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Studies of pectin HM/Eudragit® RL/Eudragit® NE film-coating formulations intended for colonic drug delivery

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Abstract

Theophylline pellets were coated with Eudragit® NE30D aqueous dispersions, containing various pectin HM/Eudragit® RL30D ionic complexes, using an Uni-Glatt fluidized-bed apparatus. Dissolution studies were then carried out on the coated pellets at pH 6.0, in absence and in presence of commercial pectinolytic enzymes. The theophylline release from the coated pellets, after an initial latency phase, occurred linearly as a function of time. The theophylline release rate was dependent on the pectin HM content of the complexes incorporated in the coatings. The lowest theophylline release from the coated pellets was obtained when the pectin HM content of the complexes was 20.0% w/w (related to Eudragit® RL), i.e. when the complexation between pectin HM and Eudragit® RL is optimal. The theophylline release from the coated pellets was slower in presence of the pectinolytic enzymes when the pectin content of complexes is higher than 20% w/w. On the other hand, the effect of the enzymes induced an increase of the theophylline release when the pectin HM content of the coatings ranged between 10.0 and 15.0% w/w (related to Eudragit® RL).

Keywords: Colonic drug delivery; Pectin; Eudragits®; Ionic complex; Enzymatic degradation; Film-coating

1. Introduction

Due to their high solubility and swelling properties in aqueous media, film coatings prepared with pectins or calcium pectinates alone are unable to prevent the release of drugs from coated dosage forms during their transit through the stomach and the small intestine.

That is the reason why a number of authors have suggested to use coatings prepared from cellulosic (Aquacoat® ECD30, Surelease®) or acrylic (Eudragit® NE30D and RS30D) insoluble polymer aqueous dispersions incorporating appropriate amounts of pectins or calcium pecti-

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nates, in order to prepare more suitable forms for targeting drugs to the colon (Wakerly et al., 1996b, 1997; Macleod et al., 1997; Semdé et al., 1998a).

These mixed coatings can prevent the swelling and the solubilization of pectins or calcium pectinates during the transit from mouth to caesum. On the other hand, the degradation of pectins and calcium pectinates by the pectinolytic enzymes of the colonic flora is expected to increase the drug release in the colon by the formation of a more porous coating structure. However in a previous work we have observed that the release of theophylline from pellets coated respectively with Aquacoat® ECD30, Eudragit® NE30D and RS30D aqueous dispersions, incorporating 10% w/w calcium pectinate (related to the insoluble polymer), is slower in presence than in absence of commercial pectinolytic enzymes (Semdé et al., 1998b, 2000).

These non-desired, unexpected results have been attributed to the increasing effect of highly water-swelling polymers on the permeability of the insoluble coatings.

In the present work, calcium pectinate has been substituted by pectin HM (polyanion)–Eudragit® RL (polycation) complexes. Pectins HM (high methoxylated) being less soluble in water and having lower negative charge density than pectins LM (low methoxylated), have been chosen to prepare pectin–Eudragit® RL complexes. Eudragit RL is a hydrophilic, slightly cationic acrylic polymer. The films obtained with this insoluble polymer swell in water, buffer solutions and digestive juices and are readily permeable to these liquids. The complexation reduces the ionic charge, the hydrophilicity and the swelling properties of both pectin HM and Eudragit® RL and allows therefore the incorporation of high amounts of pectin HM–Eudragit® RL complexes in the Eudragit® NE film-coatings without affecting dramatically their permeability. The action of the pectinolytic enzymes of the intestinal flora on such films results in the degradation and the leaching of pectin and therefore is expected to accelerate the drug release. Indeed, Eudragit® RL which is released from the complex thanks to the action of the enzymes, can recover its original properties, freely solvate, swell and induce the apparition of distortions in the film hence increasing the drug release.

The objective of this paper was to evaluate the potential of Eudragit® NE30D, containing various pectin HM/Eudragit® RL30D ionic complexes, as coating materials intended for targeting of drugs to the colon. For this purpose, in vitro dissolution studies have been carried out at pH 6.0 on theophylline pellets coated with various pectin HM/Eudragit® RL30D/Eudragit® NE30D blends. The influence of pectin HM and Eudragit® RL contents of the coatings and that of pectinolytic enzymes on the theophylline release from the coated pellets have been evaluated.

2. Materials and methods

2.1. Materials

The theophylline pellets were from the same batch used previously (Semdé et al., 2000). The water-insoluble acrylic ester polymers in form of aqueous dispersions (Eudragit® NE30D and RL30D) were gifts from Rohm Pharma (Darmstadt, Germany).

Eudragit® NE30D has been already described elsewhere (Lehmann, 1997; Semdé et al., 2000). Eudragit® RL is a slightly cationic copolymer consisting of ethylacrylate and methylmethacrylate containing quaternary ammonium groups (trimethyl-aminoethylmethacrylate chloride). Compared to the other water-insoluble polymers used for the preparation of sustained-release, film-coated oral dosage forms (ethylcellulose, Eudragit® NE and RS), Eudragit® RL is more hydrophilic, forming water-insoluble films which are characterized by higher water absorption, swelling and permeability (Lehmann, 1997).

Silicone emulsion (antifoam) and polysorbate 80 (wetting agent) were supplied from Vel S.A. and Welphar (Belgium), respectively. Pectinolytic enzymes and pectin HM were described previously (Semdé et al., 2000). All other materials used were of analytical reagent grade.

2.2. Preparation of coating dispersions

Aqueous gels containing 2.5–3.5% w/w of pectin HM, were prepared by stirring at 500 rpm (Ika Werk, Germany) pectin HM with distilled water until complete dissolution.

The pH of pectin gels and of the Eudragits® NE30D and RL30D aqueous dispersions were adjusted to 5.0 with 1 M NaOH or 1 M HCI.

A quantity of 3.2% w/w (in relation to the solid content of the Eudragit® RL30D latex) of polysorbate 80 was stirred with the specified amount of Eudragit® RL30D latex. Then an appropriate amount of pectin HM gel was slowly added with stirring. The resulting aqueous dispersions of pectin HM–Eudragit® RL30D complexes were slowly added with stirring to the specified amount of the Eudragit® NE30D latex containing 3.2% w/w (in relation to the solid content of the Eudragit® RL30D latex) of silicone emulsion.

Finally, the total solid contents of the resulting coating aqueous dispersions whose compositions are presented in Table 1 and Table 2, were adjusted to their appropriate values with distilled water.

Table 1
Formulations of the aqueous dispersions used for the preparation of the pectin HM/Eudragit® RL/Eudragit® NE mixed film-coatings, intended to studying the influence of the pectin HM content of the coatings on the theophylline release from the coated pellets[a]

Formulation	1	2	3	4	5	6
Eudragit® NE30D (in dry basis)	100.0	100.0	100.0	100.0	100.0	100.0
Eudragit® RL30D (in dry basis)	50.0	50.0	50.0	50.0	50.0	50.0
Pectin HM (in dry basis)	5.0	6.3	7.5	10.0	12.5	15.0
Polysorbate 80 (g)	1.6	1.6	1.6	1.6	1.6	1.6
Silicone emulsion (g)	1.6	1.6	1.6	1.6	1.6	1.6
Water ad (g)	1180	1000	1000	1000	1060	1100
Solid content (% w/w) of the dispersion	13.3	15.9	16.1	16.3	15.6	15.3
Pectin HM/Eudragit® RL (% w/w)	10	12.5	15.0	20.0	25.0	30.0
Pectin HM/acrylic polymers (% w/w)	3.33	4.16	5.00	6.67	8.33	10.00
Coating level (% w/w) (mean ± SD, $n = 3$)	20.2 ± 0.2	19.5 ± 0.8	19.8 ± 0.5	19.2 ± 0.1	18.9 ± 0.1	19.1 ± 0.9

[a] The Eudragit® RL content of the coatings is set at 50% w/w, in relation to that of Eudragit® NE.

Table 2
Formulations of the aqueous dispersions used for the preparation of the pectin HM/Eudragit® RL/Eudragit® NE mixed film-coatings, intended to study the influence of the Eudragit® RL content of the coatings on the theophylline release from the coated pellets[a]

Formulation	1	2	3
Eudragit® NE30D (in dry basis)	100.0	90.0	75.0
Eudragit® RL30D (in dry basis)	50.0	67.5	75.0
Pectin HM (in dry basis)	7.5	8.4	9.4
Polysorbate 80(g)	1.6	2.2	2.4
Silicone emulsion (g)	1.6	2.2	2.2
Water ad (g)	1000	1070	1000
Solid content (% w/w) of the dispersion	16.1	15.9	16.4
Pectin HM/acrylic polymers (% w/w)	5.0	5.4	6.3
Eudragit® RL/Eudragit® NE (% w/w)	50	75	100
Coating level (% w/w) (mean ± SD, $n = 3$)	19.5 ± 0.8	18.9 ± 0.3	19.4 ± 0.9

[a] The pectin HM content of the coatings is set at 12.5% w/w, in relation to that of Eudragit® RL.

The preparation of the coating aqueous dispersions has to be performed carefully (pH 5.0, presence of polysorbate 80, slow addition of pectin HM gels to the Eudragit® RL30D latex, formation of pectin HM–Eudragit® RL complexes before blending the Eudragit® RL30D and NE30Ddispersions...), in order to prevent the flocculation of NE30D latex by Eudragit® RL30D.

These two colloidal aqueous dispersions are indeed incompatible since their particles have opposite electrokinetic potential charges (Schmidt and Bodmeier, 1999).

The formation of pectin HM–Eudragit® RL complexes allows not only to neutralize the positive charges present on the particle surface of the Eudragit® RL30D latex but also to provoke at higher proportions of pectin HM, the appearance of negative charges which results in the compatibility between the Eudragit® RL30D and NE30D aqueous dispersions.

2.3. Coating process

The coating of theophylline pellets was performed as previously described (Semdé et al., 2000) in a fluidized-bed apparatus, using each coating dispersion (Table 1 and Table 2) until the desired coating level was deposited. The inlet and outlet temperatures of the drying air were 36 ± 1 and 28 ± 1°C, respectively. The coating dispersions were pumped at a flow rate of 9.5–11.5 ml/min and the pneumatic spraying pressure was 1 bar. The total spraying times ranged between 90 and 120 min.

After coating, the resulting coated pellets were cured at 60°C for 15 ± 1 h. These aging conditions have been shown to be sufficient for obtaining the complete stabilization of the permeability of coating films (Amighi and Moës, 1997). The coating levels of the coated pellets given in Table 1 and Table 2, were calculated after having determined the drug contents of the uncoated and coated pellets by UV-spectroscopy at 272 nm.

2.4. In vitro dissolution studies

The in vitro dissolution studies were carried out in the same conditions as previously (Semdé et al., 2000).

3. Results and discussion

3.1. Influence of the pectin HM content of the complexes and of the pectinolytic enzymes on the theophylline release from the coated pellets

The theophylline pellets were coated with about 19% w/w of the Pectin HM/Eudragit® RL/Eudragit NE (X:5:10) ternary blends whose pectin contents were 10.0, 12.5, 15.0, 20.0, 25.0 and 30.0% w/w, in relation to that of Eudragit® RL.

The Eudragit® RL content of the coatings was set at 50% w/w related to that of Eudragit® NE (Table 1).

Fig. 1 shows the curves of the theophylline release from the pectin HM/Eudragit® RL/Eudragit NE (X:5:10) coated pellets, obtained in absence of pectinolytic enzymes.

Except for the coating containing 10.0% pectin HM related to the Eudragit® RL, the dissolution profiles are characterized by an initial latency phase corresponding to a slow release, whose duration depends on the pectin HM content of the coatings and corresponds probably to the time required for the dissolution media to diffuse and stabilize the hydrodynamic exchanges across the coatings. After the initial phase, the theophylline release from the coated pellets is linear as a function of time. Indeed, the linear regression analysis carried out on the linear parts of the drug release curves, gives linear regression coefflcients ranging from 0.9961 to 0.9999.

The rates of theophylline release are 14.3 ± 0.4, 3.09 ± 0.02, 3.00 ± 0.02, 2.56 ± 0.07, 2.85 ± 0.01 and 3.37 ± 0.03 mg/h for the pellets coated with pectin HM/Eudragit® RL/Eudragit® NE blends for which the pectin HM contents of the coatings are, respectively 10.0, 12.5, 15.0, 20.0, 25.0 and 30.0% w/w (related to that of Eudragit® RL).

As can be seen, the theophylline release rate is highly influenced by the pectin HM content of the coatings and is minimal when the latter is 20% w/w (related to that of Eudragit® RL). These results suggest that the complexation between pectin HM and Eudragit® RL is optimal when the pectin HM content of the coating film is 20% w/w (related to that of Eudragit® RL).

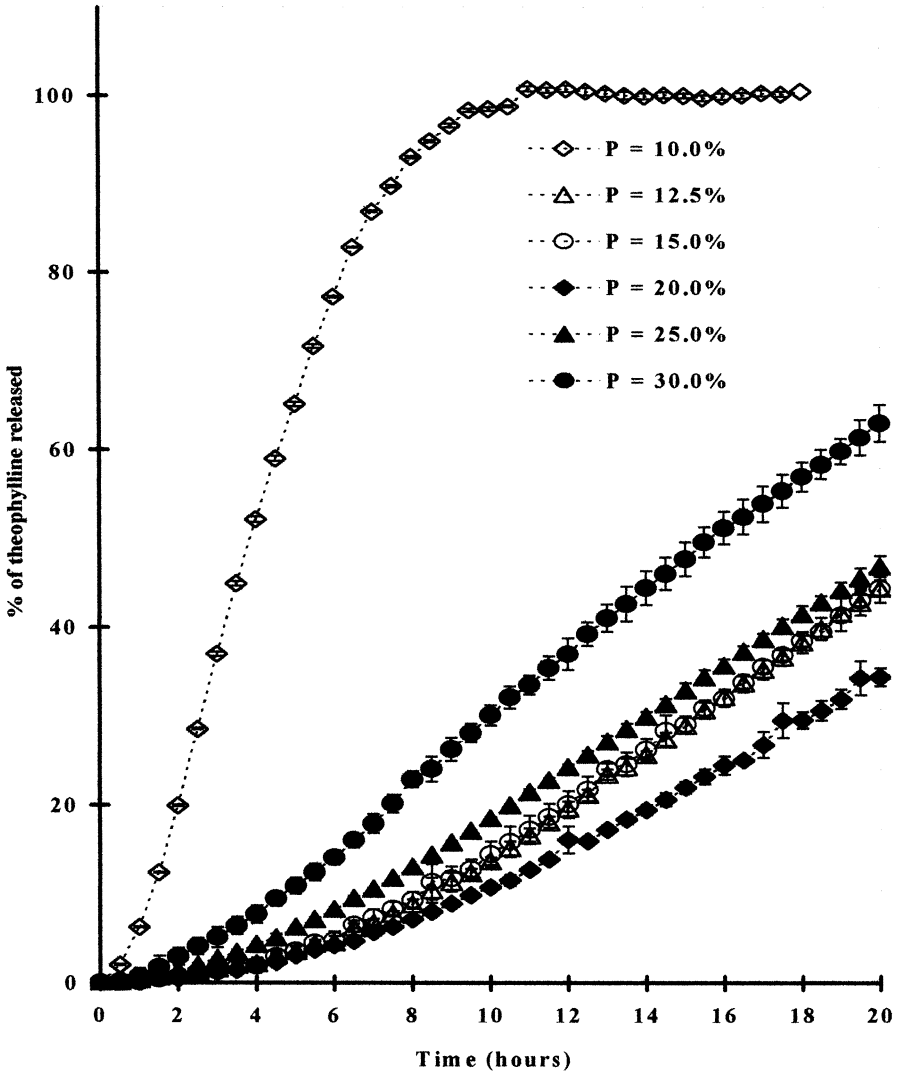

Fig. 1. Influence of the pectin HM content of the complexes (10.0, 12.5, 15.0, 20.0, 25.0 and 30.0% w/w, in relation to that of Eudragit® RL) on the theophylline release (mean ± SD, $n = 5$), at pH 6.0 and in absence of the pectinolytic enzymes, from the pellets coated with about 19% w/w of pectin HM/Eudragit® RL/Eudragit® NE (X:5:10) blends. The Eudragit® RL content of the coatings is 50% w/w, in relation to that of Eudragit® NE.

At the optimal complexation state indeed, the hydrophilicity, the ionic charge, the solvation and the swelling of pectin HM and Eudragit® RL must be minimal. Consequently, the coating permeability and the release of theophylline which is hydrophilic, from the coated pellets are also minimal.

In Fig. 1, it can be observed also that the theophylline release is much more rapid from the pellets coated with the ternary mixture of pectin HM/Eudragit® RL/Eudragit® NE (X:5:10) for which the pectin HM content of the coating is 10.0% w/w (related to that of Eudragit® RL).

The low pectin HM content of the coating is probably responsible for this fast release. In that case indeed, the amount of pectin HM available is insufficient to saturate completely the positive charges of the Eudragit® RL particles. Therefore,

after the formation of pectin HM–Eudragit® RL complexes, the excess of Eudragit® RL particles still positively charged is not only able to increase the coating permeability but also to disrupt the formation and the physical properties of the film.

Indeed, during the addition of the pectin HM–Eudragit® RL (l:10) complex to the Eudragit® NE30D latex, the flocculation of the colloidal particles followed by an increase of the viscosity of the coating dispersion have been observed.

Although the coating has been easily carried out after appropriate dilution of the coating dispersion (Table 1, formulation 1), the quality of the film-coating has been probably affected significantly. Based on this observation, film-coatings whose pectin HM content is below 10.0% w/w (related to that of Eudragit® RL) have not been studied.

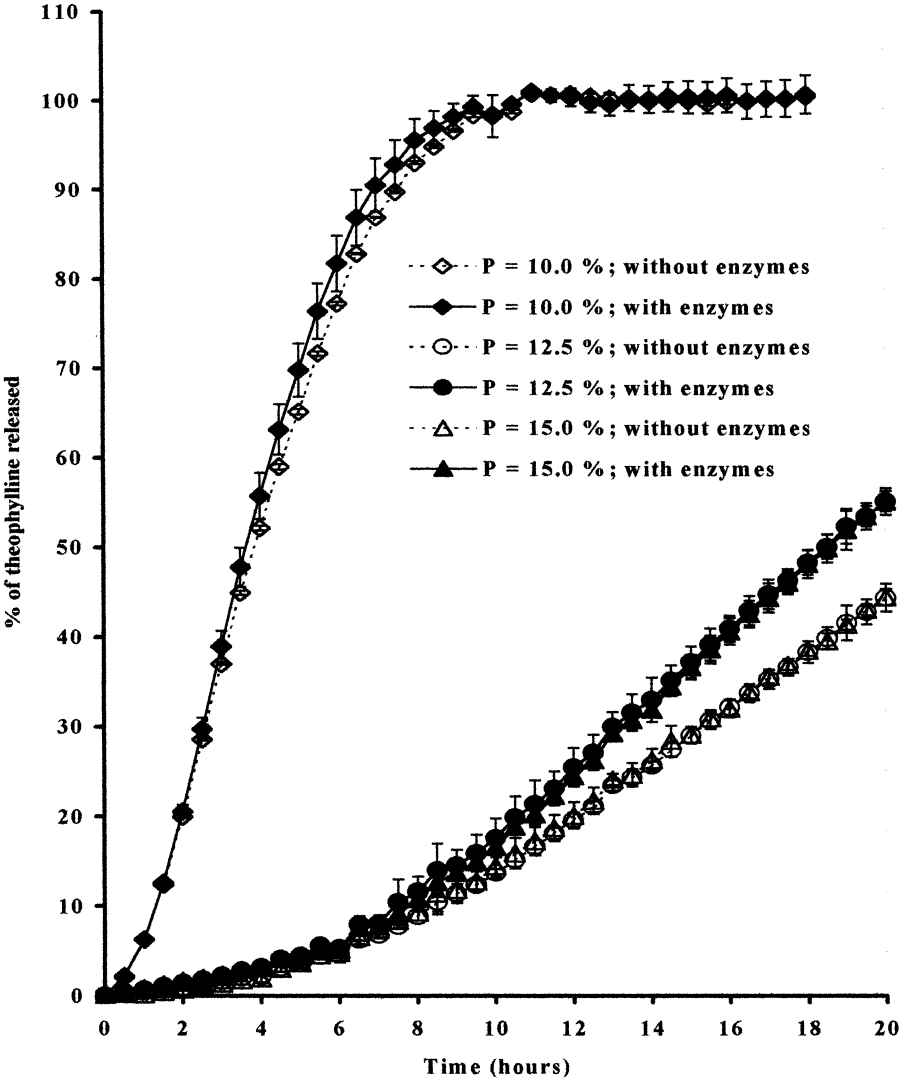

Fig. 2. Influence of the pectinolytic enzymes on the theophylline release (mean ± SD, $n = 5$), at pH 6.0, from the pellets coated with about 19% wlw of pectin HM/Eudragit® RL/Eudragit® NE (X:5:10) blends containing 10.0, 12.5, and 15.0% w/w of pectin HM, in relation to that of Eudragit® RL. Dotted lines, in absence of the enzymes, full lines, in presence of the enzymes.

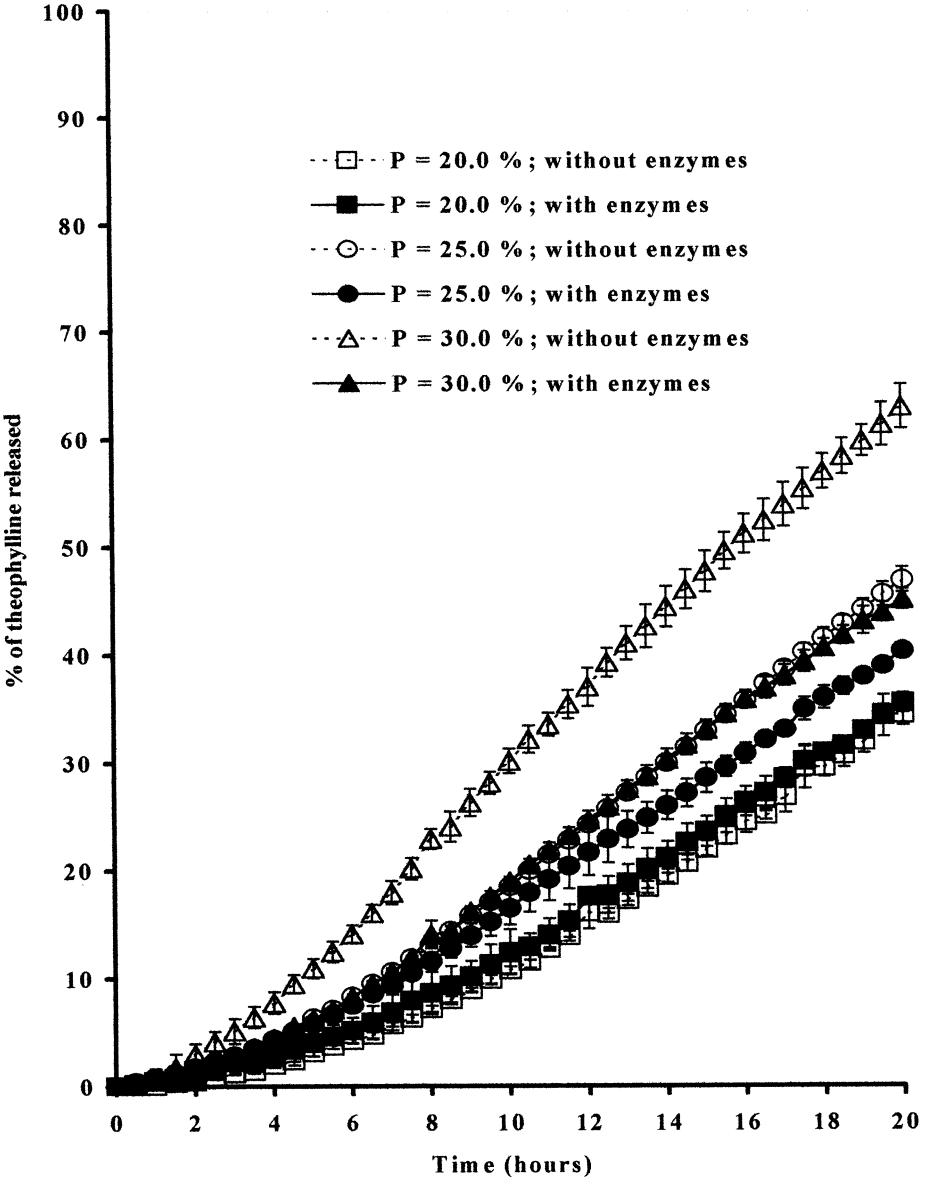

Fig. 3. Influence of the pectinolytic enzymes on the theophylline release (mean ± SD, $n = 5$), at pH 6.0, from the pellets coated with about 19% w/w of pectin HM/Eudragit® RL/Eudragit® NE (X:5:10) blends containing 20.0, 25.0, and 30.0% w/w of pectin HM, in relation to that of Eudragit® RL. Dotted lines, in absence of the enzymes; full lines, in presence of the enzymes.

Figs. 2–4 show the influence of the pectinolytic enzymes on the theophylline release from the pellets coated with pectin HM/Eudragit® RL/Eudragit® NE (X:5:10) blends. The examination of these three figures allows to observe that depending on the pectin HM content of the coatings, the presence of the enzymes in the dissolution media results in either a decrease (pectin content higher than 20% w/w related to that of Eudragit® RL), or an increase (pectin content below 20% w/w, related to that of Eudragit® RL) or non-significant modification of the theophylline release rate

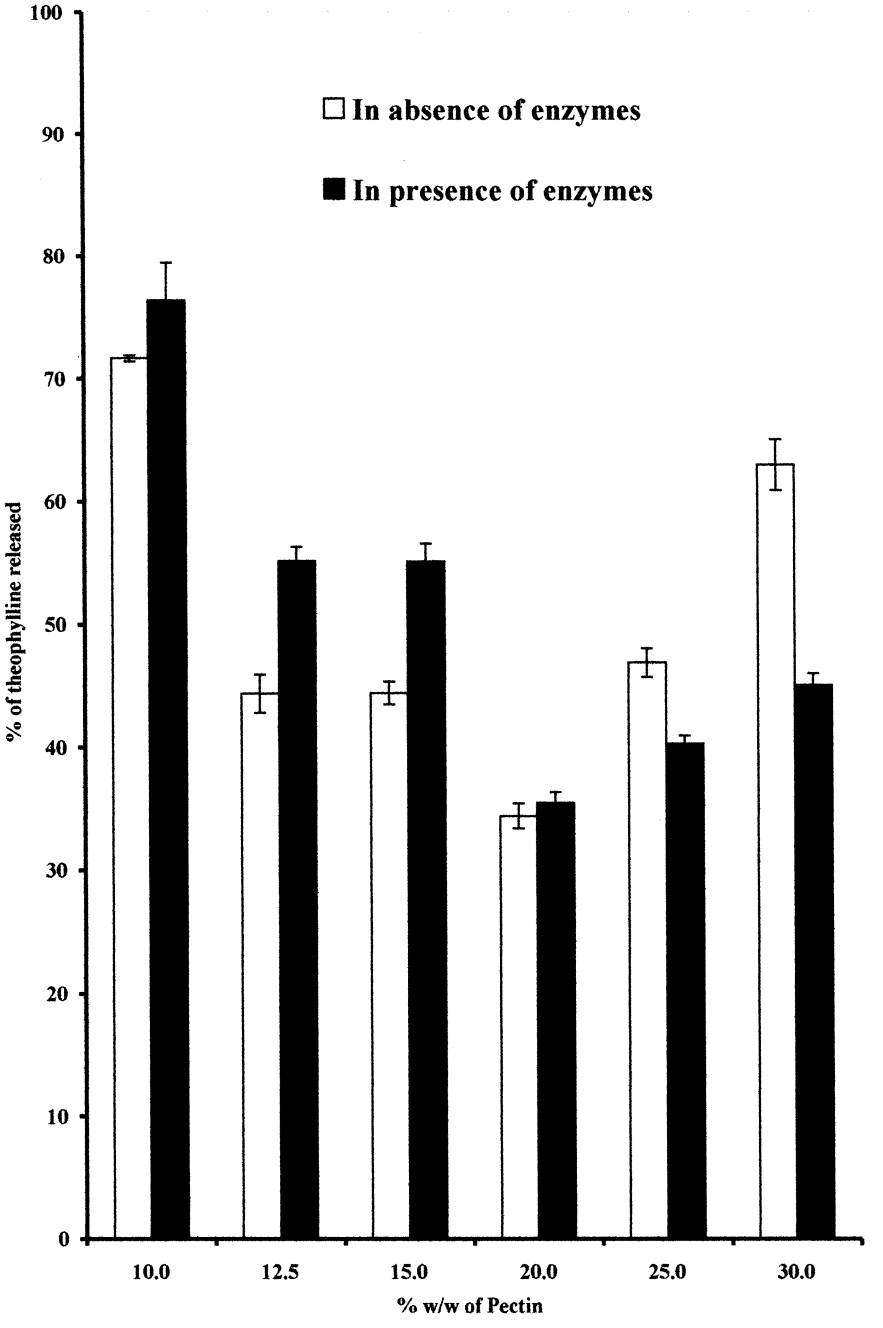

Fig. 4. Influence of the pectinolytic enzymes on the percentages of theophylline released (mean ± SD, $n = 5$), after 20 h of the dissolution tests, from the pellets coated with about 19% w/w of pectin HM/Eudragit® RL/Eudragit® NE (X:5:10) blends containing 12.5, l5.0, 20.0, 25.0, and 30.0% w/w of pectin HM, in relation to that of Eudragit® RL. For the coated pellets whose coating contains 10.0% w/w of pectin HM (in relation to that of the Eudragit® RL), the results shown are those obtained after 5 h of the dissolution tests.

(pectin content equal to 20% w/w related to that of Eudragit® RL).

When the pectin HM content of the coatings is higher than that corresponding to the optimal complexation with Eudragit® RL (20% w/w, related to that of Eudragit® RL), the action of the pectinolytic enzymes results in the slowing down of the theophylline release from the coated pellets (Figs. 3 and 4). This observation can be explained by the fact that the excess of pectin which is hydrophilic, favors the release of hydrophilic drugs such as theophylline. Consequently, the degradation and the leaching of the pectin excess from the coatings in presence of the pectinolytic enzymes will result in the decrease of the hydration and permeability of the coatings to theophylline.

When the pectin HM content of the coatings ranged from 10 to 15% w/w (related to that of Eudragit® RL), the amount of pectin present is below that which gives the optimal complexation with Eudragit® RL. The degradation and the leaching of pectin from the coatings in presence of the pectinolytic enzymes will result in the liberation of the cationic and hydrophilic molecules of Eudragit® RL. Hence, the polymer recovering its original properties, can solvate, swell and induce the appearance of distensions in the film-coatings. As a result, the release of theophylline from the coated pellets is increased in presence of the enzymes (Figs. 2 and 4).

On the other hand, no significant effect of the pectinolytic enzymes has been observed on the theophylline release from the coated pellets when the pectin HM content of the coatings is equal to 20% w/w (related to that of Eudragit® RL) (Figs. 3 and 4).

At this pectin HM content, the complexation between pectin HM (anion) and Eudragit® RL (cation) is optimal and the coating permeability is minimal (Figs. 1, 3 and 4). Therefore, it can be supposed that the coating is not permeable to the pectinolytic enzymes or the action of the enzymes results in the neutralization of two opposite effects on the coating permeability, namely the decrease of the permeability due to the leaching of the excess of pectin from the coatings and the increase of the permeability due to the liberation of the cationic and hydrophilic molecules of Eudragit® RL.

Fig. 5 shows that in absence of the pectinolytic enzymes, the release of theophylline from the pellets coated with pectin HM/Eudragit® RL/Eudragit® NE (0.75:5:10 w/w) blends is considerably influenced by the coating level. Indeed, the totality of theophylline is released in less than 20 h when the quantity of the coat deposited on the pellets is equal to $10.2 \pm 0.4\%$ w/w ($n = 3$). On the other hand, when the quantity of the coat deposited on the pellets is equal to $19.8 \pm 0.5\%$ w/w ($n = 3$), only 45% of theophylline is released within the same time.

Moreover, Fig. 5 shows that the presence of the pectinolytic enzymes in the dissolution media results in an increase of the theophylline release from the coated pellets. However, this increase does not depend on the coating level since the maximal difference observed between the percentages of theophylline released in presence of the pectinolytic enzymes (55%) and those obtained in absence of the enzymes (45%) is about 10%, whatever the amount of coating material deposited on the pellets. It can be noticed also that this maximal difference is more rapidly reached when the coating level is low (after 6 to 8 hours if the coating level is equal to $10.2 \pm 0.4\%$ w/w vs. 16–18 h when the coating level is equal to $19.8 \pm 0.5\%$ w/w).

3.2. Influence of Eudragit® RL and pectinolytic enzyme contents on the theophylline release from the coated pellets

As shown in the previous section, a slower release of theophylline occurs in absence of the pectinolytic enzymes and a more significant increase of the theophylline release is observed in presence of the enzymes when the pectin HM contents of the coatings are 12.5 or 15.0% w/w (related to that of Eudragit® RL) (Figs. 2 and 4).

Based on this observation, the pectin HM content of the coatings has been set to 12.5% w/w (related to that of Eudragiti RL) for studying the influence of the Eudragit® RL and pectinolytic enzyme contents on the theophylline release from the pellets coated with the pectin HM/Eudragit® RL/Eudragit® NE ternary mixtures.

The coating levels of the pellets were about 19% w/w and the Eudragit® RL contents of the coatings were 50, 75 and 100% w/w, in relation to those of Eudragit® NE (Table 2).

The drug release profiles from these coated pellets obtained in absence and in presence of the pectinolytic enzymes, are shown in Fig. 6.

As can be seen, in absence of pectinolytic enzymes the increase of the Eudragit® RL content of the coatings results in the increase of the drug release. As an example, the times required for releasing 40% of the theophylline content (t_{40}) in absence of enzymes are equal to 18.5, 5.5 and 4.0 h for the pellets coated with pectin HM/Eudragit®

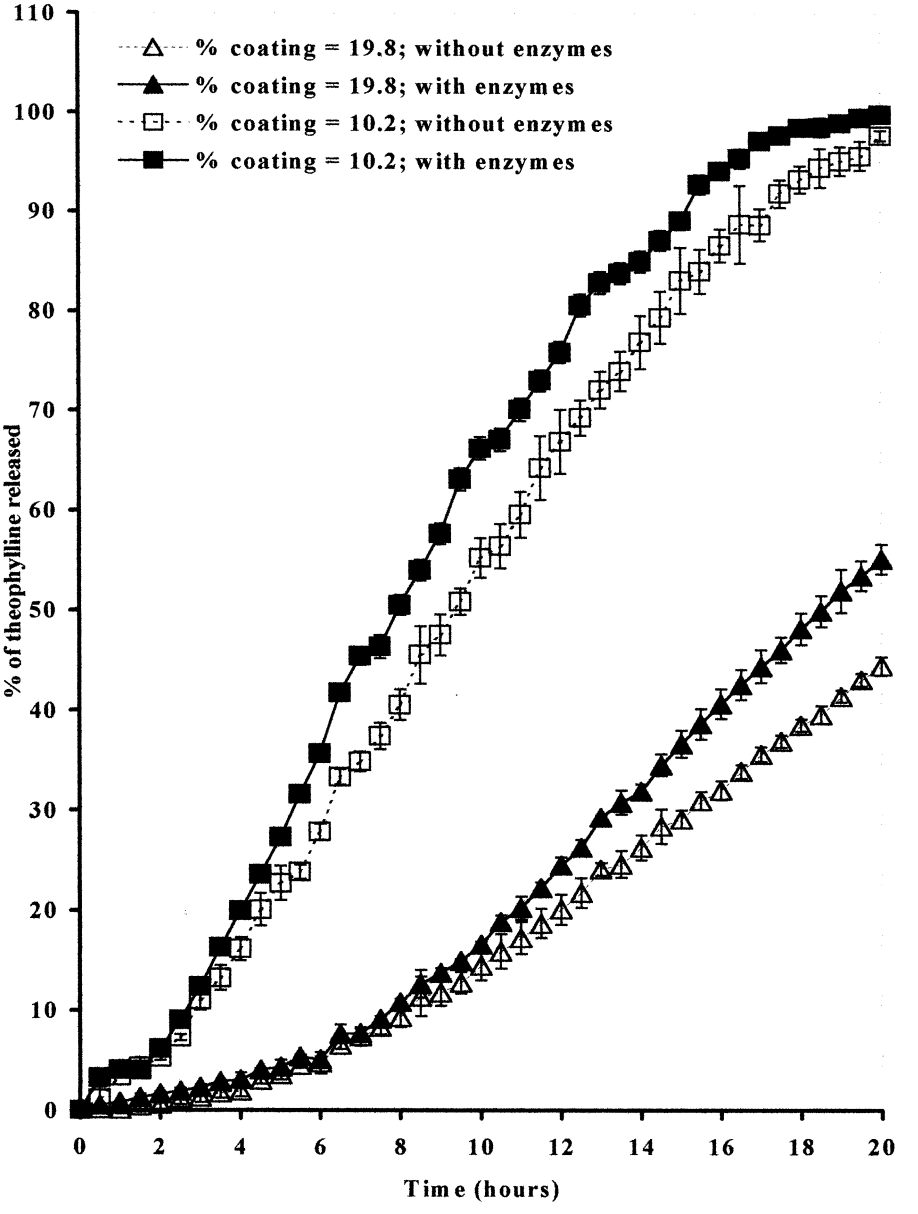

Fig. 5. Influence of the coating level (% coating) and the pectinolytic enzymes on the theophylline release (mean ± SD, $n = 5$), at pH 6.0, from the pellets coated with pectin HM/Eudragit® RL/Eudragit® NE (0.75:5:10 w/w) blends.

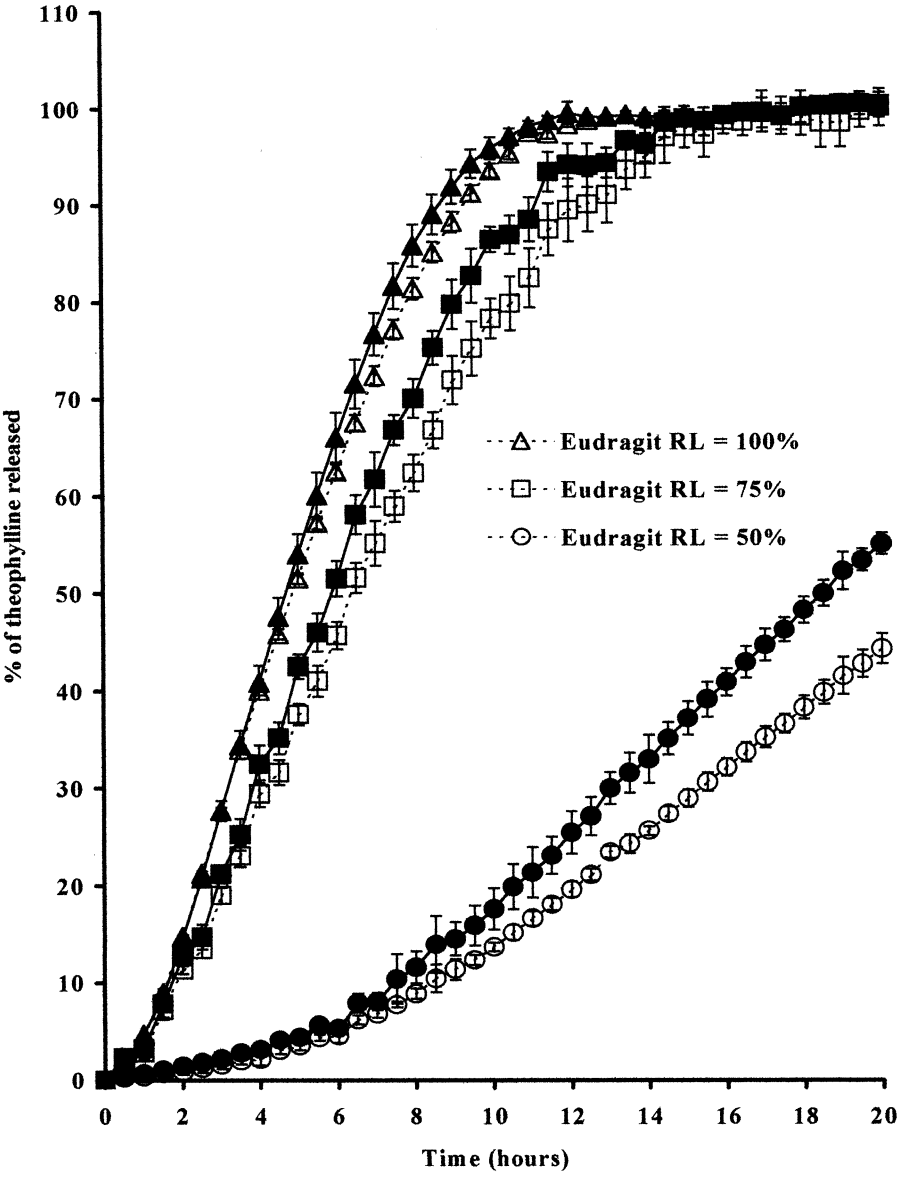

Fig. 6. Influence of the Eudragit® RL content of the coatings (50, 75 and 100% w/w, in relation to that of Eudragit® NE) and that of the pectinolytic enzymes on the theophylline release (mean ± SD, $n = 5$), at pH 6.0, from the pellets coated with about 19% w/w of pectin HM/Eudragit® RL/Eudragit® NE blends. The pectin HM content of the coatings is 12.5% w/w, in relation to that of Eudragit® RL. Dotted lines, in absence of the enzymes; full lines, in presence of the enzymes.

RL/Eudragit® NE blends, containing, respectively 50, 75 and 100% wlw Eudragit® RL (related to that of Eudragit® NE).

In Fig. 6, it can be observed also that the presence of pectinolytic enzymes in the dissolution media results in an increase of the theophylline release. As discussed above, this observation was expected since the pectin content of the coatings ranged from 10.0 to 15.0% w/w (related to that of Eudragit® RL). However, the increase of the

theophylline release rate induced by the pectinolytic enzymes is much lower when the Eudragit® RL content of the coatings is increased from 50 to 100% w/w (related to that of Eudragit® NE).

In absence of enzymes indeed, the theophylline release rates are still high and not significantly different from those obtained in presence of enzymes when the Eudragit® RL content of the coatings varies from 75 to 100% w/w.

This is due to the increase of the permeability of the coatings when the Eudragit® RL content is increased so that the influence of enzymes on the coating permeability and on the theophylline release kinetics is low.

4. Conclusions

The study of the theophylline release from pellets coated with pectin HM/Eudragit® RL/Eudragit® NE ternary mixtures has shown that the presence of pectinolytic enzymes in the dissolution media results in an increase of the drug release rate when the pectin HM content of the coatings ranges between 10.0 and 15.0% w/w (related to that of Eudragit® RL) However, the increase of the theophylline release in presence of enzymes is low when the Eudragit® RL content of the coating films is increased from 50 to 75 and 100% w/w (related to that of Eudragit® NE).

Studies on complexes based on the substitution of Eudragit® RL by a gastrosoluble cationic polymer such as Eudragit® E or chitosans are currently in progress.

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