Physical characteristics of polymer complexes in suspension obtained from cellulosic latexes with ondansetron

A. RUIZ*, J. M. LLÁCER, E. MORALES, V. GALLARDO
Department of Pharmacy and Pharmaceutical Technology, Faculty of Pharmacy, University of Granada, E-18071 Granada, Spain
E-mail: adolfina@ugr.es

Ondansetron is a carbazol with antiemetic properties. It is used primarily to control nausea and vomiting caused by cytotoxic chemotherapy and radiotherapy, as well as in post-operative vomiting in gynecological surgery. Ondansetron has a half-life of ≈ 4 h, hence it is a matter of great interest to determine the ideal conditions for the formation of a drug-polymer complex in order to prolong the duration of the therapeutic action. A stability study of the active drug was first carried out on each of the polymers (Aquateric® and Aquacoat®). The adsorption of ondansetron on the lattices was determined with respect to time, pH and concentration. The results obtained suggest that both polymers are suitable as drug carriers for the controlled-release formulations obtained. We conclude that an acid pH is evidently fundamental in the adsorption process of this drug in the latexes. Moreover, the Aquateric® latex would seem to be the best-suited polymer to use as a vehicle for drug delivery.

1. Introduction

In antineoplasic chemotherapy, one of secondary effects are emetic problems (vomiting and gagging) and nausea, affecting 70–90% of patients. This emesis causes a decrease in the quality of life for cancer patients and can result in potentially effective therapies being abandoned.

Ondansetron is a carbazol endowed with an antiemetic action that involves competitive and selective antagonism of the 5 HT_3 receptors of serotonin. It is used for controlling nausea and vomiting induced by chemotherapy and cytotoxic radiotherapy, as well as in post-operative vomiting in gynecological surgery [1–3].

As ondansetron has a short half-life (≈ 4 h) [4, 5], the aim of this work is to determine the ideal conditions for the formation of a drug–polymer complex in order to prolong the duration of the therapeutic action.

Polymers are widely used nowadays due to their numerous range of applications, particularly within the biomedical field, where they are employed in the manufacture of controlled-release pharmaceuticals [6]. Latexes are colloidal dispersions with particles smaller than 1 μm [7]. In this type of system, special attention must be paid to how they are obtained, since their properties will depend not only on their composition and chemical structure, but also on the method used in their manufacture, which effects both the final particles size and the stability of the system. These preparations are based on the adsorption mechanisms of the drug on the latex surface, with which it must be biocompatible. The large specific surface of these systems makes them capable of transporting a huge quantity of drug, obviously a great advantage, as well as providing a slow, progressive release of the active ingredient. We used the polymers Aquateric® and Aquacoat® (cellulose derivatives) because they have approval for use in the body and are adequate drug vehicles, due to their high specific surface area, which allows absorption of large amounts on to drug compounds.

A stability study of the active drug was first carried out on each of the polymers, based on the sediment volume, flocculation, and redispersion. Subsequently, we performed a two-part study of the drug–polymer complex. First, the adsorption of the ondansetron on both latexes was determined with respect to time, pH and concentration. Second, the sediments were then obtained and characterised.

2. Material and methods

2.1. Materials

Ondansetron [dihydrated (1,2,3,9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazole-1-yl)methyl]-4H-carbazol-4-one] ($C_{18}H_{19}N_{30}$) was supplied by Laboratories Vita S.A. (Barcelona, Spain).

Aquacoat® [8], provided by Foret S.A. (Spain), is an aqueous ethylcellulose dispersion obtained by polymerisation with a solids content of 30%.

Aquateric® [9], provided by Foret S.A. (Spain), is a white powder insoluble in water. It consists of 69.7% cellulose acetophthalate, 20% Pluronic F-68 (cationic

*Author to whom all correspondence should be addressed.

surfactant), 10% Myvacet 940 (monoglyceride component), and 0.3% Tween 60.

Before use, both polymers were washed with distilled water, to eliminate contaminating particles in the medium acquired during synthesis, and this produced the ideal maximum colloidal dispersion. The washing was performed by repeated centrifugation and redispersion until the supernatant had a constant conductivity.

pH was determined with 0.1 N of HCl and NaOH using a Crison pHmeter, mod. MicropH 2001.

Spectrophotometric determinations were performed with a Perkin-Elmer Running Lambda 2 apparatus (Ueberlingen, Germany).

2.2. Methods

2.2.1. Stability study

Stability was determined mainly from sedimentation, flocculation and redispersion of the suspensions of cellulose acetophthalate and ethylcellulose latexes with the drug.

The starting point of these assays was used ondansetron suspensions of 3% in cellulose acetophthalate latex and 30% in ethylcellulose latex. pH variations were obtained by adding drops of solutions to these suspensions, although without producing any significant changes in the solids concentration.

The sedimentation study consisted of determining the volume of sediment in the distinct suspensions over time for the entire pH interval studied [10]. The volume of sedimentation was measured by marking calibration fines on the test-tubes, all the experiments were run in triplicate in dispersions containing 1% (w/v) concentration of particles. The suspensions were allowed to settle in calibrated cylinders of 100-cm^3 volume, their inner diameter (4 cm) being large enough for wall effects to be negligible. The experimental error in sediment volume determinations was $\approx 0.5\ cm^3$. The ratio V_s/V_0 proposed by several authors [11] was used as a suitable value for quantifying flocculation; V_s is the volume of sedimented solids, and V_0 is the initial total volume of the suspension. Flocculation was also quantified by β, defined by the following expression:

$$\beta = F^0/F^\infty$$

which gives the relation between the sediment volume of a flocculated suspension (F^0) and that of a stable suspension (F^∞).

The redispersion properties of the sedimented suspensions were checked through a simple and reproducible technique. That is, the cylinders were placed on a vertical holder which was made to spin at 75 rev min^{-1} for 2 min [12]. Redispersion was considered complete when the quantity of substance remaining sedimented was zero. A stable, or definitive, sediment was obtained after 24 h for cellulose acetophthalate latex and 30 days for ethylcellulose latex.

2.2.2. Adsorption of the drug in the latex

Adsorption kinetics were studied as a function of time, pH, and concentration of the drug. Ondansetron was therefore placed in contact with each of the polymers (ethylcellulose and cellulose acetophthalate) at a constant temperature of 25 °C and shaking at 60 rpm, followed by 30 min of centrifugation at 14 000 rpm to separate the sediment and the supernatant. The solubilised drug is in the supernatant and then determined by spectrophotometry at $\lambda = 310$ nm (the maximum wavelength at which the drug is absorbed). The concentration of ondansetron was calculated by calibrating curves obtained with standard aqueous solutions of drug with a known concentration. The complexes were prepared once the best adsorption conditions had been determined (time = 24 h, pH = 2–4). The cellulose acetophthalate latex–ondansetron complex was prepared from a solution of 30% ondansetron, and 60% cellulose acetophthalate latex. However, the ethylcellulose latex–ondansetron complex was prepared with only 10% latex due to the high solids content of this polymer. These complexes were then incubated in a 25 °C thermostatic bath, shaking the samples at 60 rpm for 24 h. Subsequently, the samples were centrifuged for 50 min at 14 000 rpm to separate the sediment and supernatant. Spectrophotometry was used to determine the amount of drug in the supernatant, and using the difference with initial drug to determine the quantity remaining in the sediment.

3. Results and discussion

3.1. Stability study

Figs. 1 and 2 show the sediment volume over time for the entire pH range studied for both the cellulose acetophthalate and ethylcellulose polymers. The sediment volume measurements were taken after 24 h for cellulose acetophthalate latex and at 30 days for ethylcellulose latex, counting from the moment of suspension preparation. The results indicate that these respective times were sufficient to obtain a definitive sediment.

As can be observed from Fig. 1, after 60 min all the suspensions maintain a stable sediment volume whatever the pH, although the volume shows an overall increase with decreasing pH. Note that the cellulose acetophthalate latex suspensions with the most acidic pH have the greatest sediment volume. The most alkaline pH values are not shown since an alkaline pH destroys cellulose acetophthalate latex (pH 6 and greater), producing fewer particles in the medium and giving rise to an opalescent dispersion with no sediment.

In the case of cellulose acetophthalate latex, the sediments for pH values of 3, 4.5, 5, and 6 have a characteristic, ''free-layered'' sedimentation described by many authors [13]. In this model, the sediment height increases over time (as predicted by Stokes' Law) up to a maximum value after an interval long enough for all the particles to sediment out (except perhaps the smallest fraction, prevented from settling by a Brownian effect).

The sedimentation is different, however, for pH values of 2 and 2.5, at which the sediment height drops over time due to what is believed to be ''delayed'' or ''hindered'' sedimentation, as described by Bueno [14] and Delgado *et al*. [15]. This sedimentation is characterised by a drop of the sediment front from the upper level of the suspension, giving rise to a marked boundary between the front and the clarified supernatant.

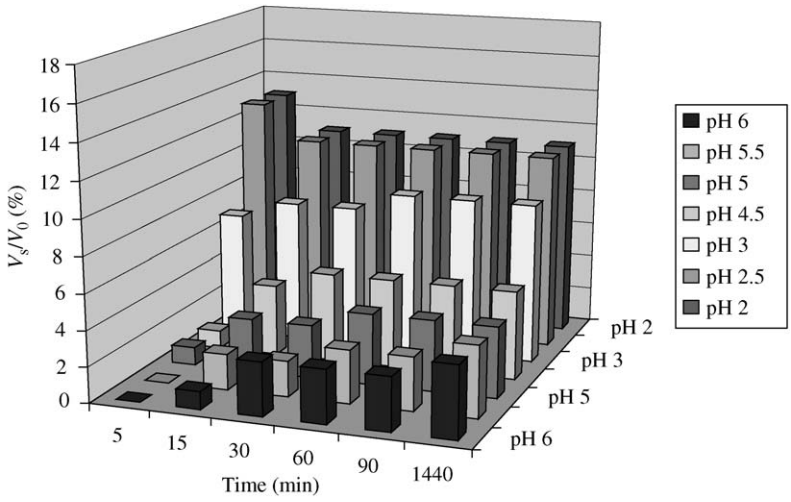

Figure 1 Sediment of Aquateric® suspension as a function of time for different pH values.

In contrast, in Fig. 2 the ethylcellulose polymer produces a much larger fraction of sediment volume that reaches a maximum of 95% for early times, which decreases to 60% at the end of the process. The time required to obtain a stable sediment (its volume constant) is also longer, however, taking about a month. Interestingly, the sediment is uniform for every pH value, with the sole exception of pH 2, where the volume reduction is more marked with increasing time. In the case of ethylcellulose polymer, the only type of sedimentation believed to occur is the ''delayed'' or ''hindered'' sedimentation introduced earlier.

Another well-known parameter allowing study of the stability of the suspensions with even greater precision is the degree of flocculation $((\beta)\beta = F^0/F^\infty)$ [12]. Fig. 3 shows the values of this coefficient as a function of the pH for the cellulose acetophthalate polymer. As can be seen, the suspensions with the highest flocculation and, therefore, the most stable ones, are those obtained at very acidic pH. For pHs greater than 4.5 the value of β decreases markedly as the cellulose acetophthalate latex begins to dissolve, which hinders the sediments volume.

In Fig. 4, the flocculation of ethylcellulose latex, varies in a different manner with pH. All the ethylcellulose suspensions present great stability, as evidenced by very uniform flocculation throughout the pH range studied (compare Fig. 4 with Fig. 3). As occurs with sedimentation, the ability of a flocculated system to redisperse itself is both theoretically and practically of interest for good dosage, whether by changing the composition of the medium (with nearly no shaking) or only by shaking. The latter case is of greater practical importance when dealing with concentrated pharmaceutical suspensions.

In the cellulose acetophthalate latex suspensions, all sediments were redispersed with light shaking over 24 h. Complete homogenisation of the latex in the dispersion medium was achieved easily and rapidly. After obtaining suspensions, the samples were allowed to settle and in all cases produced a sediment identical to the one they presented the first day of the study.

In marked contrast, the ethylcellulose latex took 1 month to redisperse, at which time ''definitive'' sediments were obtained. The samples were vigorously shaken in an attempt to achieve homogenisation of the latex in the medium. Redispersion was much more difficult to achieve than with cellulose acetophthalate latex because the sediments seemed to be more compacted making them more resistant to homogenisation by simple shaking.

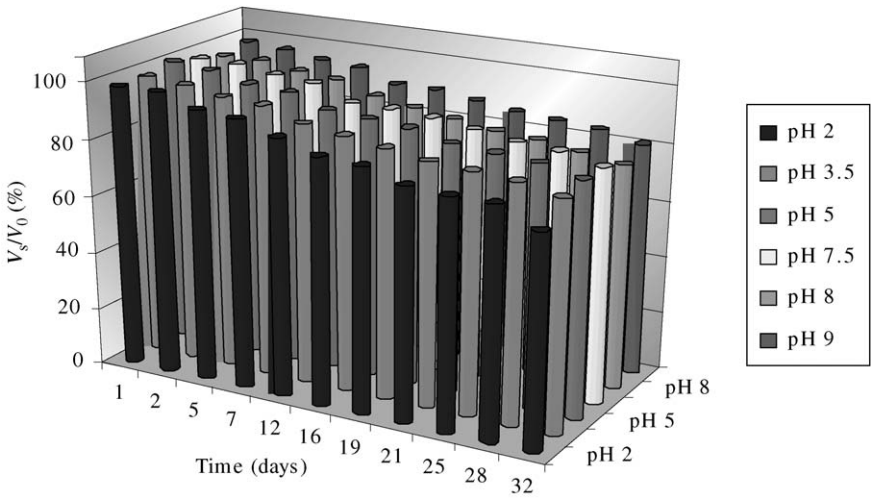

Figure 2 Sediment of Aquacoat® suspension as a function of time for different pH values.

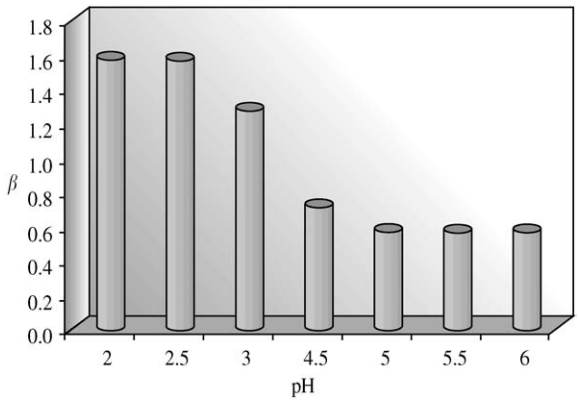

Figure 3 Flocculation ratio of Aquateric® suspensions as a function of pH.

3.2. Adsorption study

The adsorption of ondansetron in particles made of both the cellulose acetophthalate and ethylcellulose latex was studied to evaluate the potential function of a suspension as a release system for drugs. To analyse the kinetics of ondansetron adsorption, the variation of drug concentration and pH over time were taken into account so that the two latexes contained the maximum possible amount of active principle [16, 17].

Fig. 5 shows the contact time of the drug with each of the polymers a variation of percentage ondansetron adsorbed. Qualitatively, it can be seen that the two latexes perform similarly, with near total adsorption. Maximum adsorption occurs 1 h after the onset of the experiment, ranging around 97% for cellulose acetophthalate latex and 80% for ethylcellulose latex, and remains constant up to 24 h. The interval of 24 h was therefore chosen as the standard reference time for subsequent adsorption tests.

The effect of adsorption as a function of ondansetron concentration is given in Fig. 6. As can be seen, the two latexes behave similarly, thus indicating a direct relationship between the ondansetron concentration (mg/ml) and the amount of ondansetron adsorbed (μmol/l). According to Gile's classification [18], the adsorption profile is type C-1, where, as the concentration of drug increases, the concentration adsorbed by the polymer also rises. The solute is therefore distributed between the solution and the interface in a constant proportion, thus explaining the adsorption of the drug in progressive layers on the polymer particles. The greatest adsorption has occurred

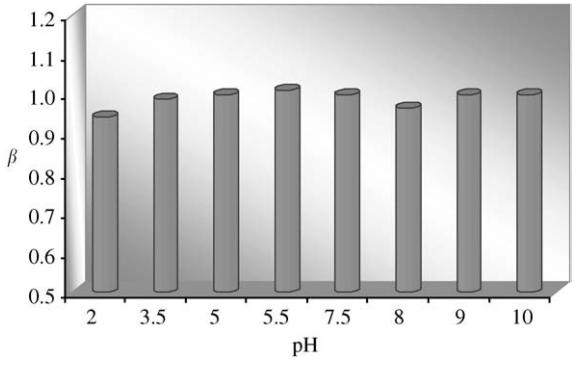

Figure 4 Flocculation ratio of Aquacoat® suspensions as a function of pH.

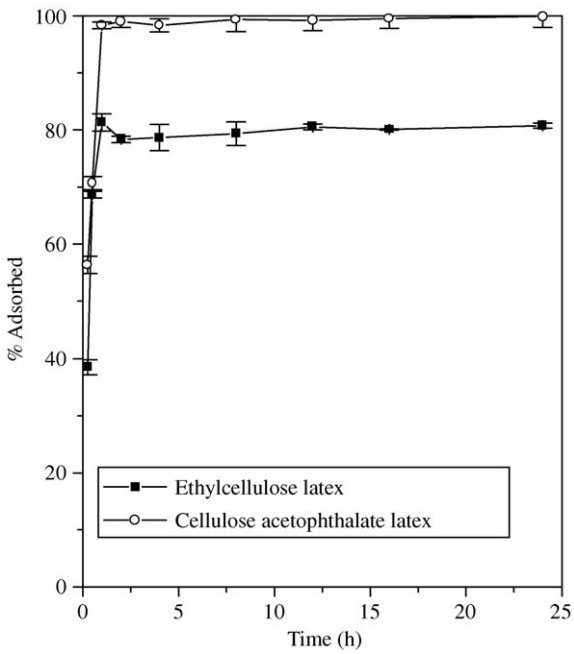

Figure 5 Ondansetron adsorption in Aquateric® and Aquacoat® over time.

in the latex micropores, where the smallest particles of drug predominate.

The effect of pH variations on ondansetron adsorption is shown in Fig. 7 for both latex. As can be seen, the maximum adsorption (98%) on cellulose acetophthalate latex occurs at an acid pH of 2–4, which drops off at a pH of 5 and reaches a minimum of 80% at a pH of 7. This effect is not unexpected given the characteristics of this polymer, which stable in acid media but break down in alkaline environments, as demonstrated in recent microscopy and electrophoresis mobility studies [19].

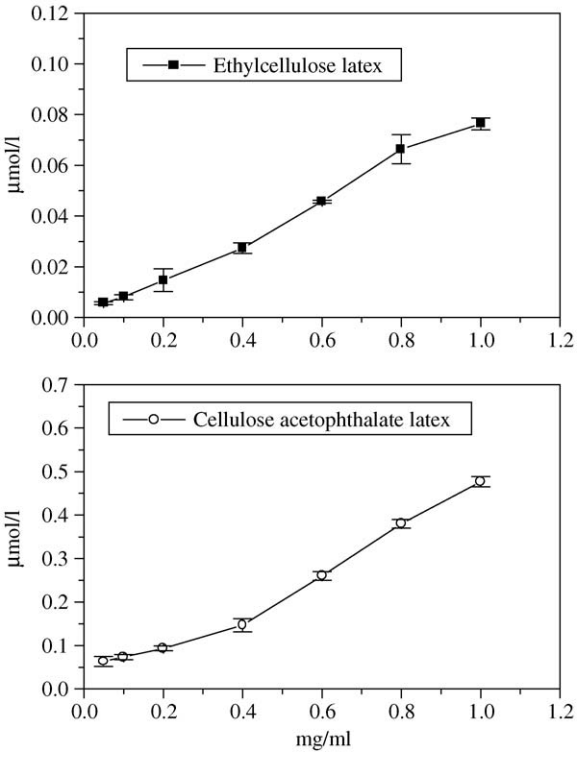

Figure 6 Density of adsorption versus concentration.

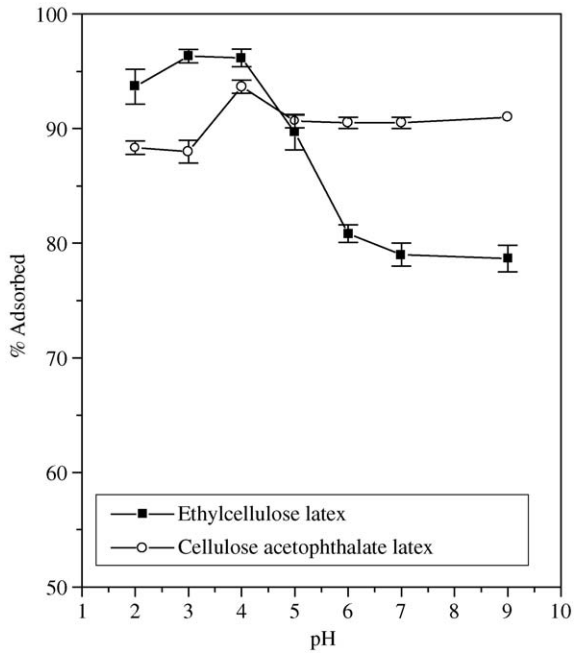

Figure 7 Ondansetron adsorption in Aquateric® and Aquacoat® versus pH.

Electrokinetic characterisation has shown that pH variations induce an ionic change on polymer's surface [20]. The more acidic the pH, the lower the electrophoresis mobility. In very acidic conditions the polymer mobility is less negative and therefore has a greater tendency to bond with the negative drug particles. That is why the largest amount of drug is adsorbed into the polymer for acidic pHs (in this case for pHs of 5 or less), where constant values of μe and ζ are obtained. In addition, ondansetron has chemical groups capable of bonding with the negative charges of the polymer, forming complexes.

In contrast, the adsorption of the drug with ethylcellulose polymer is always lower than cellulose acetophthalate polymer at any pH. For instance, at acidic pHs (2–3), adsorption is approximately 85%, and increases to a maximum of 94% at pH 4 (the natural pH of ethylcellulose polymer). This latter adsorption rate remains constant even at more alkaline pH values.

This behaviour can be accounted for by the electrokinetic characteristics of ethylcellulose latex determined by pH [21], since the absolute value of electrophoretic mobility (μe) increase concomitantly with pH. Thus, the absolute value of the mobility of latex is high at an acidic pH due to the dense arrangement of negative charge of the acidic sulphate contained in the polymer particles, which are dissociated at a pH of 2 [22, 23]. However, the variation in the mobility at a basic pH is more difficult to explain, although several theories on electrokinetic behaviour with regard to pH can be found in the literature [24]. The increase in the pH of the medium will probably displace the corresponding dissociation equilibrium in the direction of increasing the release of H^+ and hence the negative charge on the particle, as was observed.

To sum up, it is clear that, due to its electrokinetic behaviour, ethylcellulose polymer is not strongly influenced by solution pH when in solution, since its adsorption varies on a very small scale. In contrast, pH is a very influential factor in cellulose acetophthalate polymer, with higher adsorption at acidic pH and much lower values at more basic pHs.

4. Conclusions

As maximum adsorption occurs in both polymers in an acidic medium. The highest adsorption over time took place with cellulose acetophthalate latex.

The study of sedimentation, flocculation, and redispersion of cellulose acetophthalate and ethylcellulose latexes suspensions revealed that ethylcellulose latex produced the highest volume of sediment independent of pH. Of the two polymers, cellulose acetophthalate polymer, produced the lowest amount of sediment, which decreased in media with increasing alkalinity, where the polymer is almost totally destroyed.

Redispersion was much easier and faster with cellulose acetophthalate latex than the ethylcellulose latex. In view of these findings, the cellulose acetophthalate latex seems a potential candidate as a drug delivery polymer.

References

1. P. BLACKWELL and S. M. HARDING, *Eur. J. Cancer Clin. Oncol.* **25** (1989) 21.
2. A. J. FREEMAN, K. T. CUNNINGHAM and M. B. TYERSS, *Anti-cancer Drugs* **3** (1991) 79.
3. F. ROITA and A. DEL FAVERO, *Clin. Pharmacokin.* **29** (1995) 94.
4. K. G. TOLMAN, in ''Remington FARMACIA,'' 19th edition, edited by A. R. Gennaro (Panamericana Buenos Aires, 1995) p. 1350.
5. ''Clinical Pharmacy and Therapeutics'', 5th edition, edited by E. T. Herfindal, D. R. Gourley and L, Lloyd Hart (Willians & Wilkins, London, 1992) p. 428.
6. V. GALLARDO, M. E. GARCÍA and A. RUIZ, *Macromol. Chem. Phys.* **202** (2001) 2412.
7. R. GURNY, in ''Topics in Pharmaceutical Sciences'', edited by D. Breimer, P. Speiser (Elsevier Science Publishers, Amsterdam, 1983) p. 277.
8. FMC Corporation Aquacoat, Aqueous Polymeric Dispersión, Philadelphia, 1980.
9. FMC Corporation Aquateric, Aqueous Entering Coating, Philadephia, 1987.
10. S. RIGAMONTI and G. RUGGINENTI, *II Farmaco* **24** (1969) 445.
11. B. A. MATTHEWS and C. T. RHODES, *J. Pharm. Sci.* **59** (1970) 521.
12. V. GALLARDO, A. RUIZ, P. VERA, F. GONZALEZ-CABALLERO and A. V. DELGADO, *J. Pharm. Pharmacol.* **48** (1996) 450.
13. J. B. KAYES, *ibid.* **29** (1977) 163.
14. J. L. BUENO, *Fundanción Juan March* **95** (1979) 16.
15. A. DELGADO, V. GALLARDO, A. PARERA and F. GONZALEZ, *J. Pharm. Sci.* **79** (1990) 709.
16. A. K. BAJPAI, M. RAJPOOT and D. D. MISRA, *Ind. J. Chem. A* **35** (1996) 560.
17. F. GANACHAUD, A. ELAISSARI, C. PICHOT, A. LAAYOUN and P. CROS, *Langmuir*, **13** (1997) 701.
18. C. H. GILES, A. P. D'SILVA and I. A. EASTON, *J. Colloid Interface Sci.* **47** (1974) 766.
19. A. RUIZ, V. GALLARDO, I. REYES, P. VERA and A. V. DELGADO, *Therm. Acta* **313** (1998) 145.

20. P. VERA, V. GALLARDO, J. SALCEDO, A. RUIZ and A. V. DELGADO, *J. Appl. Polymer Sci.* **65** (1997) 2721.
21. Y. ZOUAKI, A. RUIZ, A. PARERA and V. GALLARDO, *Pharm. Ind.* **60** (1998) 468.
22. R. J. HUNTER, ''Zeta Potential in Colloid Sciences. Principles and Aplications'' (Academic Press, London, 1981).
23. J. STONE-MASUI and A. J. WATILLON, *Colloid Interface Sci.* **52** (1975) 479.
24. S. D. JAMES, in ''Surfaces and Colloid Science'', Vol. XI, edited by R. J. Good and R. S. Stromberg (Plenum Press, New York, 1979).

Received 21 March
and accepted 3 December 2003