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International Journal of Pharmaceutics 241 (2002) 113–125

international journal of pharmaceutics

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Evaluation of a new controlled-drug delivery concept based on the use of thermoresponsive polymers

Frederic Eeckman, André J. Moës, Karim Amighi *

Laboratoire de Pharmacie Galénique et de Biopharmacie, Université libre de Bruxelles, Campus Plaine, CP-207, Boulevard du Triomphe, 1050 Brussels, Belgium

Received 7 December 2001; received in revised form 18 March 2002; accepted 15 April 2002

Abstract

The purpose of this work is to develop a new delivery concept making a thermosensitive polymer based on poly(*N*-isopropylacrylamide) (PNIPAAm) useful as a time-controlled drug release device, without any temperature changes of the dissolution medium. It was previously found that some salts induce a decrease of the polymer lower critical solution temperature (LCST). Use is here made of that property to show that salt concentration variations can be used as a substitute for temperature changes to make the polymer coating of compression-coated tablets soluble or insoluble, consequently creating a possible new concept of drug delivery control from delivery systems containing thermoresponsive polymers. The obtained results show the influence of the type and amount of salts incorporated into compression-coated tablets on the release lag time of a model drug.

Keywords: Poly(*N*-isopropylacrylamide); Thermoresponsive polymers; Salts; Controlled-drug delivery; Compression-coated tablets

1. Introduction

The solubility of most materials generally increases when the temperature increases. Mostly, solute and solvents are miscible in all proportions if the temperature is higher than the so-called upper critical solution temperature (UCST). If the temperature is lower than the UCST, the system exhibits a phase transition and the solute precipitates (Doi, 1995). However, a number of polymers in aqueous solutions show a sharply contrasting behaviour. As the temperature increases beyond a certain point, commonly referred to as the lower critical solution temperature (LCST) or inverse phase transition temperature (Schild and Tirrell, 1990; Idziak et al., 1999; Platé et al., 1999; Liu and Zhu, 1999; Tanaka, 1978), they become insoluble. Below the LCST the polymer is soluble in the aqueous phase and the chains are extended and surrounded by water molecules. Above the LCST the polymer becomes insoluble and phase separation occurs.

The driving force for this transition is governed by the balance between hydrophilic and hydrophobic forces (Kubota et al., 1990). Examples of polymers which undergo this kind of phase transi-

* Corresponding author. Tel.: +32-2-650-5252; fax: +32-2-650-5269.

E-mail address: kamighi@ulb.ac.be (K. Amighi).

0378-5173/02/$ - see front matter
PII: S0378-5173(02)00198-9

tion are poly(*N*-isopropylacrylamide) (PNIPAAm) (Heskins and Guillet, 1968) and other polymers of N-substituted acrylamides (Platé et al., 1999; Liu and Zhu, 1999), poly(ethylene oxide) (Ataman, 1987), poly(vinyl methyl ether) (Horne et al., 1971), …

PNIPAAm is a thermoresponsive polymer which has aroused particular interest, chiefly because of the abrupt nature of its phase transition, which occurs at about 32 °C, thus near the ambient temperature and because of the reversibility of its transition, which allows repeated thermal 'switchings' (Schild, 1992; Liu et al., 1999).

Interest in the use of stimuli-responsive materials in controlled drug release systems has increased continuously over the past 15–20 years (Okano et al., 1990; Kolchob et al., 1998; Kohori et al., 1998; Yoshida et al., 1992). Thermoresponsive materials are attractive candidates for controlled release systems based on their behaviour in response to temperature changes (Ichikawa and Fukumori, 1997).

In recent years, several new drug delivery concepts, particularly targeting the colon, were developed (Watts and Illum, 1997). Among them, bacterially-triggered delivery systems (Lloyd et al., 1994), pH-triggered delivery systems (Ashford et al., 1993) and time-dependent delivery systems (Fukui et al., 2000) were investigated.

Thermoresponsive polymers have also been used to develop environment-sensitive hydrogels for drug delivery: drug molecules can be taken up and trapped within the network of a hydrogel and released in response to a change of temperature. This is particularly the case of PNIPAAm hydrogels whose water-swollen network can take up water-soluble drugs at low temperature and expel the interstitial water with the drug at higher temperatures (Gutowska et al., 1997). The method of using temperature changes has however limits as it would be rather utopian to change the human body's temperature in order to allow drug targeting to a specific site.

Aqueous solutions of PNIPAAm exhibit a phase separation phenomenon, showing a very rapid and reversible hydration–dehydration process in response to small temperature changes. The LCST of PNIPAAm homopolymer in water is known to be around 32 °C (Heskins and Guillet, 1968). Moreover, the LCST of PNIPAAm can easily be modified by copolymerisation or by addition of salts or surfactants (Schild and Tirrell, 1990). As explained below, the intended application is based on these specific properties of the polymer.

A new drug delivery approach developed in our laboratory is fundamentally based on the thermosensitive properties of PNIPAAm. The concept is based on the use of a cosolute (salt ions) together with the polymer in coated tablets. This might be a new approach to obtain controlled drug delivery in the gastrointestinal (GI) tract, and among other things, specific drug delivery to the colon.

2. Rationale of the controlled-delivery concept

In order to investigate the effect of the incorporation of salt ions on the drug release behaviour compression-coated tablets containing various amounts of salts were prepared. The expected effect is a delay in the drug release profile, depending on the type and concentration of the added salt. This phenomenon can be explained by the effect of the added salt lowering the LCST of the polymer, the so-called salting out effect (Schild and Tirrell, 1990). At 27 °C, PNIPAAm is soluble in water (LCST of 31–32 °C in pure water); but the formation of a salted microenvironment surrounding the dosage form induces a lowering of the LCST, making the polymer insoluble in that salted environment.

The effect of a wide range of physiological and non-physiological compounds like salt ions and surfactants on the LCST of PNIPAAm aqueous solutions has been investigated in a previous work (Eeckman et al., 2000). To summarize, it was found that, while considering the mean amount of salts and surfactants in the GI undiluted secretions, their effect on the LCST was reasonably small (between 1 and 3 °C). It was concluded that the behaviour of oral administered controlled-release dosage forms of the type used in this study would not be affected neither by the content of the GI secretions nor by the pH of the GI fluids.

Moreover, a ranking of various salts was established in accordance with the LCST decrease of PNIPAAm they bring about, thus suggesting a choice of the most attractive candidates for the application at hand. However, it has to be kept in mind that the behaviour observed for the salted solutions would not be exactly the same for solid tablets, where the solubility and the dissolution kinetics of salts and polymer had to be taken into account. Nevertheless, the incorporation of salts having the greatest effect on the LCST of PNIPAAm in the compression-coated tablets might be very useful in order to obtain an effective decrease of the PNIPAAm solubility at the lowest salt contents.

The mechanism of drug release according to this new drug delivery concept, based on the use of thermosensitive polymers can be stated as follows (Fig. 1). When the salt-loaded tablets are immersed in water at 27 °C, a saline micro-environment with a locally lowered LCST will be created in the surroundings of the polymer, making it insoluble or less soluble and thus preventing or delaying the drug release. The PNIPAAm solubilisation is dependent on the persistence of the salted micro-environment. The salt concentration inside the soaked tablets will however decrease by diffusion out of the form. The polymer will remain insoluble as long as the salt concentration remains sufficiently high to maintain the polymer LCST below the ambient temperature of the dissolution medium. The drug release lag time is thus dependent on the so-called salting out effect of the salt added and on the diffusion rate of the salt out of the form.

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

In the case of compression-coated tablets, the tracing agent (theophylline) is contained in the core. The release will mainly occur after dissolution of the 2-mm thick polymeric coating, implying a delay of the drug release and thus the appearance of a lag time in the release curve. The delay of the drug release can be controlled by selecting the type and the amount of salt incorporated in the form. In this way, a time-controlled release system based on the use of a thermosensitive polymer, using various amounts of salt as a controlling agent is obtained.

3. Materials and methods

3.1. Materials

NIPAAm monomer, *N*,*N*′-azobisisobutyronitrile (AIBN) and diethyl ether were purchased from Acros (Belgium). Unstabilized 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) and lactose (Pharmatose 100 mesh) were used as a model drug, binder-disintegrant and diluent, respectively. Hydroxypropyl methylcellulose (HPMC) (Methocel E5 LV Premium EP) was provided by Colorcon (Belgium). The other materials were of analytical reagent grade.

3.2. Polymer preparation

PNIPAAm was prepared by free radical polymerisation in 1,4-dioxane. This allows to obtain low molecular weight polymers ($Mw \sim 50\,000$ g/mol). Using AIBN as an initiator (1 mol%), polymerisation was carried out under nitrogen atmosphere and magnetic stirring at 70 °C for 5 h. The monomer solution (70 g in 616 ml) was bubbled with nitrogen for 30 min prior to polymerisation in order to remove the remaining oxygen.

After polymerisation, the obtained polymer was precipitated in diethyl ether by adding the polymeric solution to an excess volume of diethyl ether (2.5 l) at room temperature, under agitation. The suspension was filtered and washed with diethyl ether. The polymer was dried in vacuum oven at 60 °C. It was then dissolved in acetone (110 g/l) and precipitated again in diethyl ether (2.5 l). The resulting powder was then manually crushed in a mortar to smaller particles, and sieved with a 250-μm sieve.

The obtained polymer was found to have a LCST of 31.9 ± 0.3 °C, determined by differential

scanning calorimetry (DSC). DSC studies were performed with a Perkin–Elmer DSC-7 differential scanning calorimeter/TAC-7 thermal analysis controller with an intracooler-2 cooling system (Perkin–Elmer Instruments, USA). Aluminium-sealed pans containing PNIPAAm solutions (56 mg/ml) were heated at a scanning rate of 2 °C/min. The LCST value was chosen as the maximum of the endothermic transition peak. The onset of the transition peak was found to be equal

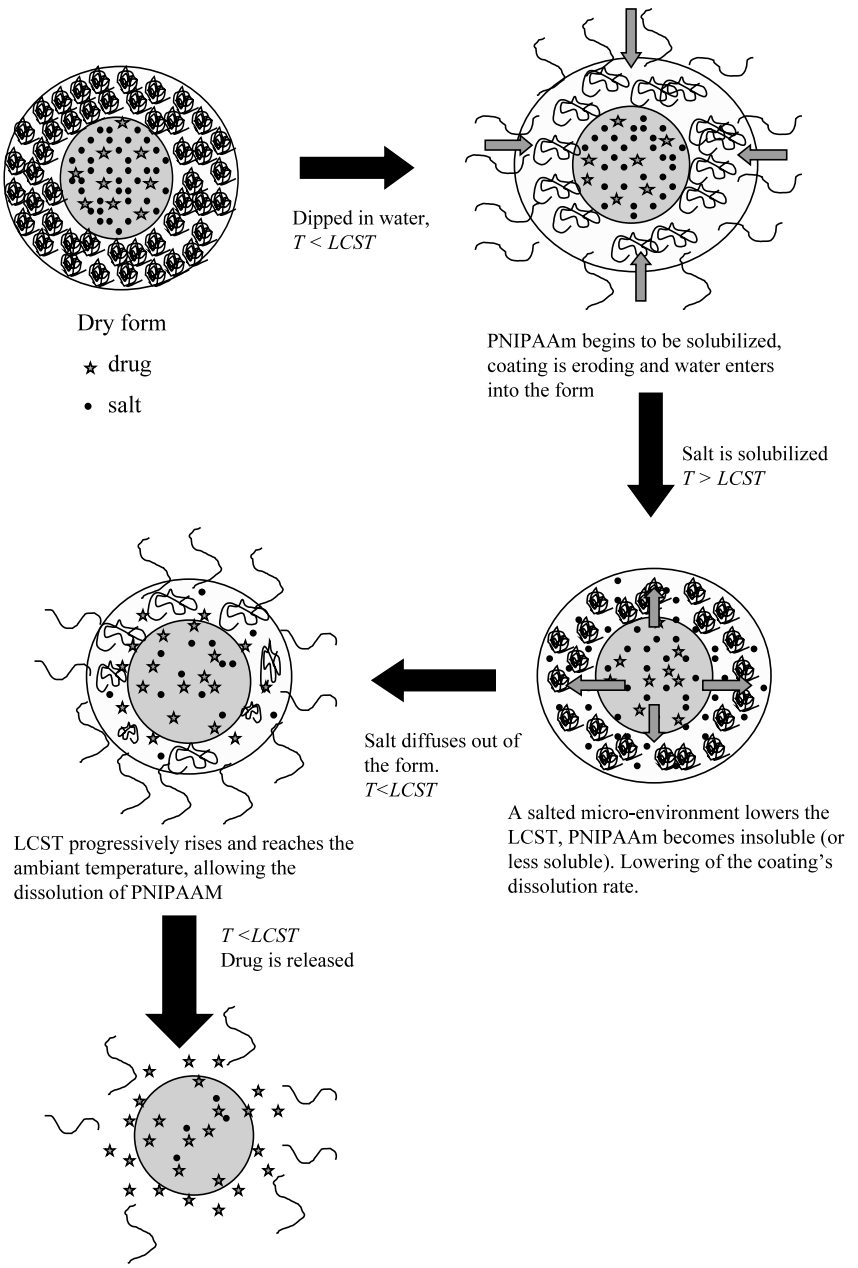

Fig. 1. Mechanism of drug release from compression-coated tablets using thermosensitive polymers in the presence of salts.

Table 1
Physical properties of the polymer

PNIPAAm	Mv[a]	Mv[b]	Mn[b]	Mw[b]	Mp[b]	Mw/Mn
	54 500 ± 850	50 000 ± 400	3900 ± 400	50 100 ± 100	81 000 ± 800	13 ± 1.5

[a] Viscometric analyses.
[b] GPC analyses.

to 30.5 ± 0.3 °C, meaning that a small fraction of the polymer began to undergo its phase transition around this onset temperature, while the bulk does at the LCST. This range of transition temperature is due to the broad molecular weight distribution of the polymer ($d = 13$) (Tong et al., 1999).

3.3. Particle size determination

The mean particle size and size distribution of the polymer were determined using a laser diffraction method, with a dry sampling system (Mastersizer 2000, Malvern Instruments, UK). The mean volume particle size, d(v; 0.5) (size of the particles at which 50% of the sample volume contain particle smaller than 'd 0.5' and the rest particles larger than) of the polymer particles was found to be about 20 μm. The d(v; 0.1) and d(v; 0.9) were found to be about 5 and 120 μm, respectively.

3.4. Molecular weight evaluation

The molecular weight of PNIPAAm can be controlled by carefully setting the polymerisation parameters (temperature, solvent type, monomer concentration, initiator concentration, …). Among those, the type of reaction medium is an important factor which allows to prepare at will low molecular weight or high molecular weight polymer samples.

In this study, low molecular weight polymer samples were used in order to obtain dissolution curves showing a desired lag time from compression-coated tablets that were used to control the drug release. 1,4-Dioxane is, in this respect, a very appropriate solvent, which allows to obtain low molecular weight polymers. This is mainly due to the chain transfer to the solvent which markedly affects the resulting molecular weight of free-radical polymerised macromolecules (Schild, 1992).

The viscometric molecular weight (Mv) (mean of three measurements) was determined by viscometric measurements using the Mark–Houwink–Sakurada equation (see Table 1). An Ubbelhode viscometer (O_c type) was used. The measurements were performed in THF at 27 °C. In those conditions the coefficients 'a' and 'k' of the equation are equal to 0.65 and 0.00959, respectively (Schild, 1992; Ringsdorf et al., 1992; Bergbreiter et al., 1998).

The molecular weight characteristics of PNIPAAm were also studied by gel permeation chromatography (GPC). An Agilent 1100 GPC (Agilent, USA) apparatus equipped with a refractive index detector and with two ultrahydrogels 2000 and 250 columns (Waters, USA) was used. The analyses were performed at 20 °C, using a 0.1 M $NaNO_3$ aqueous solution, at a flow rate of 0.6 ml/min. Monodisperse poly(acrylic acid) standards (Waters, USA) were used for calibration. The results obtained by GPC (mean of three measurements) (Table 1) confirm the results obtained by the viscometric method as the Mv values found by both methods are very close. We can also observe that the synthesised PNIPAAm had a very high polydispersity.

3.5. Tablet preparation

Compression-coated tablets (9-mm diameter) consisting of 60 mg immediate release core of 5-mm diameter, containing 10% theophylline as a tracing agent, and of coatings containing PNIPAAm, various amounts of salts (mainly 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 manually centered carefully and the remaining coating material was finally added before compression. The thickness of the coating was equal 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 a certain amount of salt (20 and 70% of Na_2SO_4 or 70% of NaCl), 20% Avicel PH 102, 1% magnesium stearate, 10% theophylline and lactose when required.

The 5-mm bi-convex cores were obtained using a compression force of 4000 ± 500 N. Their crushing strengths were equal to 24 ± 3 N for the 70% Na_2SO_4-loaded tablets, 30 ± 3 N for the 20% Na_2SO_4-loaded tablets, 34 ± 2 N for the unsalted tablets and 6 ± 1 N for the 70% NaCl loaded ones.

The 9-mm diameter bi-convex compression-coated tablets containing PNIPAAm in the coating layer were obtained by using a compression force of 400 ± 50 N. The resulting tablets had a crushing strength of about 100 N, showing the excellent compressibility of PNIPAAm powder.

Finally, 9-mm compression-coated tablets containing a water-soluble non-thermosensitive polymer, HPMC (Methocel E5 LV) and various amounts of Na_2SO_4 (0, 20%) in the coating and conventional core tablets were prepared at compression forces of 3000 ± 300 N. Their crushing strength was found to be about 100 N.

3.6. In vitro dissolution experiments

The dissolution studies were performed at fixed temperatures ranging between 27 and 31 °C, using the USP 23 No. 2 dissolution apparatus (paddle) at a stirring speed of 60 rpm. The dissolution medium was water or buffer solutions, containing 0.05% (w/w) of polysorbate 20. The volume and pH of the dissolution fluid were 750 and 7.0 ml, respectively. The theophylline release from tablets was evaluated by UV spectroscopy at 272 nm, using a Agilent 8453 UV/visible dissolution testing system (Agilent, USA). Six tablets of identical properties were simultaneously subjected to the test, under the aforementioned conditions. The percentages of tracing agent released were measured at fixed times intervals and averaged.

The dissolution of PNIPAAm from the coating was followed by performing (in duplicate) absorbance measurement of each of the six dissolution media at 500 nm, using a Shimadzu 160 spectrophotometer (Shimadzu Corp., Japan), and a Cell positionner with a Peltier temperature controller (Shimadzu CPS-240A). The measurements were performed at 55 °C, temperature at which solutions became cloudy by polymer precipitation. The amount of PNIPAAm was calculated according to a calibration with standard PNIPAAm samples.

4. Results and discussion

The in vitro release curves showing the influence of the formulation and/or of the conditions under which the dissolution tests were performed are presented in Figs. 2–9. The release curves are plots of the mean percentages of released tracing agent against time, the other parameters remaining constant. The release curves were characterized by a lag time, arbitrarily defined as the moment at which the rate of release has become higher than 0.15%/min. In most cases, those values correspond to the very early beginning of the release. The lag time mean values and standard deviations were calculated.

Fig. 2 shows the effect on the dissolution curve, in pure water at 27 °C, of salt mass fractions (0, 20, and 70%) and salt type (Na_2SO_4 vs NaCl) present in the core of compression-coated tablets, with a 2-mm thick coating composed of PNIPAAm and 1% of magnesium stearate. As it can be observed, both the dissolution lag time and the shape of release curves are modified by the salt mass fraction incorporated in the tablet cores. The dissolution lag time of the tablets without salt is 96 ± 8 min; it increases to ca. 125 min with a

70% Na_2SO_4 (125 ± 14 min) or a 70% NaCl (124 ± 23 min) mass fraction. Moreover, the shape of the release curve also changes entailing a modification of the release kinetics, but the effect of experimental parameters on the drug release kinetics is however not discussed in this paper. Finally, the lag time is nearly the same for both salts used but the release rate in the presence of Na_2SO_4 is higher. The expected effect of the presence of salts, that increase the delay before drug release, is thus confirmed although it is smaller than expected.

Fig. 3 illustrates the effect of the incorporation of different Na_2SO_4 mass fractions in the coating, while keeping constant the Na_2SO_4 mass fraction in the cores (70%). The shape of the release curves (thus the release kinetics) does not seem to depend on the salt mass fraction present in the coating,

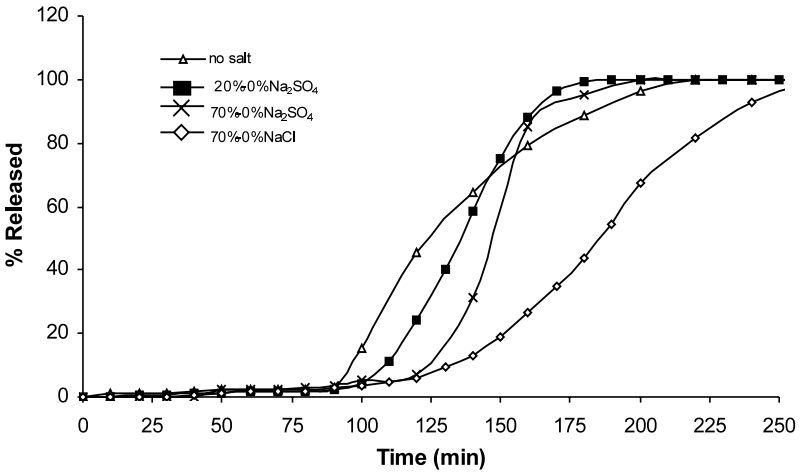

Fig. 2. Effect of the nature and concentration of salt in the core (Na_2SO_4: 0, 20 and 70%; NaCl: 70%) on the drug release behaviour of PNIPAAm-coated tablets in water at 27 °C. Lag times: 96 ± 8 (unsalted), 108 ± 9 (20% Na_2SO_4), 125 ± 14 (70% Na_2SO_4) and 124 ± 23 min (70% NaCl).

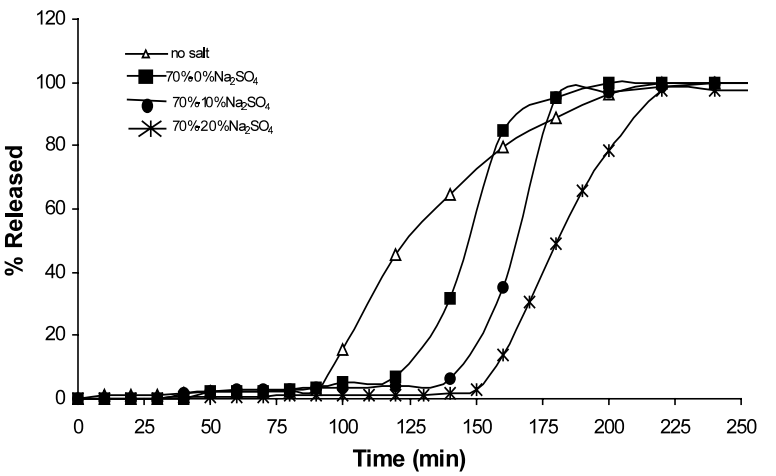

Fig. 3. Effect of the concentration of Na_2SO_4 incorporated in the coating (0, 10 and 20%) on the drug release behaviour of PNIPAAm-coated tablets in water at 27 °C.The cores contain 70% Na_2SO_4 (except for the unsalted ones). Lag times: 96 ± 8 (unsalted tablets), 125 ± 14 (salted cores), 132 ± 10 (10% Na_2SO_4) and 158 ± 23 min (20% Na_2SO_4).

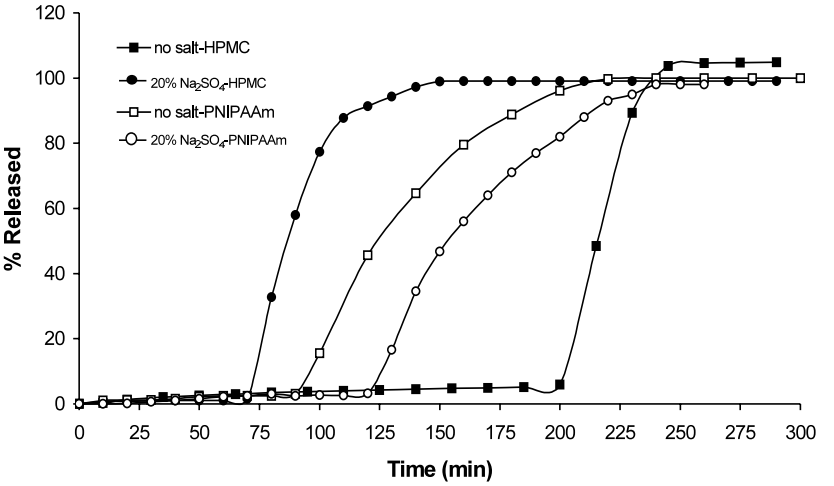

Fig. 4. PNIPAAm vs HPMC tablets: effect of the incorporation of Na_2SO_4 in the coating (0 and 20%) on the drug release behaviour in water at 27 °C (unsalted cores). Lag times: 96 ± 8 and 126 ± 5 min for PNIPAAm; 197 ± 20 and 75 ± 18 min for HPMC.

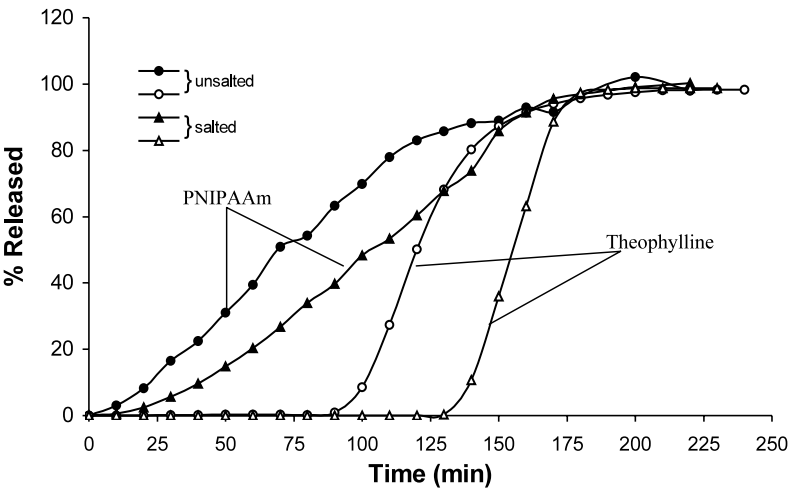

Fig. 5. Correlation between the dissolution behaviour of theophylline (open symbols) and of PNIPAAm (closed symbols) from unsalted tablets and salted tablets (70% Na_2SO_4 in the core and 10% in the coating), in water at 27 °C.

but the delay of release is seen to increase until the salt mass fraction in the coating has reached 20%, and to decrease for mass fraction values higher than 20% (not shown). The lag time decrease, observed for very high salt mass fractions, can be explained as follows: due to its high solubility, the salt in the coating dissolves rapidly which leads to the formation of hydrophilic channels in the coated layer. This eases the penetration of water into the coating and accelerates the dissolution of PNIPAAm. The presence of a maximum lag time for a mass fraction of 20% Na_2SO_4 in the coating appears thus to result from a competition between two antagonistic effects viz. the salting-out effect and the pore formation in the coated layer.

In order to uphold the interpretation that ascribes the differences in the release profiles to the effect of the salt contents on the LCST of PNIPAAm, dissolution tests have been carried out

with compression-coated tablets containing HPMC instead of PNIPAAm in the coating. HPMC is a non-thermosensitive water-soluble polymer. The results are shown in Fig. 4; they reveal that incorporation of Na_2SO_4 in such a coating leads to a drastic decrease of the lag time, contrary to the behaviour of the PNIPAAm-coated tablets. Thus, when a non-thermosensitive polymer is used, the salt will only dissolve and hydrophilic channels will be created in the coating, facilitating water penetration into the coating and dissolution of the coating. It is confirmed that the increase of the lag time obtained for the PNIPAAm coated tablets is due to the effect of the salt on the PNIPAAm solubility.

Moreover, in Fig. 5, the dissolution behaviour of PNIPAAm itself from salted and unsalted compression-coated tablets has been investigated in

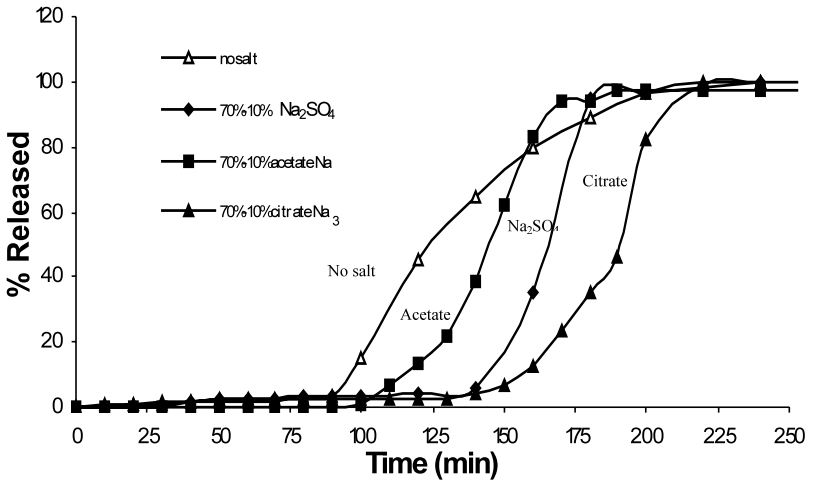

Fig. 6. Effect of the nature of the salt incorporated at an amount of 10% in the coat, on the drug release behaviour of PNIPAAm-coated tablets in water at 27 °C. The cores contain 70% of Na_2SO_4. Lag times: 109 ± 10, 132 ± 10 and 138 ± 13 min for sodium acetate, sodium citrate sodium sulfate and sodium citrate, respectively.

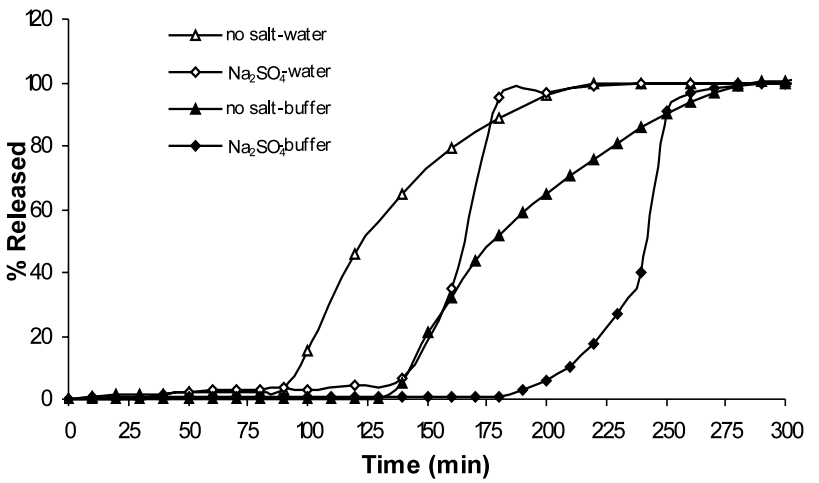

Fig. 7. Influence of the dissolution medium composition (pure water vs 0.05 M phosphate–acetate buffer at pH7) on the drug release behaviour of unsalted and salted PNIPAAm-coated tablets (Na_2SO_4, 70% in the core and 10% in the coating), at 27 °C. Lag times: 140 ± 9 and 199 ± 20 min in the buffer medium; 96 ± 8 and 132 ± 10 min in pure water.

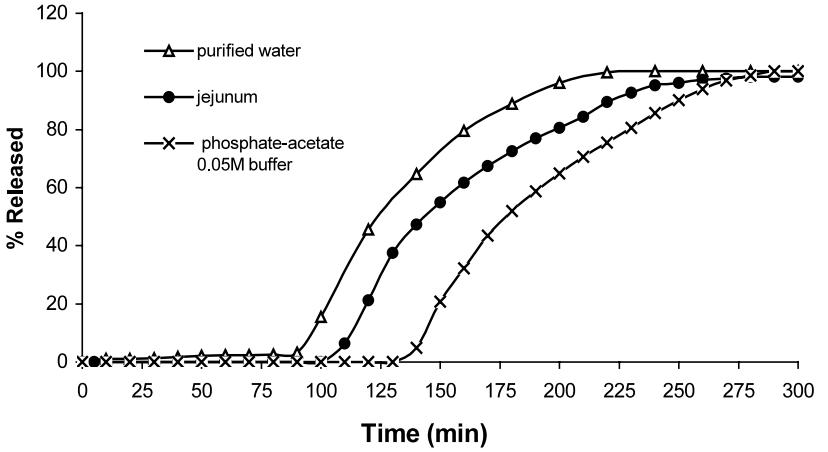

Fig. 8. Comparison of the dissolution behaviour of unsalted PNIPAAm-coated tablets at 27 °C in three different dissolution media: pure water, 0.05 M phosphate–acetate buffer and a jejunum-like medium. Lag times: 96 ± 8, 140 ± 9 and 113 ± 11 min, respectively.

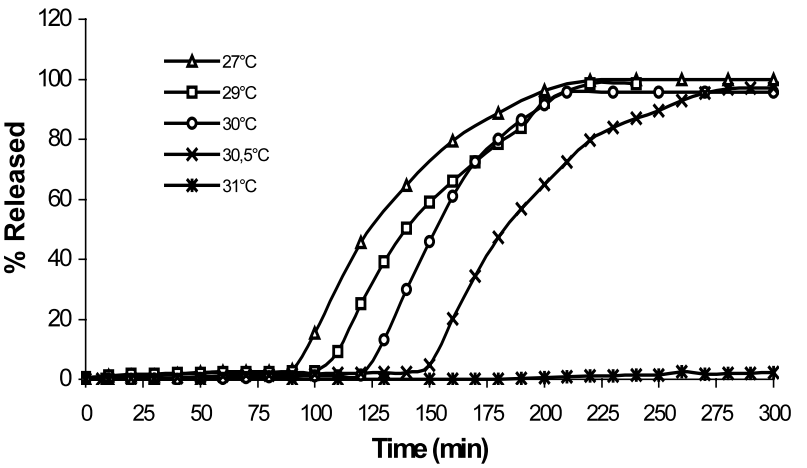

Fig. 9. Influence of the dissolution medium temperature (27, 29, 30, 30.5 and 31 °C) on the drug release behaviour of PNIPAAm-coated tablets (unsalted tablets) in water. Lag times: 96 ± 8, 109 ± 6, 117 ± 9 and 155 ± 14 min, respectively.

the course of dissolution experiments. The process was spectrophotometrically followed by measuring, at a temperature above the PNIPAAm cloud point, the absorbance of samples simultaneously taken from each of the dissolution media. As shown in Fig. 5, the dissolution process of PNIPAAm (closed symbols) from salted tablets is slowed down as compared with that obtained from unsalted tablets. The corresponding theophylline release profiles (open symbols), determined at the same time, show an increase of the lag time, in accordance with their lower PNIPAAm dissolution rate in the presence of salt. In both cases, the drug release occurs after dissolution of a substantial amount of the coating material (about 70%).

We can thus assert that the concept permits to obtain a time-controlled release system based on the use of a thermosensitive polymer, at a constant temperature, using salts as a controlling agent.

A comparison was also made between release curves obtained with different kinds of salt in the PNIPAAm coating. Fig. 6 shows the release

curves obtained from tablets containing 10% sodium sulfate, 10% sodium citrate or 10% sodium acetate in the coating, the core being still loaded with Na_2SO_4 (70% mass fraction). It reveals that the greatest lag time is obtained with sodium salt of the trivalent citrate anion. It was also found that an increase of the sodium citrate content to 20% did not substantially affect the lag time. The results are in accordance with the decreasing effect of the different salts on the LCST of PNIPAAm aqueous solutions (Eeckman et al., 2000, 2001). The greater the influence on the LCST, the greater the lag time increase.

Finally, the best results were obtained with tablets loaded with 70% Na_2SO_4 in the core and 20% in the coating, leading to an increase of about 50% of the lag time of the unsalted forms (see Fig. 3: 96 min with the unsalted tablets against 158 min with the salted ones).

The obtained lag times are obviously not high enough to reach targets, as the colon for instance. However, they can be easily extended e.g. by changing the coating thickness or the polymer molecular weight. 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, 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 small intestine (3–4 h after leaving the stomach).

So far, all dissolution tests were performed in pure water. In conformity with classical dissolution testing methods on controlled-release dosage forms, dissolution tests were performed in a 0.05 M phosphate–acetate buffer, at pH 7.0 (Amighi, 1995) with two kinds of tablets: unsalted tablets and tablets with 70% Na_2SO_4 in the core and 10% Na_2SO_4 in the coating (Fig. 7). In both cases, results show a sizeable increase of lag time in comparison with that in pure water. Although the amount of phosphate and acetate salts in the dissolution medium is small, it is sufficiently high to induce a decrease of the PNIPAAm transition temperature and consequently a decrease of the polymer hydrophilicity. It was found by DSC that the LCST of PNIPAAm was lower by ca. 3 °C in the buffer solution (28.9 ± 0.3 °C) than in pure water (31.9 ± 0.3 °C). The composition of the dissolution medium is thus an important parameter which influences the dissolution profile. In fact, the addition of salt to the dissolution medium has the same consequence that an increase of the medium temperature as it is explained and illustrated below. The prolongation of the lag time is equivalent to that obtained for a temperature rise of dissolution medium from 27 to 30 °C (Fig. 9).

It is important to notice that, even for the highest amount of salt incorporated into the dosage forms, the salt concentration present in the dissolution medium is too low and unable to lower the LCST of PNIPAAm, because of its high dilution ($\sim 7.5 \times 10^{-4}$ mol/l, for formulations containing 70–20% Na_2SO_4). As stated before, the observed lag time is effectively induced by the formation of salted micro-environment surrounding the polymer in the form.

Although the influence of the buffer medium on the LCST and thus on the lag time is quite important, it should be borne in mind that the phosphate and the acetate ions which were used to simulate the physiological conditions, induce a greater effect on the LCST than the ions present in the undiluted GI secretions (Eeckman et al., 2000, 2001). To investigate more about this, dissolution tests were carried out in a medium simulating more closely the intestinal secretions. The composition used was as follows: 0.135 M of NaCl, 0.0082 M of $NaHCO_3$, 0.5 g/l of polysorbate 20, 0.00315 M of NaH_2PO_4 and 0.005 M of K_2HPO_4. This composition simulates the jejunum undiluted secretions (Geigy Scientific Tables, 1981) in a 'light' phosphate buffer solution. This new medium had the same ionic strength as the previous phosphate–acetate buffer ($\mu = 0.160$), the same pH (7) and the same surface tension (0.05% of polysorbate 20). It was found by DSC that, in this medium, the LCST (29.8 °C) was lower by ca. 2.1 °C than in pure water (31.9 °C). The dissolution results are shown in Fig. 8. It was found that the lag time increase observed in the new dissolution medium is far less marked (17 min) than that in the phosphate–acetate buffer (44 min). This result was as expected from the fact

that the effect on the LCST of the phosphate–acetate buffer was greater than that of jejunum like medium.

It is concluded that, as has been already reported (Eeckman et al., 2001), the effects of intestinal secretions on lag times are small and so much the more that these secretions are in practice always diluted. Besides, patients would be advised to take the tablets, which contain such an ion sensitive polymer, between meals rather than during, immediately before or immediately after meals, avoiding in that way possible undesired effects of substances contained in the food.

Finally, Fig. 9 shows the results of dissolution tests conducted on unsalted compression-coated tablets, in water at various temperatures, ranging from 27 ± 0.2 to 31 ± 0.2 °C. It was found that an increase of the medium temperature lead to an increase of the lag time of dissolution. At a medium temperature of 31 ± 0.2 °C or higher no theophylline release was observed. This shows clearly a sharp phase transition occurring at temperatures above the LCST. At 30.5 °C, PNIPAAm is still soluble, whereas at 31 °C it becomes totally insoluble preventing any drug release. Comparison with the foregoing figures indicates that the salt content influences the solubility of PNIPAAm analogous to temperature change.

5. Conclusion

The solubility properties of a thermoresponsive polymer (PNIPAAm) can be used as a means of controlling the drug release from compression-coated tablets. In this respect, the present study showed a new concept of drug delivery where the solubility of thermoresponsive polymer was controlled not by a temperature change but by a variation of salt concentration in the dosage form. The variable salt concentrations appear to be equivalent to temperature changes of dissolution medium. The release control can take place without temperature change, as it is obviously imposed by physiological conditions.

For the applications, NIPAAm copolymer having LCST slightly higher than 37 °C, and more conventional procedure of coating e.g. spray coating could be used. Further work is currently in progress.

Acknowledgements

Financial support from the Région Wallonne (convention no. 14403) is gratefully acknowledged.

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