Department of Pharmacy and Pharmaceutical Technology, Faculty of Pharmacy, University of Granada, Spain

Ondansetron: design and development of oral pharmaceutical suspensions

V. Gallardo Lara, M. Lopez-Viota Gallardo, Mª E. Morales Hernandez, Mª A. Ruiz Martinez

Received July 10, 2007, accepted August 5, 2008

Dra. V. Gallardo, Dept. Pharmacy and Pharmaceutical Technology, Faculty of Pharmacy, University of Granada, E-18071 Granada, Spain
vglara@ugr.es

Pharmazie 64: 90–93 (2009) *doi: 10.1691/ph.2009.8198*

Ondansetron is a carbazol with antiemetic properties that acts as a competitive and selective antagonist for the 5 HT_3 serotonin receptors. It is used primarily to control nausea and vomiting caused by cytotoxic chemotherapy and radiotherapy, as well as in postoperative vomiting in gynecological surgery. The main aim of this work was to obtain a stable, long-acting oral suspension of ondansetron. To prolong the action, latexes are used as transport vehicles, specifically we tested, Aquateric®, which comprises mainly cellulose acetophthalate. We prepared a complex drug-polymer, and the release profile of ondansetron was evaluated at acid, basic and acid-basic pH. This complex is additioned to a vehicle with xanthan gum and sodium carboxymethylcellulose (CMCNa) as thickeners to retard as much as possible particle sedimentation and thus increase physical stability of the suspension. The results obtained for sediment volume and degree of flocculation suggest that xanthan gum provides the best results, with better organoleptic characteristics, appearance, physical stability and easy redispersability.

1. Introduction

In recent years, interest has grown considerably in suspensions, particularly those based on polymers, as alternative to administering tablets orally (Gallardo et al. 2000). Although it is apparently easy to prepare suspensions, pitfalls can be found in the attempt to obtain a pharmaceutical form that satisfies the needs of current therapeutics. Since a suspension is a thermodynamically unstable system, from the galenic viewpoint it is of interest to design and formulate a suspension that does not sediment out quickly and that can be easily re-homogenised by shaking. Moreover, the redispersion by shaking should result in a homogenous-looking product. Finally, there should be no crystal growth during storage. In short, the suspension must be physically stable (Gallardo et al. 1990).

Ondansetron is a carbazol with anti-emetic properties that acts as a competitive and selective antagonist of the 5-HT_3 receptors of serotonin. Ondansetron is used to control the nausea and vomiting induced by chemotherapy and cytotoxic radiotherapy, as well as in prophylaxis and the treatment of vomiting in gynecological surgery (Blackwell and Harding 1989; Freeman et al. 1991; Roita and Favero 1995), the elimination half-life of the drug is 3–4 hours. Long-acting forms are intended to increase the dose interval and thus facilitate dosing schedules.

The main aim of this work was to obtain a stable, long-acting oral suspension of ondansetron (no such product is currently marketed). To prolong the action of the active principle, latexes are used as transport vehicles, specifically (in this work) Aquateric® (FMC Corporation 1987), which comprises mainly cellulose acetophthalate. Xanthan gum (Bonferoni et al. 1993; Talukdar and Plaizier 1993) and sodium carboxymethylcellulose (CMCNa), were used as thickeners to retard particle sedimentation for as long as possible, and thus increase physical stability of the suspension.

2. Investigations, results and discussion

2.1. Formulation preparation

The therapeutic dosage of ondansetron is 8 mg according to the literature, so the formulations were prepared with 3 mg of free ondansetron. To prolong the action and complete the dosage, 5.4 mg of ondansetron were added as a sediment complex with cellulose acetophthalate latex (Ruiz et al. 2004). In any "ideal" suspension, certain conditions must be met and substances used so that the distribution of the internal phase and its initial properties remain the same nearly indefinitely (Gyselink et al. 1981, 1982). Therefore, apart from the dosage, a series of factors and substances that are extremely important in the preparation of a suspension must be taken into account since they confer the optimal characteristics of the final formula for administration. To this end, a thickener is added to the ondansetron-cellulose acetophthalate latex complex in order to retard as much as possible particle sedimentation and thus increase suspension stability.

The Table presents the compositions of the two formulae analysed. Formula A contains the pseudoplastic sodium carboxymethylcellulose (CMCNa) as a thickener and 1% Avicel®, which provides excellent stability and flow. Glycerine is included as a wetting agent and Kathon® CG as a preservative, which acts at an acid pH and thereby endows the formula with stability over time.

Table 1: Compositions of formulations A and B

Formulations	A	B
Ondansetron HCl	3 mg	3 mg
Ondansetron-Aquateric® sediment	135 mg	135 mg
Avicel®	1%	1%
Kathon® CG	0.1%	0.1%
Glycerine	10%	10 %
Sodium carboxymethylcellulose (CMCNa)	1.5%	–
Xanthan® Gum CG (E-415)	–	0.75%
Destilled water cs	5 ml	5 ml

In formula B CMCNa was replaced by xanthan gum (E-415), (Nakano and Ogata 1984) an anionic polysaccharide with a high molecular weight that gives the suspension a more acceptable appearance from the organoleptic properties. In both formulations the final pH is 4.2, which is optimal for the stability of the active principle.

2.2. In-vitro release of ondansetron from the formulae

The results for the release of ondansetron in Formula A at an acid, acid-basic and basic pH can be seen in Fig. 1. The release varies over time and is also dependent on the release medium. Thus, at an acid pH, 70% of the active principle have been released by the second hour, increasing to nearly 95% by the end of the test, which is a sufficient quantity to obtain a good pharmacological response. However, in an alkaline medium, only 7% of the ondansetron are released in the first 7 h, reaching a maximum of 12% at 24 h, obviously an insufficient amount for an adequate therapeutic response.

The percentage of active principle released in formula B, where xanthan gum is used as a thickener, is presented in Fig. 2. A very similar performance can be noted, with the greatest release at an acid pH, in which 50% of the ondansetron is released in the first 2 h and 97% by the end of the test. Likewise, at an alkaline pH, barely 7% are released in the first 7 h and less than 10% at 24 h. The poor performance at a basic pH is due to the destruction of the polymer, which traps the drugs and thus hinders its release. Consequently, only the free ondansetron remains in the medium (Ruiz et al. 1998).

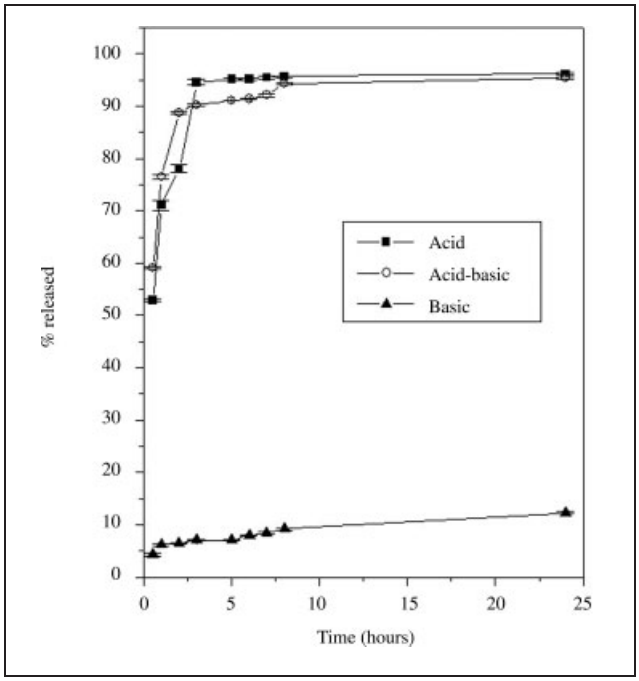

Fig. 2: Percentage of ondansetron released of the formulation B

We also studied the release for both formulations simulating the physiological conditions of the gastrointestinal tract, that is, at an acid-basic pH. As can be observed in the two figures (Figs. 1 and 2), the release was similar in both cases to that obtained at an acidic pH, although always 5–10% lower than the results at pH 1.5. Nonetheless, by the end of the process, the release is nearly the same.

Figure 3 shows for three pH values studied the percentage of active principle released of the complex obtained with ondansetron-aquateric, without incorporation of any com-

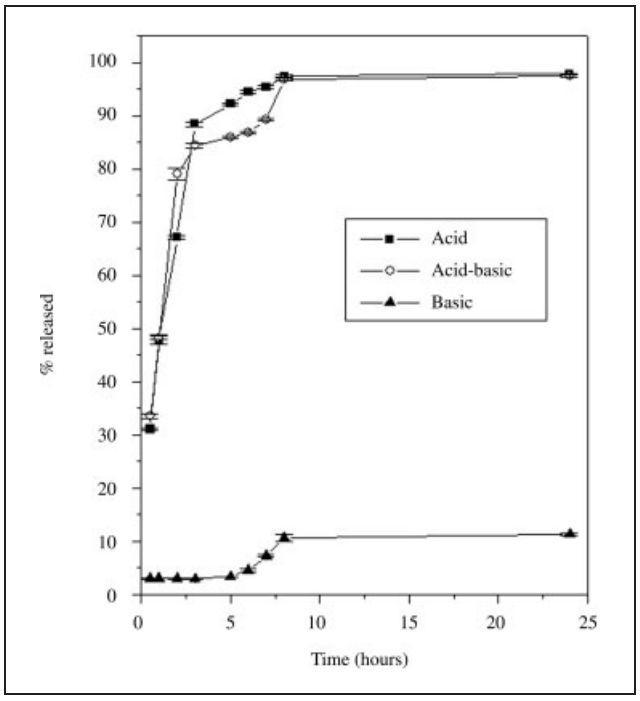

Fig. 1: Percentage of ondansetron released of the formulation A

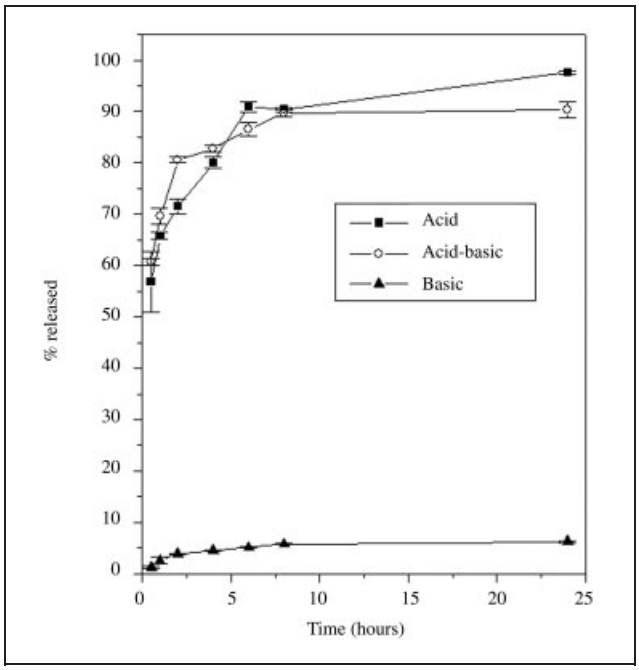

Fig. 3: The percentage of active principle released of complex ondansetron-Aquateric®

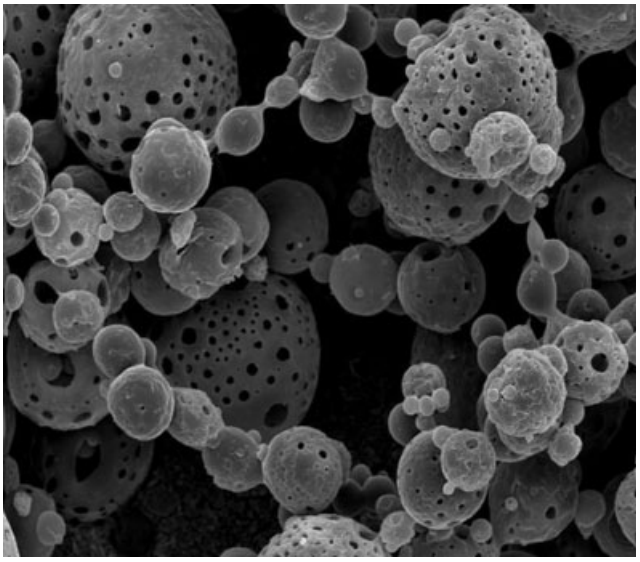

Fig. 4: SEM of complex ondansetron-Aquateric

ponent of the suspension. The profile of liberation is similar to that obtained with both formulations, i.e. major release in acid and acid-basic pH, being again lower than 10% in alkaline medium, demonstrating that the complex formed is responsible for the prolongation of the effect.

In the research reported here we used colloidal particle size latex, which allows the drug to be adsorbed both on the inside and on the outside of the hollow, porous particles. The supporting illustrations now include micrographs of the complex ondansetron-Aquateric® particles (Figs. 4 and 5). Release occurs via diffusion of the drug, at alkaline pH values release occurs through erosion of the particles: at pH 7 latex particles are disrupted.

2.3. Stability study

The stability of suspensions was experimentally characterized determining the volume of sedimented drug 24 h after the suspension was prepared and studying sedimentation over a period of 30 days. The study revealed that formula A darkened, becoming a disagreeable brown colour, whereas formula B retained its original white colour.

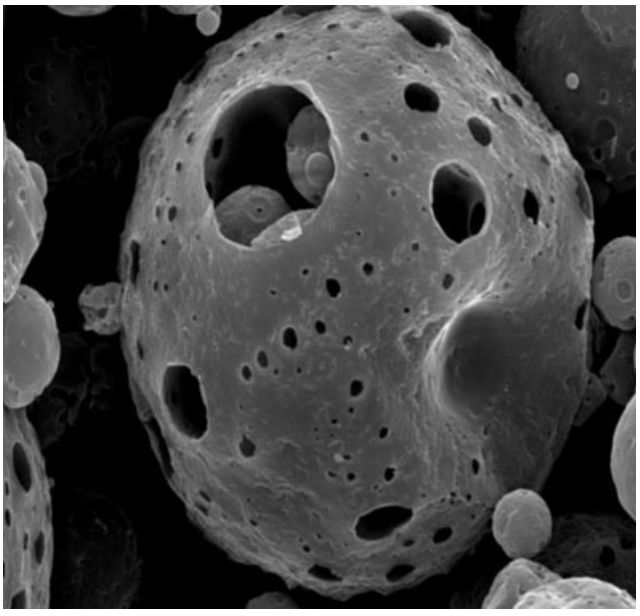

Fig. 5: SEM of complex ondansetron-Aquateric

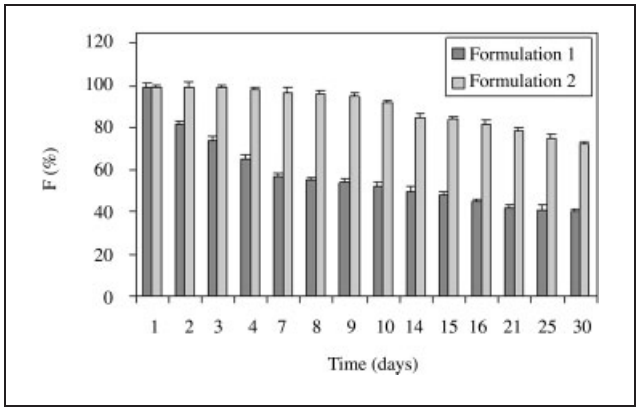

Fig. 6: Sediment volume of both formulations

The sediment volume of both formulae over time is presented in Fig. 6. The formulations both show "hindered" sedimentation, with sediment volume decreasing over time (Delgado et al. 1990). Qualitatively there is evidently a certain similarity, but quantitatively there are clear differences, as demonstrated by the greater compaction of the sediment in formula A over time. The degree of flocculation (Fig. 7), however, is much lower in formula A (CMCNa), making the formula B (xanthan gum) much more stable (Gallardo et al. 2005).

After studying the sedimentation process, the sediments were redispersed to complete homogeneity by light shaking. Formula B redispersed much more easily and quickly than formula A, which had a slightly more compact sediment.

In short, the stability study leads us to conclude that formula B is a more suitable vehicle for ondansetron due to its more appealing aspect, much slower sedimentation and much easier and quicker redispersion.

The results of this study to determine a suitable oral sus-

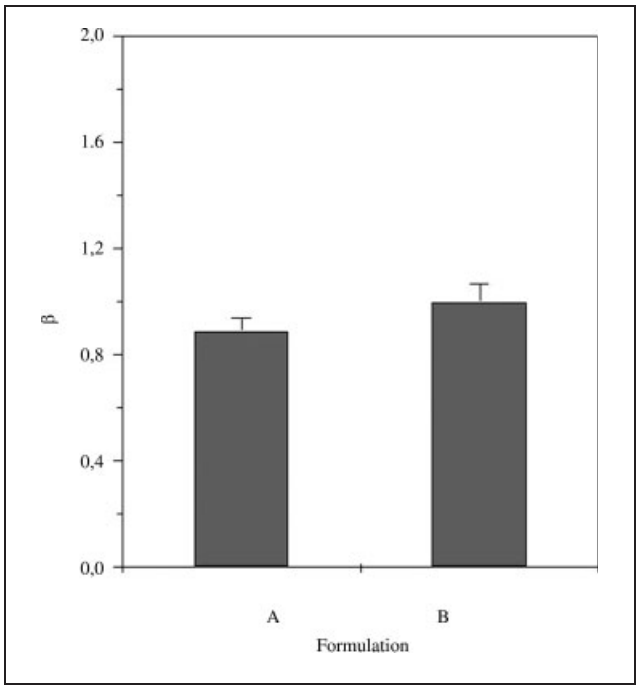

Fig. 7: Degree of flocculation of both formulations

pension for ondansetron indicate that xanthan gum provides the best results, with better appearance, stability, and long-acting. Its ease of administration to cancer patients makes it an attractive alternative to current drugs.

3. Experimental

3.1. Materials

Ondansetron [dihydrated (1,2,3,9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazole-1-yl)methyl]-4H-carbazol-4-one($C_{18}H_{19}N_3O$) was provided by laboratories Vita S.A. (Barcelona, Spain). Aquateric®, provided by Foret S.A. (Spain), is a white powder insoluble in water. It consists of 69.7% cellulose acetophthalate, 20% Pluronic F-68 (anionic surfactant), 10% Myvacet 940 (monoglyceride component), and 0.3% Tween 60. The preparation of the ondansetron-Aquateric® complexes is described in a previous work (Llácer et al. 2000).

Xanthan gum (E-415) was provided by SBI System Bio-Industries S.A. (Spain). It is soluble in water, producing a very viscous solution that is practically insoluble in organic solvents. Sodium carboxymethylcellulose (CMCNa) was provided by Roig-Farma S.A. (Barcelona, Spain). It is used at concentrations of 0.25–1%. Avicel®, provided by Roig-Farma S.A. (Barcelona, Spain), is purified, partially depolymerized cellulose occurring as a colloidal powder dispersable in water. Glycerine, also provided by Roig-Farma S.A. (Barcelona, Spain). Kathon® CG, provided by Tennero S.A. (Barcelona, Spain) is a mixture of 2 isothiazolones (5-chloro-2methyl-4-isothiazolin-3one and 2 methyl-4-isothiazolin-3 one). In this study Kathon® CG was used as a preservative to prevent the growth of microbial agents and fungi in the suspension. It acts in a pH range of 3.5–5 and the recommended to use it at concentrations of 0.04–0.1% (Kim et al. 2002).

The pH studies were performed with solutions of 0.1 N of HCl and with NaOH, using a Crison Micro pH 2001 pHmeter. Spectrophotometric determinations were carried out with a Perkin-Elmer Running Lambda 2 apparatus (Ueberlingen, Germany).

3.2. Methods

3.2.1. Preparation of the complex

The complexes were prepared after the best adsorption conditions had been determined. The cellulose acetophthalate latex-ondansetron complex was prepared from a solution of 30% ondansetron, 60% cellulose acetophthalate latex. This complex was then incubated in a 25 °C thermostatic bath with 60 rpm shaking for 24 h. It was afterwards centrifuged for 50 min at 14000 rpm to separate the sediment and supernatant. Spectrophotometry was used (at λ 310 nm, maximum wavelength at which the active principle is absorbed), to determine the amount of active principle in the supernatant, deducing the quantity remaining in the sediment by the difference. Surface characteristics, of the final particles were investigated by scanning electron microscopy (SEM).

3.2.2. Preparation of formulations

The stock suspensions were prepared by suspending ondansetron ClH and sediment of ondansetron-cellulose acetophthalate (Aquateric®) in water, and allowing the mixture to settle for 4 h in order to obtain a suspension of the homogeneous particle size fraction. To these suspensions were added appropriate volumes of thickener, wetting, Avicel® which provides excellent stability (Peng et al. 2007) and flow, and preservative to obtain the desired volume

3.2.3. In vitro release

Each of the two formulations prepared were subjected to an in vitro release study as a function of pH. The desorption study simulated physiological conditions (Kubo et al 2003; Morales et al. 2004) in order to evaluate the suitability of the ondansetron-latex complex as a vehicle for drug release. To simulate these conditions, the formulations were placed in a 37 °C bath at 60 rpm in the release media (acid, basic and acid-basic). In all the tests sink conditions are fulfilled. In the acid-basic medium, the formulations were kept at pH 1.5 for 2 h (the approximate residence time in the stomach) and then changed to pH 7.4 (intestinal pH). We thus reproduced the conditions that the complex would undergo in the stomach and intestine (Domenech 1998; Ratsimbazafy et al. 1997). The evaluation of the release was measured by spectrophotometry and at a wavelength of 310 nm, which is where ondansetron undergoes maximum absorption. The same formulations without any active principle were used as a control.

3.2.4. Stability study

Stability was studied primarily on the basis of measurements of sedimentation, flocculation and redispersion of the formulations (Rigamonti and Rugginenti 1969). Sedimentation was determined by the sediment volume of the various suspensions over time for the entire pH range studied. All tests were run in triplicate. The suspensions were placed in 100 ml testtubes with a 4 cm inner diameter, large enough to avoid wall effects during sedimentation. The experimental error in volume determination was 0.5 cm^3. The ratio Vs/Vo proposed by several authors were used as a suitable value for quantifying flocculation; Vs is the volume of sedimented solids, and Vo is the initial total volume of the suspension. Another parameter we consider interesting and which we determined is the flocculation ratio, B, defined by the following expression: $B = F / F\infty$ which gives the relation between the sediment volume of a flocculated suspension (F) and that of a stable suspension (F∞). The redispersion properties of the sedimented suspensions were investigated using a simple and reproducible technique. The samples were subjected to a 75 rev min^{-1} agitation for 2 min to determine the difficulty of each in re-attaining their initial state.

Acknowledgements: Part of this work was supported by the Spanish Ministry of Education and Science, and European Regional Development Funds under Project MAT2005–07746-C02–02 and Project of Excellence FQM 410.

References

Blackwell P, Harding SM (1989) The clinical pharmacology of ondansetron. Eur J Cancer Clin Oncol 25: 21–24.

Bonferoni MC, Rossi S, Tamayo M, Pedraz JL, Dominguez Jl, Caramella C (1993) On the employment of λ-carrageenan in a matrix system. I. Sensitivity to dissolution medium and comparison with Na carboxymethylcellulose and xanthan gum. J Control Release 26: 119–127.

Delgado AV, Gallardo V, Parera A, González F (1990) Study of the electrokinetic and stability properties of nitrofurantion suspensions. II flocculation and redispersion properties as compared with theoretical interaction energy curves. J Pharm Sci 79: 709–715.

Domenech J (1998) Biofarmacia y Farmacocinética. Vol. II, Edit. Síntesis, Madrid, p. 165.

FMC Corporation Aquateric, 1987. Aqueous Entering Coating. Philadephia,

Freeman AJ, Cunningham KT, Tyers MB (1991) Selectivity of 5-HT3 receptor antagonists and antiemetic mechanisms of action. Drugs 3: 79–85.

Gallardo V, Ruiz MA, Parera A, Delgado AV (1990) A DSC study of the chemical stability of nitrofurantoin in pharmaceutical suspensions. Pharmazie, 45: 633–634.

Gallardo, V, Ruiz, MA, Delgado AV (2000) Pharmaceutical suspensions and their applications. In: Nielloud F, Marti-Mestres G (ed.). Pharmaceutical Emulsions and Suspensions, Edit. Marcel Dekker, USA pp. 409–464.

Gallardo V, Morales ME, Ruiz MA, Delgado AV (2005) An experimental investigation of the stability of ethylcellulose latex – correlation between zeta potential and sedimentation. Eur J Pharm Sci 25: 170–175.

Gyselink P, Severen R van, Braeckman P, Schacht E (1981) Drug polymer combinations. Part 1: the preparation of sustained release drugs by combination with ion exchanging resins. Pharmazie 36: 769–772.

Gyselink P, Severen R van, Braeckman P, Schacht E. (1982) Drug polymer combinations. Part 2: influence of the testing method on the in vitro drug release from ion exchange resins. Pharmazie 37: 672–681.

Kim BR, Anderson JE, Mueller SA, Gaines WA, Kendall AM (2002) Literature review – efficacy of various disinfectants against *Legionella* in water systems. Research 36: 4433–4444.

Kubo W, Miyazaki S, Attwood D (2003) Oral sustained delivery of paracetamol from in situ-gelling gellan and sodium alginate formulations. Int J Pharm 258: 55–64.

Llácer JM, Ruiz MA, Parera A, Gallardo V (2000) Adsorption-desorption of ondansetron on latex particles. Drug Dev Ind Pharm 26: 237–242.

Morales ME, Gallardo V, Calpena A, Domenech J, Ruiz MA (2004) Comparative study of morphine diffusion from sustained release polymeric suspensions. J Control Release 96: 75–81.

Nakano M, Ogata A (1984) Examination of natural gums as matrices for sustained release of theophylline. Chem Pharm Bull 32: 782–785.

Peng HT, Martineau L, Shek PN (2007) Hydrogel-elastomer composite biomaterials: 1. Preparation of interpenetrating polymer networks and in vitro characterization of swelling stability and mechanical properties. J Mater Sci Mater Med 18: 975–986.

Ratsimbazafy V, Bourret E, Brossard C (1997) Influence of the manufacturing process on the release of proxyphylline from lipid matrices. Pharmazie 52: 863–866.

Rigamonti S, Rugginenti G (1969) Pharmaceutical suspensions. Farmaco 24: 445–489.

Roita F, Del Favero A (1995) Ondansetron clinical pharmacokinetics. Clin. Pharmacokin 29: 94–108.

Ruiz MA, Gallardo V, Reyes I, Vera P, Delgado AV (1998) Stability of cellulose acetophthalate latex. Therm Acta 313: 145–154.

Ruiz MA, LLacer JM, Morales ME, Gallardo V (2004) Physical characteristics of polymer complexes in suspension obtained from cellulosic latexes with Ondansetron. J Mater Sci Mater Medic 15: 659–664.

Talukdar MM, Plaizier J (1993) Evaluation of xanthan gum as a hydrophilic matrix for controlled-release dosage form preparations. Drug Dev Ind Pharm 19: 1037–1046.