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Influence of Complex Solubility on Formulations Based on Lambda Carrageenan and Basic Drugs

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ABASTRACT The purpose of the present work was to compare the behavior of some drug/carrageenan complexes having different solubility in water, in a controlled release formulation. Diltiazem HCl, bupropion HCl, metoprolol tartrate, and tramadol HCl were used as model drugs. The complexes were characterized by means of solubility measurements, release test at constant surface area, and water uptake measurements, and the results were related to their performance in controlled release formulations. For the more soluble complexes (involving metoprolol and tramadol) the occurrence of gelation after hydration was observed, while diltiazem complex apparently did not gellify; bupropion behavior was intermediate. A correspondence was found between the observed differences in complex solubility and hydration-gelation behavior and the drug release profiles. For all the drugs considered, the release was completed in about 10 to 12 hours, but different kinetics were observed depending on the solubility of the complexes. All the considered complexes seem suitable for controlled release purposes, although the data obtained show the relevance of the complex solubility to drug release profiles.

KEYWORDS:

INTRODUCTION In hydrophilic matrices the polymer hydrates and swells to form around the tablet a gellified layer that represents a diffusional barrier for the release of the drug. Unless this layer's thickness is maintained, the release rate will vary and usually will decrease depending on the square root of time.

Researchers have recently begun to study polymer-drug interactions in pharmaceutical formulations, considering them not as a detrimental occurrence but rather as a beneficial event that helps control drug release [1].In the case of hydrophilic matrix tablets, a drug-polymer interaction can in fact be exploited to reduce the initial release rate of especially highly soluble drugs and to obtain more linear release profiles [2,3].Lambda carrageenan, an anionic sulfated polysaccharide from algae, is one of the polymers that have been studied for their ability to interact with oppositely charged drugs in oral controlled release tablets. Lambda carrageenan is characterized by the highest amount of sulfate groups in comparison with the analogous kappa and iota types [4].Previous studies have demonstrated that lambda carrageenan can interact strongly with basic drugs and that this interaction can be exploited in controlled release formulations especially in the case of very soluble drugs [5,6].A further approach involves obtaining the polymer-drug interaction product, which can be subsequently put into tablet form. In particular, a complex between carrageenan and diltiazem was used to prepare tablets giving almost constant drug release for up to 20 hours [7-9].

Some drugs, all characterized by high $pK_a$and high water solubility, have been shown to interact with lambda carrageenan in different ways. In some cases, the drug-polymer interaction produces a complex precipitation (such as with diltiazem), while in some other cases, although the occurrence of drug-polymer interaction is proved by dialysis equilibrium studies, the obtained complex is soluble and does not precipitate [10].

The aim of the present work is to study how complex solubility influenced performance in controlled release formulations. Drugs with high water solubility and quite high daily dose were chosen, because these characteristics make drug release control by means of classical matrix systems more difficult. A preliminary

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screening of complex solubility in water was performed by turbidimetric measurements, which give evidence of the precipitation of the complex. Bupropion HCl (BPH), an antidepressive drug, and diltiazem HCl (DTZ), used for the treatment of angina pectoris and hypertension, were chosen because their complexes with carrageenan have poor water solubility. Metoprolol tartrate (MTP), used in chronic antihypertensive therapy, and tramadol HCl (TRD), an analgesic drug, were chosen among the actives whose complex with carrageenan is soluble and does not produce any precipitate. The solubility of the complexes at 37°C was assessed by measuring the drug concentration in equilibrium with the solid in distilled water, gastric fluid with pH 1.2, and phosphate buffer with pH 6.8 (pH 5.8 was used in the case of bupropion for stability reasons). "Water uptake" measurements were effected on each complex at different particle sizes. The same test was performed also on lambda carrageenan for comparison purposes. A dissolution test at constant surface area was performed in the same 3 media as described above on the tableted complexes.
Finally, a formulation previously developed for diltiazem-lambda carrageenan complex [8]was used to prepare controlled release systems based on bupropion, metoprolol, and tramadol complexes. This formulation required a small amount of excipients to be added to the complexes, thus allowing the different complexes to be compared for their ability to control the drug release. Release tests were performed in gastric fluid with pH 1.2 and phosphate buffer with pH 6.8 (pH 5.8 in the case of bupropion for stability reasons).

MATERIALS AND METHODS

Materials

Lambda carrageenan was a high-viscosity grade Viscarin GP 209 (FMC, Prodotti Gianni, Milan, Italy). BPH and TRD were obtained from Dipharma (Milan, Italy); DTZ was obtained from Profarmaco (Milan, Italy); and MTP was obtained from Moehs (Barcelona, Spain). Hydroxypropylmethylcellulose (HPMC) Methocel K4M and Methocel E15 (Colorcon, Arpington, UK) were employed in matrix formulations. Cellulose acetate propionate 482 (Eastman-Kodak, Kingsport, TN, USA) was used for tablet coating.

Preparation of the complex

The complexes, hereafter referred to as BPH/carr, DTZ/carr, MTP/carr, and TRD/carr, were prepared using the following procedure [7].About 100 g of drug powders and carrageenan were blended in a turbula mixer (W. Bachofen, Basil, Switzerland) for 10 minutes. The following drug/carrageenan ratios were used: 51:49 (wt/wt) for BPH, 63:37 (wt/wt) for DTZ, 67:33 (wt/wt) for MTP, and 50:50 (wt/wt) for TRD. These ratios corresponded to the maximum binding capacity as obtained from interaction isotherms [11].

The minimum amount of distilled water necessary to obtain a paste was added, and kneading was effected at 37°C for about 20 minutes. The products were then dried in an oven at 45°C overnight, milled (ball miller IG.W2/E, Giuliani, Torino, Italy), and sieved. The content of drug in each complex was assayed spectrophotometrically (Spectracomp 602, Advanced Products, Milan, Italy) after dissolution of 100 mg of powder in 100 mL of HCl 0.1M. The following sieve fractions were obtained: 75 to 105 µm, <75 µm, and <45 µm.

Turbidimetric measurements

A 0.5% wt/vol solution of carrageenan in distilled water was dropped into a 5mM solution of drug in distilled water under constant stirring. The increasing turbidity that occurred when the complex precipitated was measured by spectrophotometry at 420 nm.

Solubility measurements

The solubility of the complexes (<75 µm fractions) at 37°C was assessed by measuring the drug concentration in equilibrium with the solid. After the equilibrium was reached (about 24 hours) the samples were quickly filtered, and the drug concentration was spectrophotometrically read. The solubility was determined in distilled water, simulated gastric buffer (without enzymes) with pH 1.2 (USP 24), and 0.05M KH_2PO_4/NaOH buffer (USP 24) that was adjusted to pH 6.8 for diltiazem, metoprolol, and tramadol and to pH 5.8 for bupropion, which showed a degradation at higher pH values.

Water-uptake measurements

The water-uptake versus time curves were determined by modified Enslin apparatus [12].Powder samples (100 mg) of 2 granulometric fractions of each complex were used (<45 µm and 75-105 µm). For comparison, the test was performed also in 100 mg of carrageenan (not sieved). The measures were done during 60 minutes in the same media used for the solubility measurements.

Release rate measurements at constant surface area

Exactly 250 mg of the complex (<75 µm fraction) were directly compressed in a Perkin-Elmer hydraulic press for KBr tablets with flat 13-mm punches at 5 tons for 1 minute. All the surfaces of the tablet except for 1 face (1.33 cm^2area) were coated with cellulose acetate propionate 15% wt/vol in acetone.
The coated face of the tablet was glued to a metallic disc to be maintained at the bottom of the vessel. The drug release was measured spectrophotometrically every 5 minutes in a USP 24 apparatus 2 (Sotax AT7, Sotax AG, Basel, Switzerland) at 50 rpm and 37°C in 500 mL of fluid. The drug release rate was expressed as mg released per unit of time and area (mg/min/cm^2) by linear fitting of the experimental points during the intervals 0 to 30, and 30 to 120, minutes.

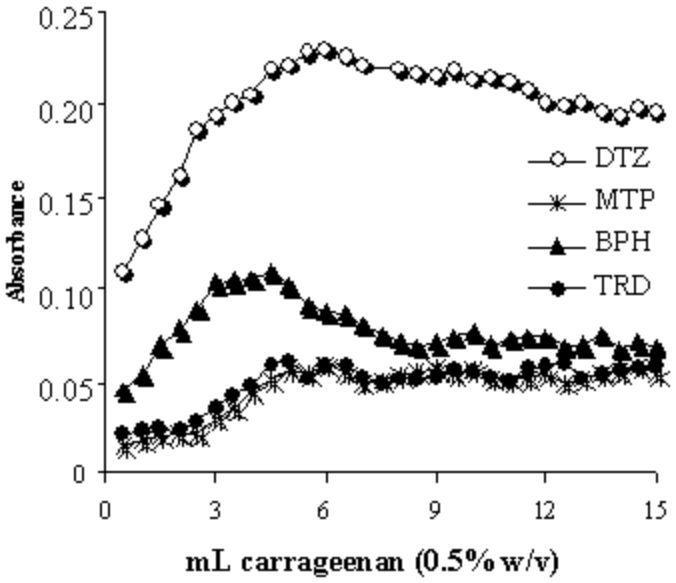

Figure 1. Turbidimetric curves from the interaction of the drugs (5mM) and carrageenan (0.5% wt/vol) solutions.

Some tablets, prepared as described, but of 10 mm diameter and uncoated, were hydrated in phosphate buffer pH 6.8 for 3 hours, without agitation, so that photographs could be taken.

Preparation of the tablets and release test

About 50 g of the interaction products (<75 µm fraction) were mixed with 5% wt/vol methocel K4M and granulated with a 5% (wt/vol) solution of methocel E15 in water. The wet mass was forced through a 700-µm sieve and dried at 50°C overnight. The content of drug in the granulate was assayed spectrophotometrically after dissolution of about 100 mg of granulate in 100 mL of HCl 0.1N.

After adding 2% of talc, the granulate was compressed in a Killian KIS reciprocating tableting machine (Guarneri and Mantelli, Milan, Italy) equipped with 11-mm convex punches. Small batches of about 50 tablets were obtained. Tablets containing 150 mg of bupropion, 200 mg of metoprolol, and 150 mg of tramadol were prepared.

The release test was performed in a USP 24 apparatus 1 at 100 rpm and 37°C in 500 mL of fluid. All the tablets were tested in pH 1.2 simulated gastric fluid (USP 24, without enzymes) and in 0.05M KH_2PO_4/NaOH buffer whose pH was adjusted to 6.8 for metoprolol and tramadol, and to 5.8 for bupropion. The drug release was determined spectrophotometrically. Experimental curves were fitted until 60% release according to the power law equation [13], by logarithmic linearization.

RESULTS AND DISCUSSION

Turbidimetric measurements

Figure 1 shows the results of turbidimetric measurements and gives evidence of the occurrence of interaction product precipitation. For DTZ/carr and, to a lesser extent, for BPH/carr, the curves show an increase of absorbance after addition of the lambda carrageenan solution. After the absorbance reaches a maximum, a decrease follows because of dilution of the sample. MTP/carr and TRD/carr absorbance is maintained always at quite low levels according to the lack of precipitation that characterizes the interaction of carrageenan with these drugs.

Table 1. Solubility of the Complexes Expressed as Drug Concentration at the Equilibrium*

Interaction Product	Solubility (mg/mL)			
	H_2O	pH 1.2	pH 6.8	pH 5.8
PH/carr	4.19	10.23	—	11.15
DTZ/carr	0.86	2.20	1.79	—
MTP/carr	>30	>30	>30	—
TRD/carr	>30	>30	>30	—

*BPH/carr indicates buproprion HCl/carrageenan; DTZ/carr, diltiazem HCl/carrageenan; MTP/carr, metoprolol tartrate/carrageenan; TRD/carr, tramadol HCl/carrageenan.

Solubility measurements

In **Table 1** , the solubilities of the complexes in the different media are given. The values obtained are in line with what was observed in the turbidimetric measurements.

DTZ/carr has the lowest solubility in all the media. In the case of MTP/carr and TRD/carr, it was impossible to attain an equilibrium in the presence of a solid phase, because the hydration continues to produce a viscous mass. BPH/carr shows solubility values intermediate between those of DTZ/carr and those of the other 2 drugs.

Water uptake measurements

Figure 2 shows the water uptake profiles of the 4 complexes at the 75 to 105 µm (**Figure 2a**) and <45 µm (**Figure 2b**) granulometric fractions. For comparison, the water uptake profile of lambda carrageenan is given in both figures. It can be seen that the behavior of the complexes is clearly different from that of the pure polymer. The polymer in fact absorbs water continuously, while it gellifies. After 1 hour (data not shown in the figure), the amount of water absorbed by carrageenan is about 6 g/g of polymer - that is, about 3 times higher than the amount absorbed by both the granulometric fractions of the complexes, and it appears to be still increasing. For the drug-polymer complexes, where the effect of the particle size has also been tested, it is evident that the highest granulometric fraction (75-105 µm) absorbs more water than the <45 µm fraction, probably because of the very high porosity of the powder samples. Especially for the 75 to 105 µm fraction, the absorption is quicker at the beginning of the test, but for both the granulometric fractions, the curves

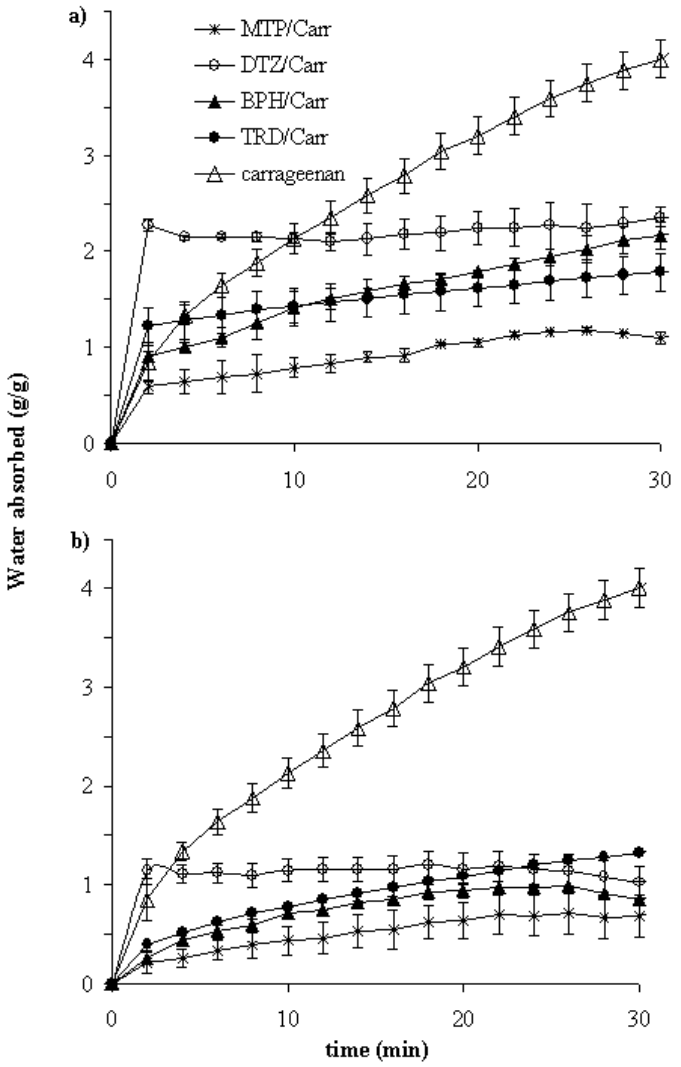

Figure 2. Water uptake curves of the 75 to 105 µm (a) and <45 µm (b) granulometric fractions of the 4 complexes, and of lambda carrageenan (unsieved) (mean values ± SD; 3 replicates).

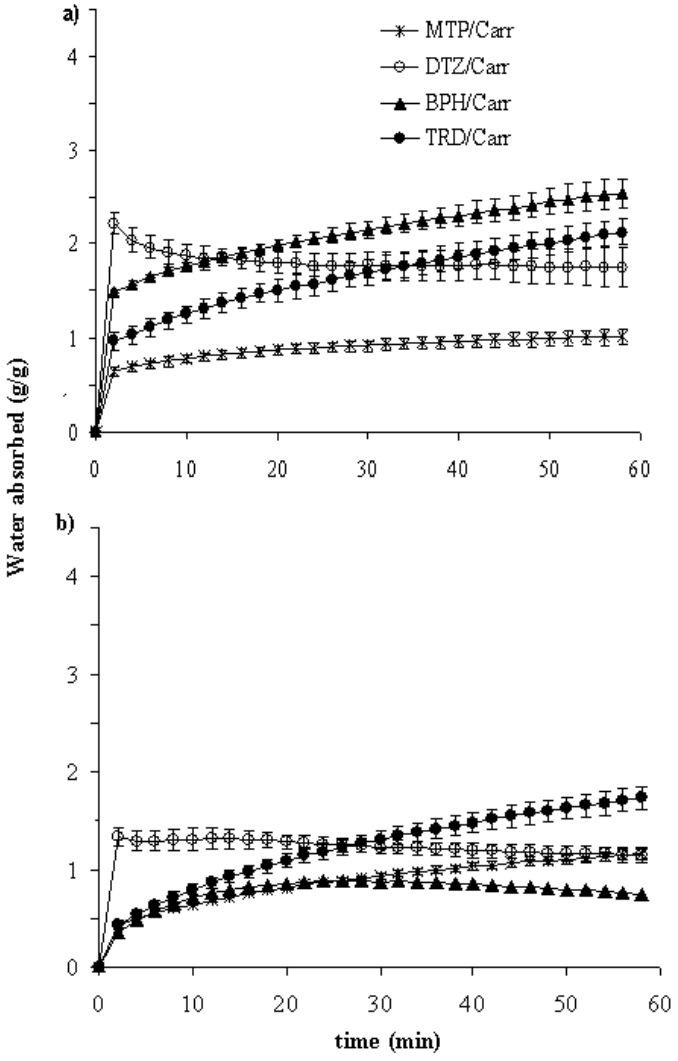

Figure 3. Curves of pH 1.2 buffer uptake for the 75 to 105 µm (a) and <45 µm (b) granulometric fractions of the 4 complexes (mean values ± SD; 3 replicates).

level off in a plateau. This behavior is most evident for DTZ/carr.

In **Figures 3** and **4** , the absorption profiles of pH 1.2 and pH 6.8 buffers are given, respectively. The results obtained with the 2 granulometric fractions are compared: **Figures 3a** and **4a** refer to the 75 to 105 µm fraction, and **Figures 3b** and **4b** refer to the <45 µm fraction.

It is possible to appreciate that also when the buffers are used in the test the absorption profiles of DTZ/carr are different from those of the other drugs, since they show a particularly abrupt increase and thereafter immediately stop. In pH 1.2 buffer, all curves obtained are quite similar to those of the test performed in distilled water. In pH 6.8 buffer, quick absorption of a large amount of buffer can be observed, especially for BPH/carr and TRD/carr. Also, MTP/carr absorbs in this case more than in water and in pH 1.2 buffer, although its profiles are in all cases the lowest.

Release rate at constant surface area

In **Table 2** , the results of the release rate test at constant surface area for all the interaction products in the 3 different media are given.

DTZ/carr is the only sample for which no relevant differences can be observed in all 3 media between the release rate during the first 30 minutes of the test and the release rate in the interval between 30 and 120 minutes. This means that the DTZ release profiles are linear. For all the other complexes, after 30 minutes a decrease in release rate occurs. This phenomenon is more pronounced in the case of MTP/carr, which also has the highest release rates. It can be assumed that the deviation from linearity that occurs after 30 minutes is related to the gelation of the complex. It was in fact possible to observe that at the end of the test, a gel layer was present at the surface of the tablets prepared with the most soluble products, such as MTP/carr and

Table 2. Release Rate at Constant Surface Area During the First 30 Minutes and in the Interval 30-120 Minutes from

Starting Test

Interaction Product	Release Rate (mg/min/cm²)							
	H_2O		pH 1.2		pH 6.8		pH 5.8	
	30 min	120 min	30 min	120 min	30 min	120 min	30 min	120 min
BPH/carr	0.39	0.20	0.37	0.23	—	—	0.35	0.12
DTZ/carr	0.08	0.08	0.09	0.07	0.09	0.07	—	—
MTP/carr	0.42	0.36	0.60	0.35	0.37	0.20	—	—
TRD/carr	0.25	0.17	0.30	0.21	0.28	0.14	—	—

*BPH/carr indicates buproprion HCl/carrageenan; DTZ/carr, diltiazem HCl/carrageenan; MTP/carr, metoprolol tartrate/carrageenan; TRD/carr, tramadol HCl/carrageenan.

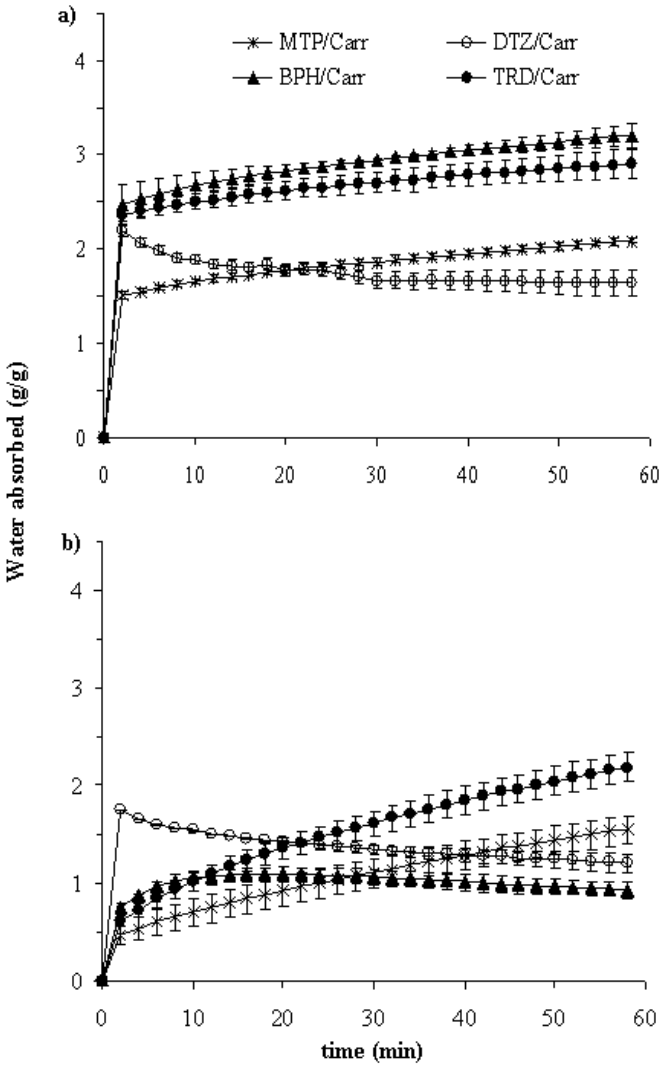

Figure 4. Curves of pH 6.8 buffer uptake for the 75 to 105 µm (a) and <45 µm (b) granulometric fractions of the 4 complexes (mean values ± SD; 3 replicates).

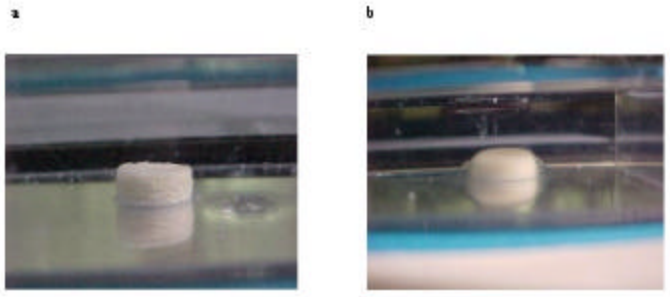

Figure 5. Pictures of MTP/carr (a) and DTZ/carr (b) complex tablets after 3-hour hydration in pH 6.8 phosphate buffer.

TRD/carr. No apparent gelation could be observed for DTZ/carr, while BPH/carr showed, in this respect, intermediate behavior.

A constant release rate can be expected from this test if the dissolution of the complex at the surface of tablet is the rate-limiting phenomenon. When a gel layer forms, it is possible that ions of medium come through it, interact with drug-polymer complex, and displace the drug, which in turn diffuses outside. The lower release rates observed in phosphate buffer could be in accordance with this hypothesis, as in neutral media the viscosity of lambda carrageenan is higher [14]and the carrageenan erosion is slower [15].

The different gelation of the complexes was confirmed by photographs of the tablets taken after hydration for 3 hours in phosphate buffer. In **Figure 5** , an example of 2 different behaviors is given. In the case of MTP/carr there is a gel layer around the tablet that is not visible at the surface of DTZ/carr.

Release test

Release profiles from formulations based on MTP/carr, TRD/carr, and BPH/carr granulated with HPMC are given in **Figures 6** , **7** , and **8** , respectively. Release rates are in all cases compatible with the aim of controlled release and are comparable with those obtained in the similar formulation based on DTZ/carr, previously described [8].In **Table 3** , the values of the parameters obtained by fitting the experimental curves

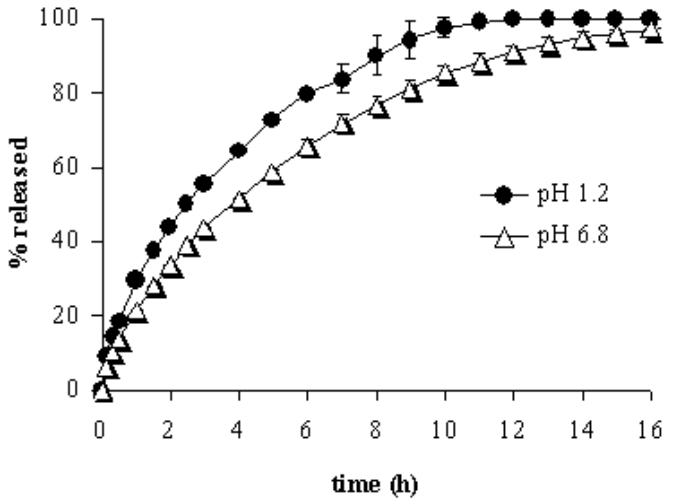

Figure 6. Release profiles of MTP in pH 1.2 and pH 6.8 buffers, from tablets containing 200 mg of drug (mean values ± SD; 3 replicates).

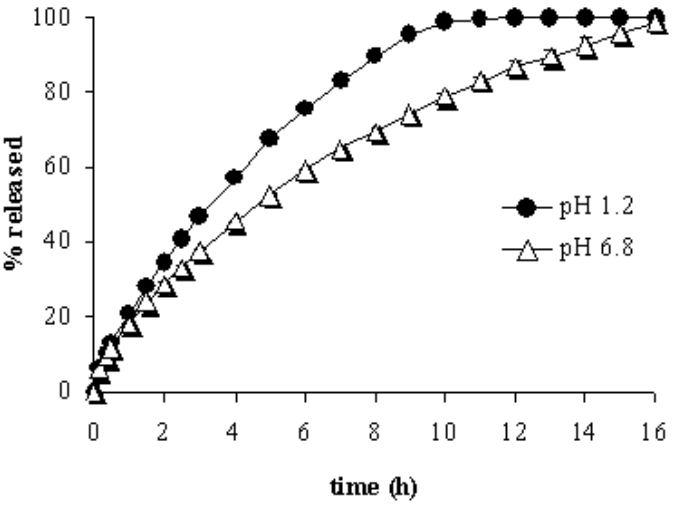

Figure 7. Release profiles of TRD in pH 1.2 and pH 6.8 buffers, from tablets containing 150 mg of drug (mean values ± SD; 3 replicates).

with the power law equation are given. The values obtained from the data of the same formulation previously developed for DTZ/carr [8]are also included, for comparison. The exponential parameter *n* in particular is useful to compare the release profiles and the possible mechanisms involved in the drug release.

Figure 6 shows that in the case of MTP/carr tablets, the drug release is prolonged for about 12 hours. The profiles are typically diffusive, as it is confirmed by the values of the power law exponent *n* (**Table 3**) that, for MTP release curves, are near 0.5. This is in accord with the occurrence of a gel layer at the surface of the MTP/carr tablets.

In **Figure 7** , it can be observed that the TRD release is prolonged for about 12 hours. The kinetic parameters *k* (**Table 3**) are comparable in both media with those of MTP, and, as in the case of MTP, show a higher release rate in pH 1.2 than in pH 6.8 buffer. Also in this case the *n* values are slightly higher than 0.5, suggesting that drug diffusion across a gel layer represents an important mechanism of release in this case as well.

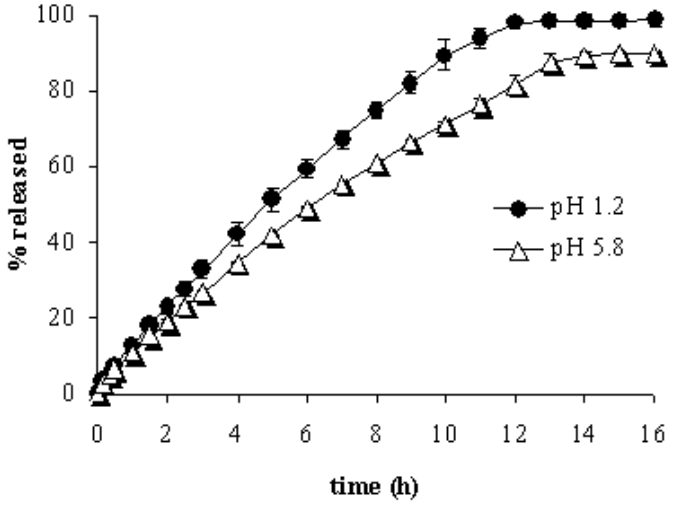

Figure 8. Release profiles of BPH in pH 1.2 and pH 6.8 buffers, from tablets containing 150 mg of drug (mean values ± SD; 3 replicates).

Table 3. Parameters of Power Law Equation for the Release Curves of the 4 Drugs*

Interaction Product	pH 1.2		pH 6.8		pH 5.8	
	n	*k*	*n*	*k*	*n*	*k*
BPH/carr	0.812	13.46	—	—	0.791	11.43
DTZ/carr	0.980	6.823	1.042	7.194	—	—
MTP/carr	0.615	28.57	0.653	21.04	—	—
TRD/carr	0.686	21.83	0.636	18.66	—	—

*BPH/carr indicates buproprion HCl/carrageenan; DTZ/carr, diltiazem HCl/carrageenan; MTP/carr, metoprolol tartrate/carrageenan; TRD/carr, tramadol HCl/carrageenan.

Figure 8 shows that BPH release is also prolonged for about 12 hours in both dissolution media. The release curves in the 2 buffers are closer in this case, as also indicated by the values of parameters *k* (**Table 3**). The profiles are closer to linearity than are those for MTP and TRD, as confirmed by the higher value of the exponent *n* of the power law. It can be supposed that in this case both slight gelation and erosion play a role in the mechanism of drug release.

CONCLUSION

Water uptake measurements in the 3 media are consistent with the solubility of the 4 complexes. DTZ/carr has a low solubility and absorbs immediately all the medium by capillarity; after that, it reaches an equilibrium and no more gelation seems to occur. MTP/carr and TRD/carr show slow but continuous absorption that suggests gelation, although one quantitatively lower than that of the original polymer. This proves that also in the case of soluble complexes the interaction with the drug involves a strong decrease in the polymer's original hydrophilic properties.

The release rate tests at constant surface area are also in accordance with water uptake results. In this test the

more pronounced differences can be observed between DTZ/carr, where no gelation could be observed at the surface of the tablet, and MTP/carr. This complex is in fact characterized by the highest release rate, and the occurrence of a gel layer at the tablets' surface suggests the importance of drug diffusion during the release and explains the lack of linearity in the release. The behavior of BPH/carr is in all cases intermediate between DTZ and the other drugs.

All these differences correspond with the release from the tested controlled release formulation. For the more soluble complexes a diffusive component in the release mechanism is evident, and it seems, at the moment, more difficult to obtain linear release profiles. In all examined cases, however, we have confirmed the suitability of systems based on drug-polymer interactions for the controlled release of those drugs that are very soluble and used at high dosages.

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