temperature, fractions of the polymer samples having a phase transition temperature higher than 42 °C were still soluble and were removed by filtration. The process was repeated twice, and after drying, the purified polymers were dissolved in acetone (112 g/l), precipitated in diethyl ether, dried, crushed in smaller particles and sieved with a 250 μm sieve.

2.3. Differential scanning calorimetry (DSC)

The DSC method was used for the examination of the phase transition phenomenon.

The T_d value was arbitrarily defined as the abscissa of the maximum of the endothermic transition peak (average of four measurements). The analyses were performed using a Perkin Elmer DSC-7 differential scanning calorimeter/TAC-7 thermal analysis controller with a intracooler-2 cooling system (Perkin Elmer Instruments, USA). Aluminium sealed pans containing 10 μl of the various polymer aqueous solutions (56 g/l) were heated at a scanning rate of 2 °C min^{-1}, using nitrogen as blanket gas. Calibration was performed using cyclohexane and indium as standards.

2.4. Transmittance measurements

The phase transitions were also examined by performing transmittance measurements of the polymer solutions at 500 nm, using a Shimadzu 160 spectrophotometer (Shimadzu Corp., Japan). The temperature of the polymeric solutions (14 g/l), was raised by 0.1 °C steps, using a Cell positioner with a Peltier temperature controller (Shimadzu CPS-240A). The cloud point (CP) value (average of two measurements) was determined as the abscissa of the inflexion

Table 2
Physico-chemical properties of the purified copolymers; "∗" from Ref. Eeckman et al. (2002)

Polymer	M_n	M_w	M_w/M_n	CP (°C)	T_d (°C)
PNIPAAm-co-VPL	20100	57800	2.9	39.6	40.2 ± 0.5
PNIPAAm-co-AAm	10900	52000	4.8	38.7	39.9 ± 0.3
PNIPAAm-co-NVA	20400	79500	3.9	38.2	38.6 ± 0.4
PNIPAAm-co-MVA	26200	62300	2.4	38.1	38.6 ± 0.4
PNIPAAm∗	3900	50100	13.0	32.4	31.9 ± 0.3

point of the transmittance versus temperature curves. Results are presented in Table 2.

2.5. Particle size determination

Mean particle size and size distribution of the particles of the different polymers were determined by a laser diffraction method, with a dry sampling system (Mastersizer 2000, Malvern Instruments, UK). The mean volume particles sizes, $d(v; 0.5)$ (size of the particles for which 50% of the sample volume contains only particles smaller than "d 0.5", the other particles being larger than "d 0.5"), $d(v; 0.1)$ and $d(v; 0.9)$ can be read from Table 3.

2.6. Molecular weight evaluation

The molecular weight characteristics of the copolymers were studied by gel permeation chromatography (GPC). An Agilent 1100 GPC (Agilent, USA) apparatus equipped with a refractive index detector and with two Ultrahydrogel 2000 and 250 columns (Waters, USA) was used. The analyses were performed at 20 °C, at a flow rate of 0.6 ml min^{-1}, using a 0.1 mol l^{-1} $NaNO_3$ aqueous solution as mobile phase. Mono-disperse polyacrylic acid standards (Waters, USA) were used for calibration. The obtained results (average of two measurements) are presented in Table 2.

Table 3
Characteristics of the polymer powders; "∗" from Ref. Eeckman et al. (2002)

Powder type	$d(v; 0.1)$ (μm)	$d(v; 0.5)$ (μm)	$d(v; 0.9)$ (μm)
PNIPAAm-co-VPL	3	21	127
PNIPAAm-co-AAm	2	22	68
PNIPAAm-co-NVA	3	22	142
PNIPAAm-co-MVA	4	20	111
PNIPAAm∗	5	22	124

2.7. Tablet preparation

Compression-coated tablets (9 mm diameter) consisting of 60 mg immediate release cores of 5 mm diameter, containing 10% theophylline as a tracing agent, and of coatings containing a copolymer, various amounts of Na_2SO_4 and 1% of magnesium stearate as lubricant, were prepared by direct compression with a Korsch EKOD alternative tableting machine. To prepare coated tablets, half of the quantity of each coat was placed in the compression die, the core was then carefully manually centred and the remaining coating material was finally added before compression. The thickness of the coating was set to 2.0 ± 0.1 mm, and the final weight of the tablet was about 300 mg, depending on the coating density.

Two main types of 10% theophylline loaded cores were evaluated:

1. Conventional unsalted cores containing usual excipients, i.e. 69% of lactose, 20% of Avicel PH 102, 10% of theophylline and 1% of magnesium stearate.
2. Cores containing 70% of Na_2SO_4, 19% of Avicel PH 102, 10% of theophylline, and 1% of magnesium stearate.

The 5 mm diameter bi-convex cores were obtained using a compression force of 4000 ± 500 N. Their crushing strengths was 24 ± 3 N for the tablets loaded with 70% of Na_2SO_4 and 34 ± 2 N for the unsalted tablets.

The 9 mm diameter bi-convex compression-coated tablets containing a copolymer in the coating layer were obtained by using a compression force of 350 ± 50 N. The tablets had a crushing strength of about 100 N, showing the excellent compressibility properties of the polymers powders.

For writing convenience, tablets will be referred to by two numbers, the first one relating to the salt

Table 4
Average drug release lag times and standard deviations, in min as measured from Figs. 4–7; "∗" from Ref. Eeckman et al. (2002)

Dissolution test, $T = 37\,^{\circ}C$	Tablet type				
	0–0	70–0	70–10	70–20	70–30
PNIPAAm-co-VPL (Fig. 4)	110 ± 5	124 ± 18	154 ± 9	148 ± 8	152 ± 26
PNIPAAm-co-AAm (Fig. 5)	95 ± 11	108 ± 11	122 ± 12	132 ± 17	142 ± 25
PNIPAAm-co-NVA (Fig. 6)	122 ± 14	157 ± 36	173 ± 12	195 ± 14	233± 10
PNIPAAm-co-MVA (Fig. 7)	125 ± 9	157 ± 10	195 ± 21	231 ± 10	228 ± 33
PNIPAAm ($T = 27\,^{\circ}C$)*	96 ± 8	125 ± 14	132 ± 10	158 ± 23	130 ± 8

mass-fraction in the core and the second one relating to the salt mass-fraction in the coating. As an example, tablets containing a Na_2SO_4 mass-fraction of 70% in the core and of 20% in the coating will be noted "70–20".

2.8. In vitro dissolution experiments

The dissolution studies were mainly performed at $37.0 \pm 0.2\,^{\circ}C$, using the USP 25 no. 2 dissolution apparatus (paddle) at a stirring speed of 60 rpm. Purified water was used as dissolution medium. The volume and pH of the dissolution fluid were 750 ml and 7.0, respectively. The theophylline release from tablets was measured by UV spectroscopy at 272 nm, using an Agilent 8453 UV/visible Dissolution Testing System (Agilent, USA). Six identical tablets were simultaneously subjected to the test in the apparatus, under the aforementioned conditions. The fractions of tracing agent released were measured at fixed times and averaged. The release curves were characterised by a lag time, arbitrarily defined as the moment at which the rate of release has become higher than $0.15\%\,min^{-1}$ (dissolved drug percentage per minute). In most cases those values correspond to the very early beginning of the release. The lag time mean values and standard deviations were calculated. They are given in Table 4 and in the legend of Fig. 8. For the clarity of the figures the errors bars for the dissolution curves have been omitted. They are consistent with the values of the standard deviations of Table 4.

3. Results and discussion

3.1. Copolymer properties

The copolymers assigned to take the place of PNIPAAm to control the delivery at 37 °C should have phase transition temperatures slightly higher than 37 °C—considering that they have to be soluble at physiological temperature—and in addition to that requirement, the sharpness of their phase transition should be comparable to that of the homopolymer, so as to ensure an optimal effect of the salt. This means that the width of the DSC phase transition peak should be sufficiently small.

Fig. 1 shows the DSC thermograms of the purified copolymers and, for comparison, of PNIPAAm-homopolymer. It can be seen that the first requirement is obviously met. However, when compared to that of PNIPAAm, the endothermic phase transition peaks are quite broader, although the additional purification process was shown to improve the situation, as illustrated in Fig. 2 and discussed elsewhere (Eeckman et al., 2004, in press). Briefly, that broadening phenomenon is presumably due to a non-uniformity of the distribution of the comonomers over the molecules of the polymers, which results in a non-homogeneity of the copolymers samples, all their molecules having not the same phase transition temperature. The obtained behaviour was nevertheless considered acceptable for the intended application, which is borne out by the results reported in the following.

The rationale of the new delivery concept is based on the salting out effect, i.e. on the capability of salts to lower the T_d of the polymer. It was found (Eeckman et al., 2001, 2002) that, for the homopolymer solutions, Na_2SO_4 was in this respect the most efficient salt in the sense that it maximises the ratio $\Delta T_d/\Delta N$, where N is the salt mass-fraction, i.e. the ratio of the demixing temperature decrease to the added salt quantity.

In Fig. 3 the CP of the copolymers aqueous solutions, and for comparison of PNIPAAm-homopolymer solutions, is plotted against the concentration of added Na_2SO_4. It can be observed that the effect of Na_2SO_4 on the phase transition temperature of the copolymers

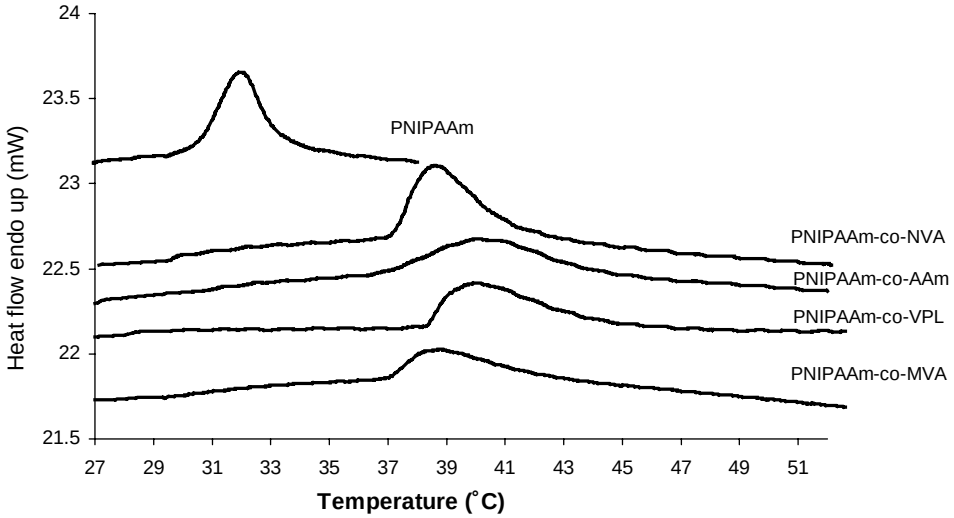


Fig. 1. DSC thermograms of aqueous solutions (56 g/l) of the purified copolymers.

is roughly the same as for the homopolymer. One could thus expect qualitatively similar dissolution test results for copolymer-coated tablets as for the PNIPAAm-coated ones (Eeckman et al., 2002).

3.2. Dissolution studies

Figs. 4–7 show the effect of incorporation of different mass-fractions of Na_2SO_4 in the coating, on the dissolution, at 37 °C, of respectively PNIPAAm-co-VPL, PNIPAAm-co-AAm, PNIPAAm-co-NVA and PNIPAAm-co-MVA coated tablets, containing constant mass-fraction of Na_2SO_4 in the core. In each case, the dissolution curve of the tablet without salt neither in the core nor in the coating (0–0 type) is given for comparison and drug release lag time results are summarised in Table 4.

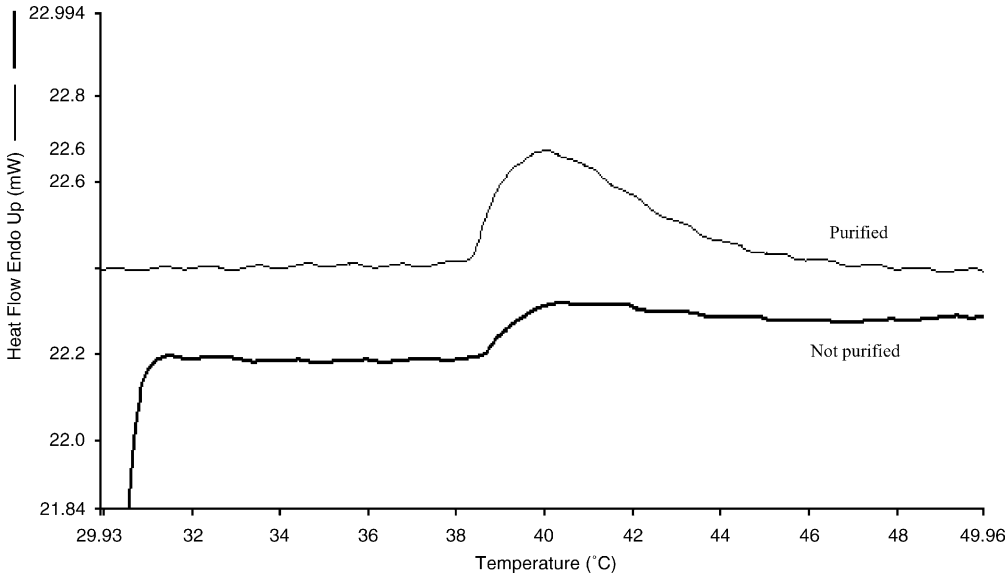


Fig. 2. DSC thermograms of PNIPAAm-co-VPL aqueous solutions with and without the additional purification.

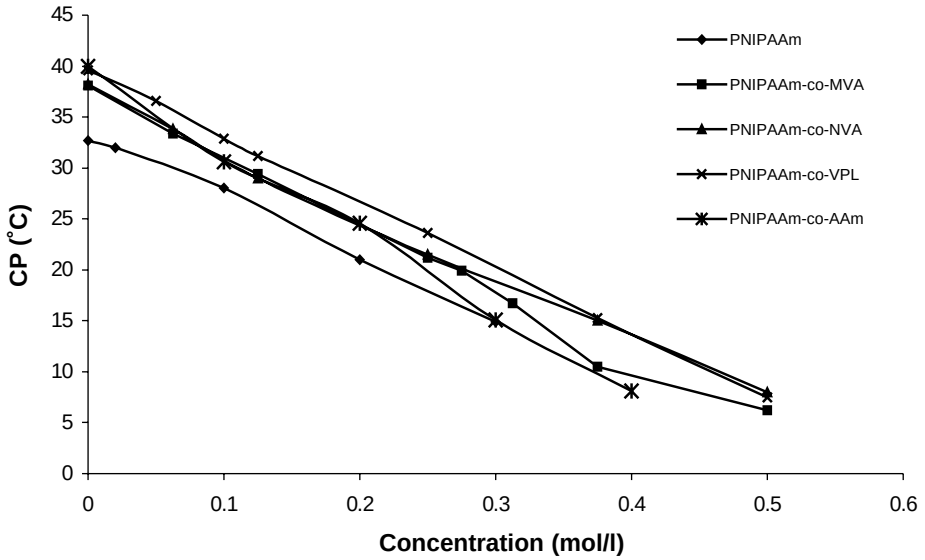


Fig. 3. Effect of the Na_2SO_4 concentration on the cloud point of 14 g/l polymers aqueous solutions.

It can be observed that, as it was the case for the PNIPAAm-homopolymer coatings (Eeckman et al., 2002), the incorporation of salt in the coating brings about an increase of the lag time in the dissolution curves, in the mass-fraction interval 0–30%. For instance, the dissolution lag time of PNIPAAm-co-NVA coated tablets without salt (0–0) is 122 ± 14 min; it increases approximately to 233 ± 10 min for tablets with 70% Na_2SO_4-loaded cores and 30% Na_2SO_4-loaded coatings (70–30) (Table 4 and Fig. 6).

Moreover, the shape of the release curve also changes, entailing a modification of the release kinetics. The release shape modification is probably due to the intrinsic release properties of the different core tablets and/or to the formation of a poorly soluble thin polymeric layer on the surface of the salted cores, but the effect of experimental parameters on the drug release kinetics will not be discussed in this paper. Nevertheless, it is observed that incorporation of different Na_2SO_4 mass-fractions in the coating,

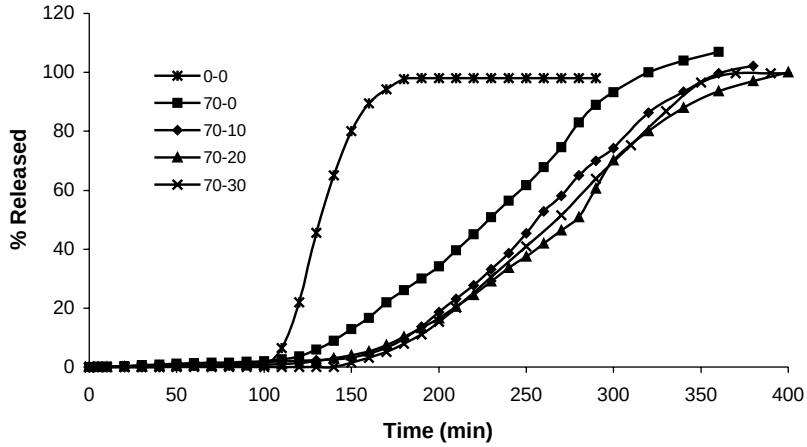


Fig. 4. Effect of the mass-fraction of Na_2SO_4 present in the coating on the drug release behaviour from PNIPAAm-co-VPL coated tablets (water, 37 °C).

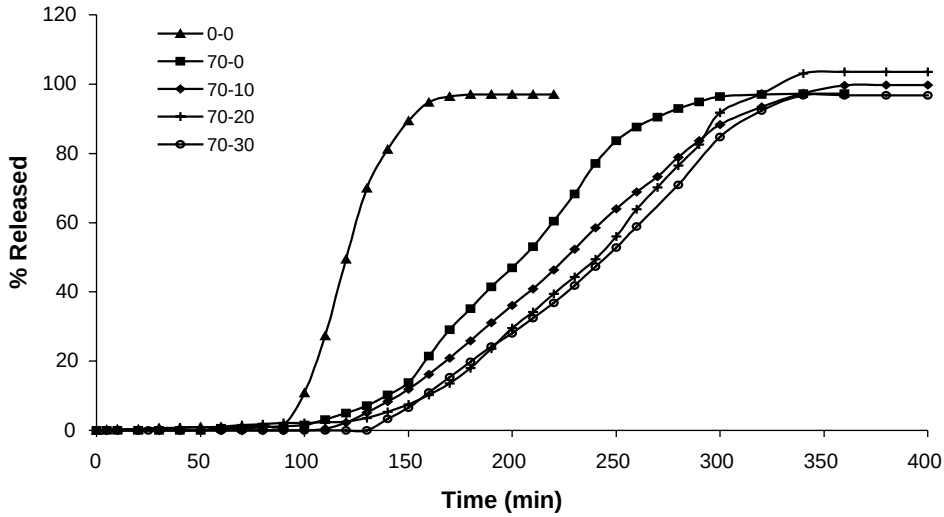


Fig. 5. Effect of the mass-fraction of Na_2SO_4 present in the coating on the drug release behaviour from PNIPAAm-co-AAm coated tablets (water, 37 °C).

while keeping the Na_2SO_4 mass-fraction in the cores (70%) constant induces no modification of the shape of the release curves, and the delay of release is seen to increase until the salt mass fraction in the coating has reached 20 or 30%. A decrease of the lag time was observed for higher salt mass-fractions (data not shown), as it was previously found for PNIPAAm-coated tablets (Eeckman et al., 2002). As already discussed (Eeckman et al., 2002), this is the outcome of two antagonistic effects, viz. the salting out effect and the pore formation in the coated layer due to the presence of the salt.

By the way it is remarked that even for the highest amounts of salt present in the form, the concentrations in the dissolution medium remain low ($\sim 10^{-3}$ mol l^{-1} for 70–30 formulations) and is incapable to lower significantly the T_d of the copolymers (cf. Fig. 3). This proves that the obtained dissolution lag is effectively well a result of the mechanism described before viz. the creation of a salted micro-environment reducing

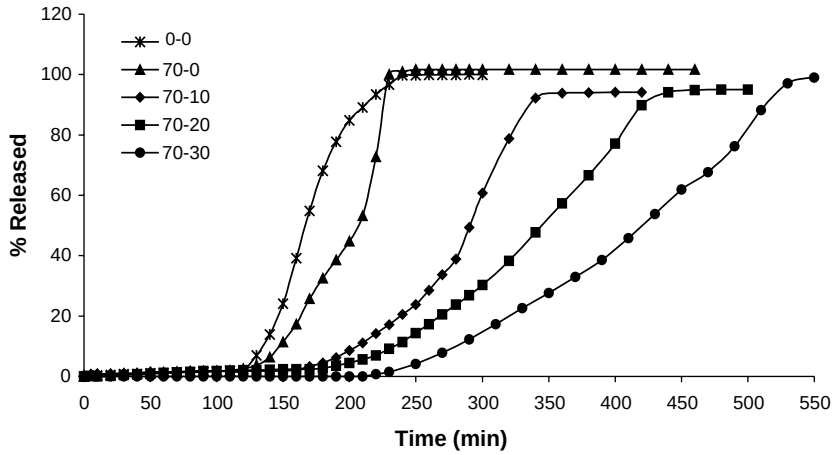


Fig. 6. Effect of the mass-fraction of Na_2SO_4 present in the coating on the drug release behaviour from PNIPAAm-co-NVA coated tablets (water, 37 °C).

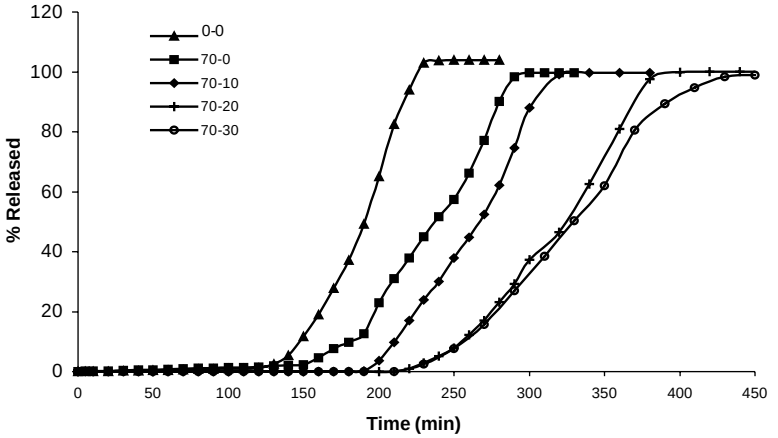


Fig. 7. Effect of the mass-fraction of Na_2SO_4 present in the coating on the drug release behaviour from PNIPAAm-co-MVA coated tablets (water, 37 °C).

the solubility of the polymer and hence increasing the lag time.

Besides, Table 4 reveals that the greatest lag time increases are obtained with PNIPAAm-co-NVA and PNIPAAm-co-MVA-coatings. This should be due to the fact that the T_d of these two copolymers are closer to the ambient temperature (37 °C) than those of the other two (Fig. 1). The incorporation of 70% Na_2SO_4 in the cores and 20% in the coatings brings about an increase of the lag time of ca. 35, 40, 60 and 85% for tablets coated with PNIPAAm-co-VPL, PNIPAAm-co-AAm, PNIPAAm-co-NVA and PNIPAAm-co-MVA, respectively, as compared with their corresponding unsalted tablets. It can be reasonably admitted that quite more similar results could be obtained with copolymers whose T_d are adequately adjusted. The effect of the chemical structure of the comonomer is addressed in a forthcoming paper (Eeckman et al., 2004, in press).

As was already shown for the PNIPAAm-homopolymer (Eeckman et al., 2002) and is now extended to the case of the copolymers, greater closeness of the T_d to the ambient temperature results in a greater effect of the incorporated salt on the lag time. This is

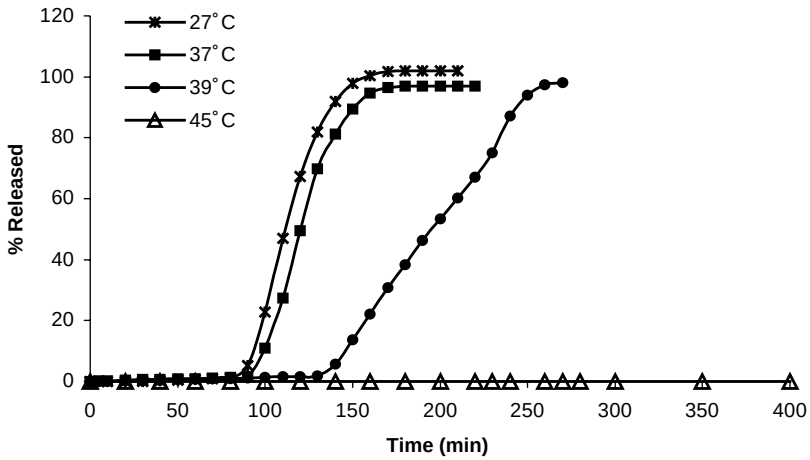


Fig. 8. Effect of the temperature on the drug release behaviour from PNIPAAm-co-AAm coated tablets (0–0 type), in water. Lag times: 84 ± 11, 95 ± 11, and 130 ± 13 min and no release at 27, 37, 39 and 45 °C, respectively.

also illustrated in Fig. 8 where the dissolution curves of unsalted PNIPAAm-co-AAm compression-coated tablets, at temperatures ranging from 27.0 to 45.0 °C, are plotted against time. At a medium temperature of 45 °C or higher, the copolymer is totally insoluble and no theophylline release is observed. Moreover, the difference of the lag times pertaining to tests performed at 27 and 37 °C is minor as compared to the difference of lag times pertaining to tests performed at 37 and 39 °C. So, the enhanced sensitivity of the solubility of the copolymer in the neighbourhood of the phase transition temperature is made conspicuous.

The obtained lag times can obviously be extended or reduced by changing the coating thickness or the polymer molecular weight and the salt content of the coating should be considered as a means of more accurately modulating the lag time. In the case of drug delivery to the colon or to the small intestine, the problem posed by the huge variability of the transit time inherent to the gastric emptying could be solved by using an outer enteric coating, reducing in this way the transit time to that of the small intestine (3–4 h after leaving the stomach).

Dissolution tests presented in this paper were carried out in pure water. That choice was motivated by previous findings (Eeckman et al., 2001, 2002), where the effect of intestinal secretions on the solubility (hence on the lag time) of PNIPAAm were found to be acceptably small.

The development of a more conventional coating process, i.e. spray coating is in progress and will be described in a further paper.

4. Conclusions

A new original way of time-controlled drug release is being developed. The incorporation of four new thermosensitive copolymers of NIPAAm, with phase transition temperature values higher than 37 °C, and of Na_2SO_4 in compression-coated tablets allows a control of the release, at constant physiological temperature.

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References

Brasel, C.S., Peppas, N.A., 1996. Pulsatile local delivery of thrombolytic and antithrombotic agents using poly(*N*-isopropylacrylamide-co-methacrylic acid) hydrogels. J. Contr. Rel. 39, 57–64.

Durand, A., Hourdet, D., 2000. Thermoassociative graft copolymers based on poly(*N*-isopropylacrylamide): effect of added co-solutes on the rheological behaviour. Polymer 41, 545–555.

Eeckman, F., Amighi, K., Moës, A.J., 2001. Effect of some physiological and non-physiological compounds on the phase transition temperature of thermoresponsive polymers intended for oral controlled-drug delivery. Int. J. Pharm. 222, 259–270.

Eeckman, F., Moës, A.J., Amighi, K., 2002. Evaluation of a new controlled-drug delivery concept based on the use of thermoresponsive polymers. Int. J. Pharm. 241, 113–125.

Eeckman, F., Moës, A.J., Amighi, K., 2004. Synthesis and characterisation of thermosensitive copolymers for oral controlled drug delivery. Eur. Polym. J., in press.

Feil, H., Bae, H., Feijen, J., Kim, S.W., 1993. Effect of comonomer hydrophilicity and ionization on the lower critical solution temperature of *N*-isopropylacrylamide copolymers. Macromolecules 26, 2496–2500.

Fujishige, S., Kubota, K., Ando, I., 1989. Phase transition of aqueous solutions of poly(*N*-isopropylacrylamide) and poly(*N*-isopropylmethacrylamide). J. Phys. Chem. 93, 3311–3313.

Hahn, M., Görnitz, E., Dautzenberg, H., 1998. Synthesis and properties of ionically modified polymers with LCST behavior. Macromolecules 31, 5616–5623.

Heskins, M., Guillet, J.E., 1968. Solutions properties of poly(*N*-isopropylacrylamide). J. Macromol. Sci.-Chem. A2, 1441–1455.

Ichikawa, H., Fukumori, Y., 2000. A novel positively thermosensitive controlled-release microcapsule with membrane of nano-sized poly(*N*-isopropylacrylamide) gel dispersed in ethylcellulose matrix. J. Contr. Rel. 63, 107–119.

Idziak, I., Avoce, D., Lessard, D., Gravel, D., Zhu, X.X., 1999. Thermosensitivity of aqueous solutions of poly(*N*,*N*-diethylacrylamide). Macromolecules 32, 1260–1263.

Kolchob, T., Kimura, S., Imanishi, Y., 1998. Thermoresponsive release from poly(glucone)-block-poly(sar) microcapsules with surface-grafting of poly(*N*-isopropylacrylamide). J. Contr. Rel. 50, 205–214.

Kubota, K., Fujishige, S., Ando, I., 1990. Single chain transition of poly(*N*-isopropylacrylamide) in water. J. Phys. Chem. 94, 5154–5158.

Okano, T., Bae, Y.H., Jacobs, H., Kim, S.W., 1990. Thermally on–off switching polymers for drug permeation and release. J. Contr. Rel. 11, 255–265.

Platé, N.A., Lebedeva, T.L., Valuev, L.I., 1999. Lower critical solution temperature in aqueous solutions of *N*-alkyl-substituted polyacrylamides. Polym. J. 31, 21–27.

Schild, H.G., 1992. Poly(*N*-isopropylacrylamide): experiment, theory and application. Prog. Polym. Sci. 17, 163–249.

Schild, H.G., Tirrell, D.A., 1990. Microcalorimetric detection of lower critical solution temperature in aqueous polymer solution. J. Phys. Chem. 94, 4352–4356.

Schild, H.G., Tirrell, D.A., 1991. Interaction of poly(*N*-isopropylacrylamide) with sodium *n*-alkyl sulfates in aqueous solution. Langmuir 7, 665–671.

Wu, C., Zhou, S., 1997. Volume phase of transition of swollen gels: discontinuous or continuous? Macromolecules 30, 574–576.

Xue, W., Champ, S., Huglin, M.B., 2001. Thermoreversible swelling behaviour of hydrogels based on *N*-isopropylacrylamide with a zwitterionic comonomer. Eur. Polym. J. 37, 869–875.

Yoshida, R., Sakai, K., Okano, T., Sakurai, Y., 1992. Drug release profiles in the shrinking process of thermoresponsive poly(*N*-isopropylacrylamide-co-alkyl methacrylate) gels. Ind. Eng. Chem. Res. 31, 2339–2345.

Zhang, X.-Z., Zhuo, R.-X., Cui, J.-Z., Zhang, J.-T., 2002. A novel thermo-responsive drug delivery system with positive controlled-release. Int. J. Pharm. 235, 43–50.