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Polyelectrolyte–Drug Complexes of Lambda Carrageenan and Basic Drugs: Relevance of Particle Size and Moisture Content on Compaction and Drug Release Behavior

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The interaction between polyelectrolytes (PE) and oppositely charged drugs (D) results in complexes (PE–D) that can be exploited in controlled release drug delivery systems. The aim of this work is to better understand the relevance of some preparative parameters such as moisture content and particle size on the performance of two PE–D complexes to be used in oral controlled release tablets. PE–D complexes containing diltiazem HCL (DTZ) or metoprolol tartrate (MTP) and lambda carrageenan were obtained at two particle size levels (<45 μm and 75–105 μm), maintained at different values of relative humidity (RH) (11, 52, 75, and 93%), and compressed. The tablets were characterized for porosity, hardness, moisture content, and contact angle. Drug release profiles were fitted to the Weibull equation, and a factorial design was used to understand the relevance of particle size and RH% on release rate as a function of medium pH. The results indicated that the hydrophobic character of the complex between PE and D depended on the drug and in the present case was more pronounced for DTZ than for MTP. This in turn affected the possible release mechanism and therefore the importance of particle size and RH%.

Keywords polyelectrolyte–drug complexes; lambda carrageenan; diltiazem; metoprolol; controlled release

INTRODUCTION

When polyelectrolytes (PE) are used as excipients in pharmaceutical formulations, the release of oppositely charged drugs (D) can be strongly influenced by ionic interactions. These interactions can be exploited to prepare polyelectrolyte–drug complexes (PE–D) that can be compacted in tablet matrix systems. The PE–D complexes contain a molecular dispersion of D in the mass of the matrix because D is ionically bonded to the functional groups of PE.

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The PE–D complexes in some cases can result in the occurrence of insoluble products from which the drug is displaced over time by means of the ions present in the medium. This mechanism presents some similarities with that of ion exchange resins, which are still a suitable and quite widely used technology for controlled release. The employment of soluble polymers instead of cross-linked resins can, in some cases, bring about additional advantages, especially in the case of oral drug delivery. In fact, because of the combination of dissociation and erosion, a pseudo-zero order drug release can be maintained for a long period of time, and after the drug is released, the polymer dissolves completely (Konar & Kim, 2001).

In literature, it is possible to find many applications of the PE–D systems, based on carrageenan (Bonferoni et al., 1998), carbomer (Lu et al., 1991), Eudragit (Holgado et al., 1995), and methyl methacrylate derivatives (Konar & Kim, 1999; Nujoma & Kim, 1996). A systematic study of their properties is not available, however, and many aspects of their behavior need further investigation.

Still recently, swellable drug–PE matrices obtained by compaction of powdered complexes of Carbomer 934-P fully or partially neutralized with an ionizable drug (D) have been characterized for their swelling behavior in different media (Bettini, Zanellotti, Colombo, Bonferoni, & Caramella, 2003; Jimenez Kairuz, Llabot, Allemandi, & Manzo, 2005).

Among the carrageenan–drug complexes, matrices aimed at being administered once or twice a day for controlled release of diltiazem were prepared by compaction of the complex that was previously dried and milled (Bonferoni, Rossi, Ferrari, & Caramella, 2004). Taking the critical steps of the preparative procedure into account, it seemed necessary to investigate the influence of both moisture content and particle size of the interaction product on its tableting properties and on its drug release profiles. It is known that water, in opportune amount, can act as a plasticizer by improving tableting behavior. Also the particle size can be relevant for tablet

consolidation as it is related to the surface area involved in interparticle bonds (Malamataris, Karidas, & Goidas, 1994; Nokhodchi & Javadzadeh, 2007).

In this work, diltiazem HCl (DTZ) and metoprolol tartrate (MTP) were chosen as model drugs because the complexes that they form with lambda carrageenan have been previously characterized (Bonferoni, Rossi, Ferrari, Bettinetti, & Caramella, 2000; Viseras et al., 2000). In particular it was observed that in the case of DTZ, a poorly soluble product is obtained, whereas the complex of carrageenan with MTP easily hydrates to give a viscous solution (Aguzzi et al., 2002). The present investigation also enhances the understanding of the peculiar behavior of carrageenan-based PE–D systems.

MATERIALS AND METHODS

Materials

Lambda carrageenan was of high-viscosity grade (Viscarin® (GP 209, FMC, Prodotti Gianni, Milan, Italy). DTZ (Profarmaco, Milan, Italy) and MTP (Moehs, Barcelona, Spain) were used as model drugs.

Methods

Preparation of the PE–D Complex

The interaction products (PE–D) were prepared as previously described (Bonferoni et al., 2004). Briefly, drug and carrageenan powders were mixed in a drug:polymer ratio corresponding to the maximum binding capacity (63:37 wt/wt for DTZ; 67:33 wt/wt for MTP) as previously calculated by interaction isotherms. It was previously confirmed that, in this way, the drug and polymer amounts corresponded to the stoichiometry of the PE–D complexes (Aguzzi et al., 2002; Bonferoni et al., 2000). The powders were blended for 10 min (roller mixer Bibby Sterlin, UK) and then wetted with distilled water at 37°C to obtain a paste. Afterwards, they were kneaded for about 20 min to allow the reaction between polymer and drug to occur. The products were dried in an oven at 45°C overnight, milled (ball miller IG.W2/E, Giuliani, Turin, Italy), and sieved. The following sieve fractions were obtained: 75–105 μm and <45 μm.

Tablet Preparation

Before compression, PE–D complexes were dried in the presence of P_2O_5 and then stored in desiccators at controlled relative humidity until constant weight was reached (about 15 days). Four humidity levels (from 11 to 93%) were obtained by placing saturated salt solutions in the desiccators at 25ºC (Table 1) (Callahan et al., 1982).

PE–D complexes were then compressed at 3 tons for 30 s by means of a hydraulic press (Perkin-Elmer, Milan, Italy) equipped with 10-mm flat punches. Tablets containing 200 mg of drug were prepared. All the tablets were equilibrated for 24 h at constant RH (11, 52, 75, and 93%) before testing.

TABLE 1
Saturated Salt Solutions and Corresponding RH Levels

Saturated Salt Solution (25ºC)	RH (%)
LiCl	11
$Mg(NO_3)_2$	52
NaCl	75
KNO_3	93

Tablet Characterization

Contact Angle Measurements. Measurements were carried out by means of a surface wettability tester (AB Lorentzen & Wettre, Stockholm, Sweden), by measuring height (*h*) and diameter (*d*) of a water droplet laying on the tablet surface. All the measurements were carried out in triplicate.

Porosity. Tablet porosity (ε) at time zero and after 24 h was calculated as follows:

$$\varepsilon(\%) = \left[1 - \left(\frac{4w}{\pi d^2 h \rho}\right)\right] \times 100 \quad (1)$$

where *w* is the tablet weight, *d* is the tablet diameter, *h* is the tablet height, and ρ is the true density of the powder.

Tablet diameter and tablet height were measured by using a micrometer (mod. 7305, Mitutoyo Co., Tokyo, Japan). True density was determined by means of a Helium picnometer (Micromeritics, Atlanta, GA, USA). All the measurements were carried out in triplicate.

Tablet Crushing Strength. A crushing test was carried out by means of Schleuninger-2E equipment (Tecnogalenica, Milan, Italy). All the measurements were carried out in triplicate.

Drug Release Studies

Release tests were performed using dissolution equipment (Sotax AT7, Sotax, Milan, Italy) having a peristaltic pump (Esapump, Advanced Products, Milan, Italy) and a UV-VIS detector (Spectracomp 602, Advanced Products). A preliminary investigation was made to be sure that carrageenan did not interfere with drug absorbance. Measurements were carried out using the basket apparatus (USP 30) at 37°C, 100 rpm, with 500 mL of dissolution fluid. Tablets were tested in pH 1.2 simulated gastric fluid (SGF) without enzymes (USP 30) and in pH 6.8 simulated intestinal fluid (SIF) without enzymes (USP 30).

Measurements were carried out in triplicate.

Statistical Analysis. Effects of RH%, particle size of PE–D powder, and pH of the medium on drug release were studied in a 3^2 full factorial design. The design was divided in three blocks (Bolton, 1997), each one including two consecutive levels of humidity (11–52; 52–75; 75–93%), two levels of particle size (low level: <45 μm; high level: 105–75 μm,), and two levels of pH (low level: pH1.2; high level: pH 6.8), as shown in Table 2.

The response variable was the release rate, indicated by the time at which 63.2% of the labelled amount of drug was released from the tablet (td), calculated by fitting dissolution curves with the Weibull equation (Langenbucher, 1976). Fitting was performed on raw data from the release test by means of a non-linear regression software.

Significance of factor effects and of their interactions was assessed by analysis of variance (ANOVA) of the experimental responses performed by means of Statgraphics® 5.0 statistical package (Statistical Graphics Corporation, Rockville, MD, USA).

TABLE 2
Matrix of the Factorial Design

Block	Run	Factors		
		RH (%)	Particle Size (μm)	pH
1	1	11 *(–1)*	<45 *(–1)*	1.2 *(–1)*
	2	52 *(1)*	<45 *(–1)*	1.2 *(–1)*
	3	11 *(–1)*	75–105 *(1)*	1.2 *(–1)*
	4	52 *(1)*	75–105 *(1)*	1.2 *(–1)*
	5	11 *(–1)*	<45 *(–1)*	6.8 *(1)*
	6	52 *(1)*	<45 *(–1)*	6.8 *(1)*
	7	11 *(–1)*	75–105 *(1)*	6.8 *(1)*
	8	52 *(1)*	75–105 *(1)*	6.8 *(1)*
2	9	52 *(–1)*	<45 *(–1)*	1.2 *(–1)*
	10	75 *(1)*	<45 *(–1)*	1.2 *(–1)*
	11	52 *(–1)*	75–105 *(1)*	1.2 *(–1)*
	12	75 *(1)*	75–105 *(1)*	1.2 *(–1)*
	13	52 *(–1)*	<45 *(–1)*	6.8 *(1)*
	14	75 *(1)*	<45 *(–1)*	6.8 *(1)*
	15	52 *(–1)*	75–105 *(1)*	6.8 *(1)*
	16	75 *(1)*	75–105 *(1)*	6.8 *(1)*
3	17	75 *(–1)*	<45 *(–1)*	1.2 *(–1)*
	18	93 *(1)*	<45 *(–1)*	1.2 *(–1)*
	19	75 *(–1)*	75–105 *(1)*	1.2 *(–1)*
	20	93 *(1)*	75–105 *(1)*	1.2 *(–1)*
	21	75 *(–1)*	<45 *(–1)*	6.8 *(1)*
	22	93 *(1)*	<45 *(–1)*	6.8 *(1)*
	23	75 *(–1)*	75–105 *(1)*	6.8 *(1)*
	24	93 *(1)*	75–105 *(1)*	6.8 *(1)*

() Coded levels.

RESULTS AND DISCUSSION

Tablet Characterization

In Figure 1, the porosity of DTZ tablets is given, for the <45 μm and for the 75–105 μm particle size fractions. Contact angle and tablet crushing strength values are given in Table 3.

At time zero, as was expected, the porosity of the tablets prepared with the fine particles was always lower than that of the tablets prepared with the 75–105 μm fraction. For both the particle size fractions, the tablet porosity decreased with the increase of the RH% level at which the powders were stored. This behavior can be explained by a plasticizing effect of moisture that during compaction favors plane- and particle-slipping, increasing the particle deformation and therefore the final area of contact between the particles. After 24 h, with the only exception of the lowest RH level (11%), porosity increased with respect to time zero, and the increase in RH% corresponded to an increase in tablet porosity. This seemed more evident especially in the highest sieve fraction (75–105 μm). This effect can be interpreted as an instability of the compacts, and it can be explained with the occurrence of elastic recovery. This hypothesis would be in line with the relationship

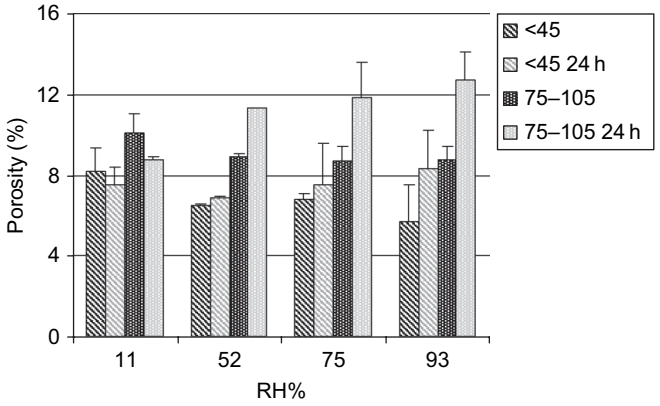

FIGURE 1. Porosity of the tablets based on DTZ–carrageenan complex, <45 μm and 75–105 μm fractions, measured immediately after preparation and after 24 h.

TABLE 3
Characterization of the DTZ–Carrageenan Tablets

RH%	Contact Angle		Crushing Strength (Kp)		Moisture Absorbed (%)	
	<45 μm	75–105 μm	<45 μm	75–105 μm	<45 μm	75–105 μm
11	43 (± 1.5)	50 (± 2.7)	>20	12.3 (± 0.9)	ND	ND
52	30 (± 5.5)	49 (± 0.3)	>20	11.9 (± 0.2)	2.6	4.0
75	26 (± 3.2)	37 (± 1.5)	17.6 (± 0.6)	11.1 (± 0.6)	3.7	4.7
93	32 (± 4.7)	15 (± 0.9)	8.2 (± 0.6)	9.6 (± 0.6)	10.8	8.3

that can be observed between RH% levels and the crushing strength values of the tablets (Table 3): we can consider that the tablets prepared with the PE–D complex stored at higher moisture levels have poorer mechanical characteristics. This can be explained with the more important increase in porosity observed during the first 24 h at 75 and 93% RH% levels. Some different works in literature point out the effects of water on compaction behavior of polymers such as hydroxypropylmethyl cellulose (HPMC), depending on the strength of association of moisture to the polymer particles (Malamataris et al., 1994). Water adsorbed as a monomolecular layer should increase Van der Waals forces, smooth the surface micro-irregularities, favor the plastic behavior, and, as a result, increase the tablet strength. Although in this work, complete sorption–desorption isotherms have not been obtained, it seems likely that water adsorption reduces tablet tensile strength because of condensation and multilayer adsorption occurrence (Malamataris et al., 1994; Nokhodchi & Javadzadeh, 2007).

Finally, as was expected, the higher the RH% level, the easier the wetting of the tablets was, as indicated by the decrease of contact angle values (Table 3).

Analogous considerations could be made in the case of MTP–carrageenan tablets, whose characterization is illustrated in Figure 2 and Table 4. Also in this case, at time zero, the porosity of MTP tablets decreased with increasing moisture level. After 24 h, porosity increased at all RH% values for the higher fraction, but only at 75% RH% for the <45 μm fraction.

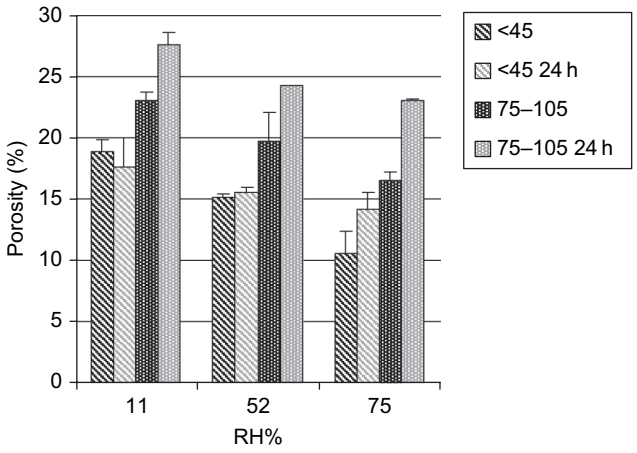

FIGURE 2. Porosity of the tablets based on MTP–carrageenan complex, <45 μm and 75–105 μm fractions, measured immediately after preparation and after 24 h.

However, in the case of MTP, some important differences were observed in comparison with DTZ. Wetting measurements showed that the MTP interaction product was significantly more hydrophilic in comparison with DTZ, as the contact angle values were always lower, even at 11% RH%. At 93% RH%, for the high amount of water adsorbed (16%, wt/wt), the MTP–carrageenan complex became too soft and impossible to be compressed. The sample stored at the highest RH% level was therefore not considered for tablet characterization and release tests. Crushing strength was always significantly lower than for the DTZ–carrageenan based tablets and not even detectable at 75% RH%.

Moreover, It must be considered that the amount of water adsorbed by both DTZ and MTP based PE-D products is not particularly as high as could be expected with carrageenan polymer. In fact it is reported in literature that this polymer can contain from 14% to 17% (wt/wt) water after exposure to 50% RH (Picker, 1999). The results obtained in the present study with drug–carrageenan complexes, confirm that the interaction with the drug results in a product more hydrophobic with respect to the polymer.

Release Test and Statistical Analysis

DTZ–Carrageenan Complex

Figure 3 illustrates the drug release profiles obtained with the tablets prepared with DTZ–carrageenan complex of lower particle size fraction (<45 μm). The profiles obtained with powders maintained at the different RH% values are compared. Figure 3a and 3b refer to the release profiles in pH 1.2 and in pH 6.8 buffer, respectively. Similarly, Figure 4a and 4b compare the effects of different RH% storage in the case of the coarser particle size fraction (75–105 μm), at pH 1.2 and 6.8 respectively. A different sensitivity of the two particle size fractions to the RH% effect appears immediately evident. To better clarify this aspect but also to highlight the relevance of the medium pH, a statistical analysis was performed using the values of the td parameter obtained by the fitting of the release curves according to the Weibull equation. Among the parameters of this equation, the td, that can be related to the time necessary to release the 63% of the dose, was used as an

TABLE 4
Characterization of the MTP–Carrageenan Tablets

	Contact Angle		Crushing Strength (Kp)		Moisture Absorbed (%)	
RH%	<45 μm	75–105 μm	<45 μm	75–105 μm	<45 μm	75–105 μm
11	27 (± 2.4)	23 (± 0.1)	7.8 (± 0.2)	2.2 (± 0.4)	ND	ND
52	27 (± 4.2)	16 (± 1.6)	8.9 (± 0.1)	3.0 (± 0.1)	3.0	4.0
75	19 (± 3.2)	24 (± 3.2)	ND	ND	4.2	5.9
93	ND	ND	ND	ND	16.6	16

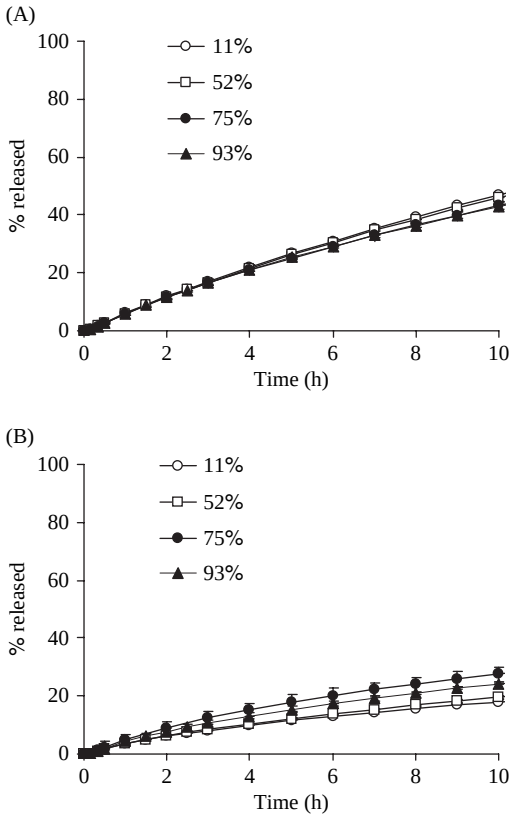

FIGURE 3. Release profiles obtained with DTZ size fraction <45 μm. The profiles obtained with powders maintained at the different RH% values are compared in pH 1.2 (a) and pH 6.8 (b).

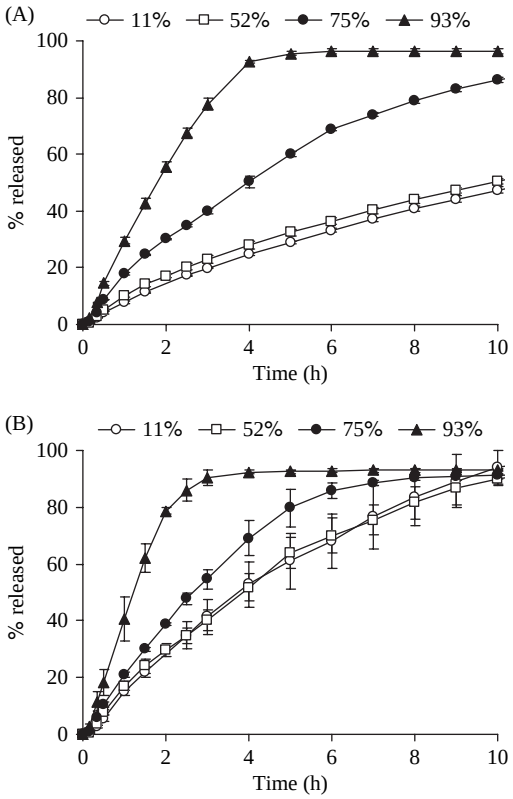

FIGURE 4. Release profiles obtained with DTZ size fraction 75–105 μm. The profiles obtained with powders maintained at the different RH% values are compared in pH 1.2 (a) and pH 6.8 (b).

expression of the release rate. The comparison of td values for the different curves was performed within each block of the factorial design, considering the relevance of RH% step by step: three ANOVA were therefore performed, referring to the effects of the increase in RH% from 11% to 52%, from 52% to 75%, and from 75% to 93%. For all three blocks, all the main factors studied (particle size RH% and release medium pH) significantly affected drug release ($P < 0.05$). The estimated values of the main effects are given in Table 5. It should be remembered that negative effects mean that td decreases, and therefore the drug release rate increases as the factor level increases. So from Table 5 it can be seen that the drug release is always faster for particle size fraction 75–105 μm with respect to the fraction <45 μm, while it is always slower when a medium at pH 6.8 instead of one at pH 1.2 is used. Nevertheless, it can be observed that in all three blocks the absolute values of RH% effect is much lower than that of particle size and medium pH effect, indicating that this parameter, although statistically significant, is not so important for the overall system performance. In Figure 5, the interactions between the considered factors are illustrated. Significant interactions were observed in all cases except, in block 52–75% RH, between particle size and RH% and between RH% and medium pH.

TABLE 5
Main Effects Estimated for td Parameter (*h*) of the DTZ Release Curves

	RH% Levels		
	11–52%	52–75%	75–93%
Average	30.10	23.92	22.08
Particle size	–40.11	–33.24	–37.45
RH%	–4.27	–8.08	4.40
Medium pH	29.85	23.46	24.74

The interaction between particle size and RH% was significant in blocks 11–52% and 75–93%, although with opposite signs. This can suggest that the effect of particle size, that corresponds to slower releases at lower particle sizes, is less important at 52% RH% than at 11% RH%, and is more important at 93% than at 75% RH. A non linear RH% influence on particle size effect can be therefore envisaged. A similar trend can be found for the interaction between humidity and pH that was significant in block 11–52% with negative sign, and in block 75–93% with positive sign. In this case the highest RH% level corresponds to a higher sensitivity of the formulation to medium pH. It is therefore possible to see that the interactions

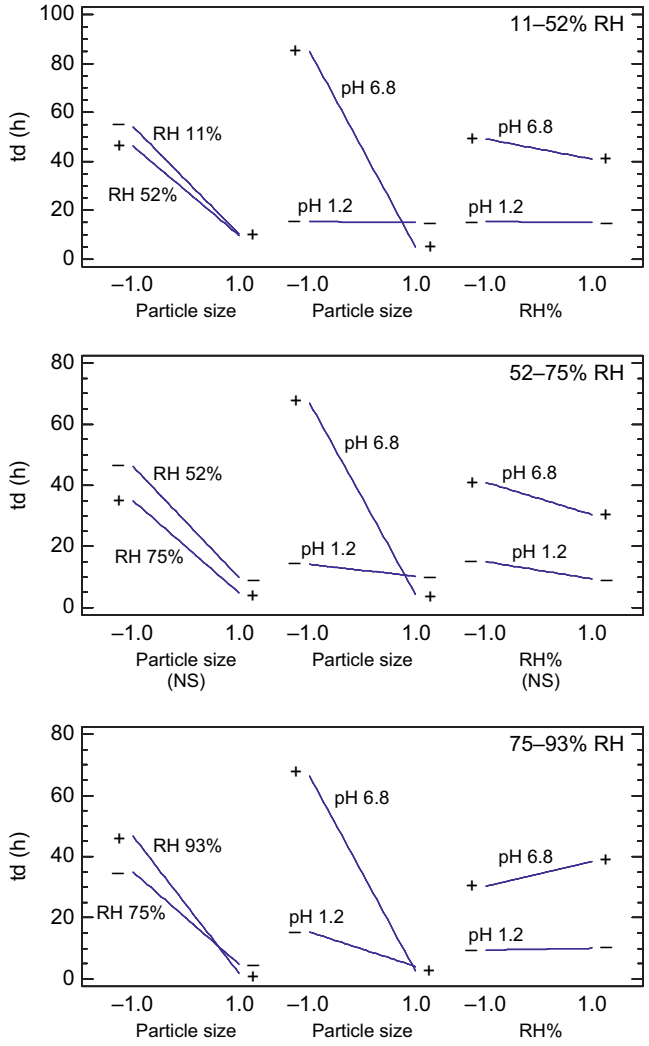

FIGURE 5. Interactions between the factors considered for the DTZ release (td parameter). The interaction between particle size and RH%, particle size and medium pH, RH% and medium pH are given for each block. The statistically non-significant interactions are indicated with (NS).

TABLE 6
Main Effects Estimated of the Considered Factors on the td Parameter (h) of the MTP Release Curves

	RH% Levels	
	11–52%	52–75%
Average	3.00	3.26
Particle size	–0.28	–0.27
RH%	0.08	0.42
Medium pH	1.47	1.76

involving RH% (AB and BC), although statistically significant, are weaker than that between particle size and medium pH. In particular, particle size effect was much stronger at pH 6.8 than at pH 1.2, and the pH effect was much lower for the low particle size fraction (<45 μm), confirming previous data obtained with the same drug (Bonferoni et al., 2004).

All the data obtained suggest that porosity plays a relevant role in the release behavior of DTZ–carrageenan tablets. This could, in fact, explain the relevance of particle size parameter on drug release. The DTZ–carrageenan system is characterized by a relatively high hydrophobic character, as previously observed (Aguzzi et al., 2002), and seems to be confirmed in the present work by the contact angle and moisture absorption data. Hence, it is conceivable that the release medium penetrates inside the tablet without inducing those phenomena of particle swelling and gel forming that are characteristics of hydrophilic matrices.

This is in line with what is pointed out in the literature, where a relationship was found between release mechanism, that can be swelling-based or leaching-based, and sensitivity to porosity and humidity of different kinds of matrix systems. In particular, where the release is mainly leaching-based, higher sensitivity to porosity can be expected (Nokhodchi & Javadzadeh, 2007).

MTP–Carrageenan Complex

Figure 6 illustrates the drug release profiles obtained with the tablets prepared with MTP–carrageenan complex of lower

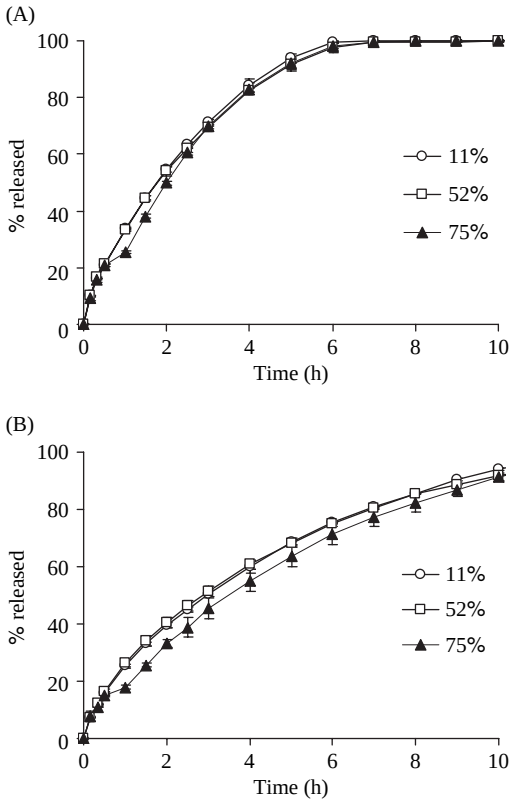

FIGURE 6. Release profiles obtained with MTP size fraction <45 μm. The profiles obtained with powders maintained at the different RH% values are compared in pH 1.2 (a) and pH 6.8 (b).

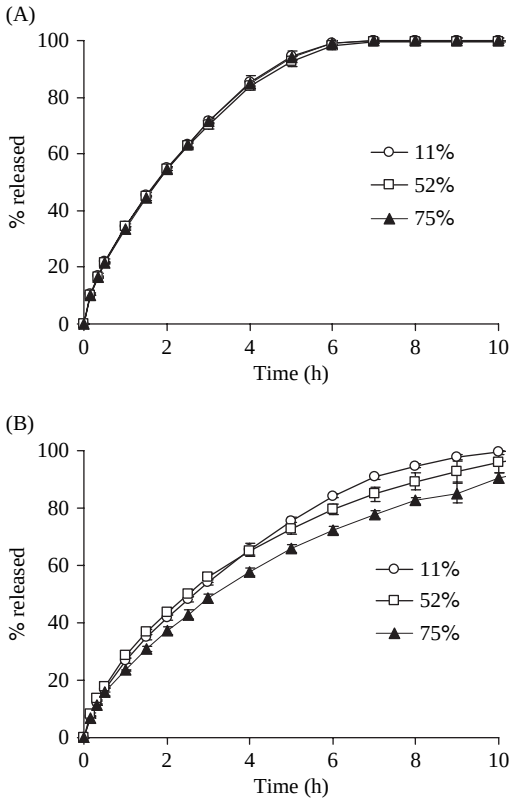

FIGURE 7. Release profiles obtained with MTP size fraction 75–105 μm. The profiles obtained with powders maintained at the different RH% values are compared in pH 1.2 (a) and pH 6.8 (b).

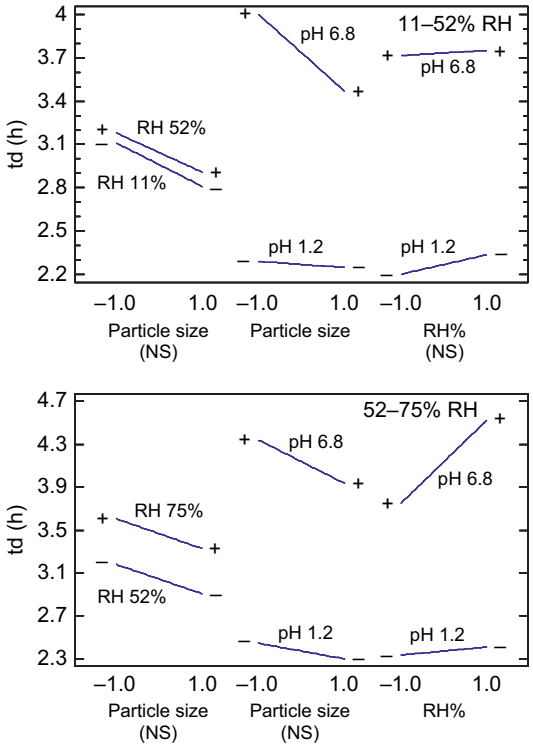

FIGURE 8. Interactions between the factors considered for the MTP release (td parameter). The interaction between particle size and RH%, particle size and medium pH, RH% and medium pH are given for the 11–52% and 52–75% RH blocks. The statistically non-significant interactions are indicated with (NS).

particle size fraction (<45 μm). The profiles obtained with powders maintained at the different RH% values are compared. Figure 6a and 6b refer to the release profiles in pH 1.2 and in pH 6.8 buffer, respectively. Figure 7a and 7b compare the effects of different RH% storage in the case of the coarser particle size fraction (75–105 μm), at pH 1.2 and 6.8 respectively. Looking at these release profiles, it is possible to see that differences between low and high particle size fractions are less pronounced that in the case of DTZ–carrageenan system. This was confirmed by the statistical analysis on the effect of the considered factors particle size, RH% and medium pH on td values as response. The ANOVA results showed that all the main factor effects were significant, like in the DTZ case, except for RH% in block 1. Nevertheless, as shown in Table 6, the absolute values of the main factor effects were noticeably lower in comparison with DTZ. In both the blocks the greater effect corresponded to the medium pH: release rate decreased with the increase of pH from 1.2 to 6.8. Less important was the particle size effect, particularly if compared to that observed with DTZ. Among the interactions (Figure 8), particle size-pH interaction was the only significant one for MTP and, as previously observed for DTZ, the effect of the particle size was greater at higher pH (6.8). The overall variability observed between the responses in the case of MTP was generally lower than that of DTZ. This behavior can be explained by the more hydrophilic character of this system compared to DTZ–carrageenan, as was previously reported (Aguzzi et al., 2002) and confirmed in the present work by the powder characterization. This accounts for MTP–carrageenan swelling and gel forming capacity during release test, and in turn makes the porosity of the tablet, whose release mechanism is conceivably based on erosion of the hydrated matrix, less relevant.

CONCLUSIONS

The results here reported show that for both the PE-D systems considered, especially particle size and to a much lower extent moisture content affected the compression behavior. The interaction between lambda carrageenan and basic drugs, as already shown in previous papers, greatly affected the properties of the polymer, changing its hydrophilic character and therefore both the hydration and the particle swelling. This can be suitably exploited for drug controlled release. Nevertheless, some important differences were observed, depending on the drug involved. The interaction between carrageenan and DTZ resulted in a poorly soluble and more hydrophobic complex compared to that obtained with MTP. The data here obtained indicate that DTZ–carrageenan tablets were not as sensitive to powder moisture content as the MTP–carrageenan ones. The

stronger hydrophilic character of the complex with MTP, allows it to more easily absorb moisture to levels where the particles become too soft to be compressed. For the same reason, however, the matrices swell and form a gel layer during the drug release that occurs with an erosion mechanism and is less sensitive to porosity and particle size. DTZ release profiles were on the contrary greatly affected by particle size, which was not so critical a factor for MTP. This is in line with the importance of porosity of the DTZ–carrageenan system. The statistical analysis confirmed that the choice of a suitable particle size fraction allows to obtain release profiles that are not only less variable but also less sensitive to the medium pH.

Finally, it must be considered that the tablets, object of this study, were obtained by direct compression of the PE-D complexes only, and probably the presence of some excipients and a suitable formulation will improve both the mechanical characteristics and release properties.

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