molecular pharmaceutics

ARTICLE

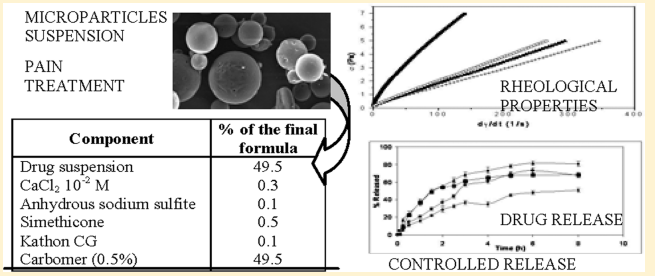
pubs.acs.org/molecularpharmaceutics

Oral Suspensions of Morphine Hydrochloride for Controlled Release: Rheological Properties and Drug Release

M. E. Morales, G. López, V. Gallardo, and M. A. Ruiz*

Department of Pharmacy and Pharmaceutical Technology, School of Pharmacy, University of Granada, 18071 Granada, Spain

ABSTRACT: Recent developments in pharmaceutical technology have facilitated the design and production of modified release formulas for drugs whose physical, chemical or biological properties impede release and thus might compromise their efficacy or safety. One such drug is morphine, whose short half-life requires repeated doses at short intervals. The use of biocompatible polymers such as ethylcellulose has made it possible to develop microencapsulated formulations which facilitate liquid, sustained-release pharmaceutical formulas for oral administration. We developed a stable final formulation of morphine with an acceptable release profile by comparing the rheological properties and stability of formulations with different thickeners (xanthan gum, Carbopol, and carboxymethylcellulose with microcrystalline cellulose) at different concentrations from 0.25% to 1.0%. Release assays in a Franz-type cell were done to determine the most suitable release profile for the formulation.



KEYWORDS: sustained release, ethylcellulose, morphine, microencapsulation, oral administration

INTRODUCTION

Basic pharmaceutical research has traditionally centered on the search for new molecules that are more potent, specific and selective than their predecessors. This important aspect of basic research notwithstanding, current efforts within the pharmaceutical industry are aimed mainly at enhancing the use of active principles by designing new formulations. Certain large groups of drugs are characterized by unfavorable physical, chemical or biological properties which compromise their efficacy or safety, and thus require new formulation strategies to overcome these obstacles.

One representative case is morphine, a drug which is well-known for its short elimination half-life (half-life in plasma about 2 to 3 h and plasmatic clearance about 15 to 20 mL/min/kg).[1−4] As a result of this characteristic, conventional pharmaceutical formulations must be administered every four hours, a frequency which often compromises patient compliance.[5] A modified release formulation would increase the dosage interval and thus reduce fluctuations in circulating concentrations of the drug. Moreover, such preparations would reduce the adverse effects of morphine and improve its therapeutic activity.

Recent developments in pharmaceutical technology have facilitated the design and production of modified release formulas. This was made possible, in part, by the introduction of biocompatible polymers.[6−9] Among polymeric materials suitable for microencapsulation, considerable efforts have been devoted to developing ethylcellulose as the drug carrier because it has been widely used in oral pharmaceutical formulations and food products, and is generally regarded as a nontoxic, nonirritant, safe and stable material. We therefore chose ethylcellulose as a model encapsulation material[10] in the experiments reported below. To our knowledge most of the reports on drug-releasing systems have been related to solid systems, such as tablets, but less work has been made with liquid forms.

On the basis of earlier research that showed ethylcellulose pseudolatex particles to be able to microencapsulate morphine,[11] we used a colloidal suspension of these particles produced in our laboratory as the vehicle for the active principle. The suspension was used to prepare a sustained-release liquid pharmaceutical formulation intended for oral use, the route of administration considered most convenient and that most patients prefer. Liquid formulations have further advantages for patients who have difficulties swallowing, such as small children and older patients. Having developed an effective microencapsulation process for the active drug, we turned our attention to the development of a stable final pharmaceutical form with suitable organoleptic properties. In the work reported here, we compared different formulations with different thickeners used at different concentrations. We have chosen these thickening agents due to their widely known use in the production of medicaments, which ensure their safety and tolerance.

Here we report the results of rheological and release assays to quantify behaviors related with physical stability (i.e., settling and redispersion)—studies that provide information on the system's internal structure. The mode of *in vitro* drug release is of particular interest from a pharmaceutical standpoint. Accordingly, we compared the release kinetics of each test formulation in

Received: January 13, 2011
Accepted: January 26, 2011
Published: January 27, 2011

Table 1. Concentration of Each of the Components in the Final Formula

component	% of the final formula
drug suspension	49.5
$CaCl_2$ 10^{-2} M	0.3
anhydrous sodium sulfite	0.1
simethicone	0.5
Kathon CG	0.1
thickener	49.5

Franz-type cells. Information about the rheological characteristics of the formulation provides data about how these characteristics influence the release profile of the morphine.

MATERIALS AND METHODS

Materials. The ethylcellulose polymer (9004-57-3) was supplied by ICN Pharmaceuticals (Aurora, OH, USA). Morphine hydrochloride was from Alcaliber S.A. (Madrid, Spain) and met the requirements of the Royal Spanish Pharmacopeia. Of the thickeners we tested, xanthan gum was from SBI System Bio-Industries S.A. (Barcelona, Spain), Carbopol 934-P was from Quimidroga S.A. (Barcelona, Spain), and sodium carboxymethylcellulose 110-200 and Avicel (microcrystalline cellulose) were from Labor Tecnic (Barcelona, Spain).

All chemicals were analytical quality and manufactured by Panreac (Barcelona, Spain). Water used to prepared the solutions and suspensions was of Milli-Q quality (Milli-Q Academic, Millipore, France).

Methods. *Ethylcellulose Pseudolatex Preparation.* The latex was prepared with the technique proposed by Vanderhoff et al.[12] with some modifications. Specifically, we omitted the stabilizing emulsifier (cetyl alcohol) and increased the amount of sodium lauryl sulfate. The cellulose polymer is not soluble in aqueous media and was therefore prepared by polymer emulsification. Synthesis was started by dissolving ethylcellulose in a suitable mixture of solvents (ethanol and benzene in a 15:85 proportion) and emulsifying the monomers in water with sodium lauryl sulfate at a concentration of 0.4%. Emulsification was performed by mechanical stirring.

Design and Preparation of the Final Formula. We tested three different thickeners: the natural polysaccharide xanthan gum, the synthetic thickener Carbopol 934-P (for internal use), and the semisynthetic thickener sodium carboxymethylcellulose 110-200 and Avicel. Each was tested at concentrations from 0.25% to 1.0% to determine its effect on the pharmaceutical formula. To all thickeners we added calcium chloride at a concentration of 10^{-2} M to obtain a weakly flocculated suspension that was easily redispersible. On the basis of earlier studies on the design of polymer suspensions for oral administration,[13] we added simethicone to the final formula as an antifoaming and antibloating agent to counteract the effects of the emulsifier, anhydrous sodium sulfite as an antioxidant and Kathon GC as an antimicrobial (Table 1).

Analytical Methods. The concentration of morphine was measured by UV spectrophotometry at 285 nm (λ_{max}). The method was previously validated and verified for accuracy, precision and linearity. Standard solutions were prepared by diluting the stock solution (500 μm mL^{-1}) with phosphate-buffered saline to the following concentrations: 15.62, 31.25, 62.5,125.0, 250.0, and 375.0 μm mL^{-1}. A Perkin-Elmer UV−vis Lambda 40 UV spectrophotometer was used for all measurements.

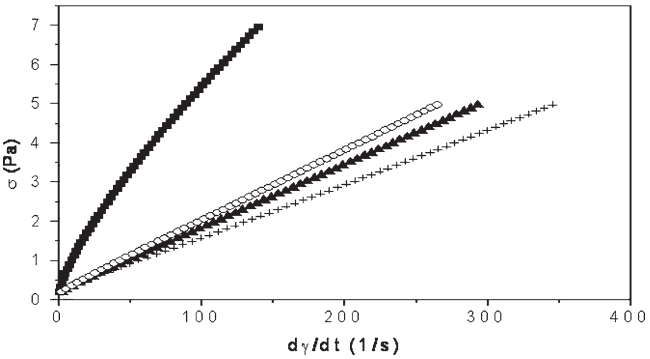


Figure 1. Rheogram of formulas prepared with Carbopol 1.0% (■), 0.75% (○), 0.5%(▲) and 0.25% (×).

Rheological Behavior. We used a Bohlin CS-25 stress-controlled rheometer. The device applies a preset shear stress to the sample and records shear strain. A motor applied shear stress and an angular position sensor on the spindle detected movement in the system being assayed. The preinstalled software automatically converted torque values and sensor readings into shear stress and shear strain.

We used coaxial cylinder measurement geometry with a 25 mm, 2.5 mL capacity CSS-25 sample holder. This allowed us to work with low-viscosity samples since the large surface area afforded by this setup ensured high sensitivity and precision for low-viscosity samples and low shear rates.

We ran two types of experiment in accordance with earlier research on polymer behavior:[14] viscosimetric (steady flow) and dynamic (oscillatory stress). Samples were preconditioned in the same manner before analysis to ensure that all had the same history of mechanical manipulation. A stress of σ = 3.5 Pa was applied for 30 s to break down the structure of the system, followed by a 120 s waiting time.

Viscoelastic properties of the different formulas have been characterized by oscillometric rheology, a technique that provides an estimation the value of elastic modulus (G') and loss modulus (G''). To calculate the lineal viscosity interval, an oscillatory stress sweep was carried out establishing a constant value of angular viscosity of 1 Hz. These assays were done for suspensions that showed plastic or pseudoplastic behavior, i.e., formulas that showed a degree of viscoelasticity. Viscoelastic materials display viscous flow combined with elastic deformation when subjected to shear stress.

These rheologic assays were carried out with the previously mentioned formulations which contain the microparticle suspension with encapsulated morphine, thickening agent, electrolyte solution (10^{-2} M), simethicone and antioxidant and antimicrobial agents.

For creep-recovery assays we subjected samples to a constant stress of σ = 1.5 Pa (within the range of linear viscoelastic response) for 120 s, and measured the compliance (creep) modulus (J) during this period. Recovery of the system was measured during 120 s after removing the stress.

Diffusion Experiments. Most published studies used a Franz-type cell.[15,16] The FDC-400 cell we used (Vidra-Foc, Barcelona, Spain) consisted of two compartments with a membrane clamped between the donor and receiver chambers. The receptor phase was phosphate-buffered saline, pH 6.2. This pH was chosen

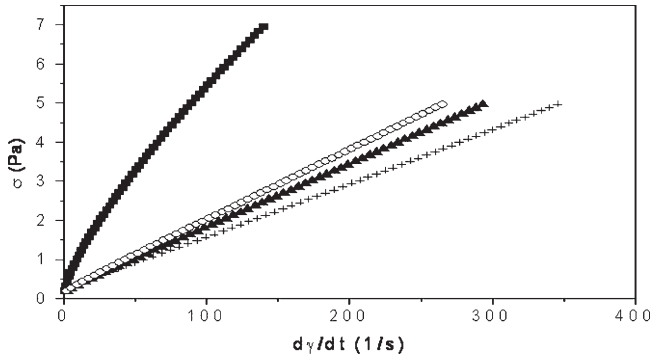


Figure 2. Rheogram of formulas prepared with xanthan gum at 1.0% (■), 0.75% (○),0.5% (▲) and 0.25% (×).

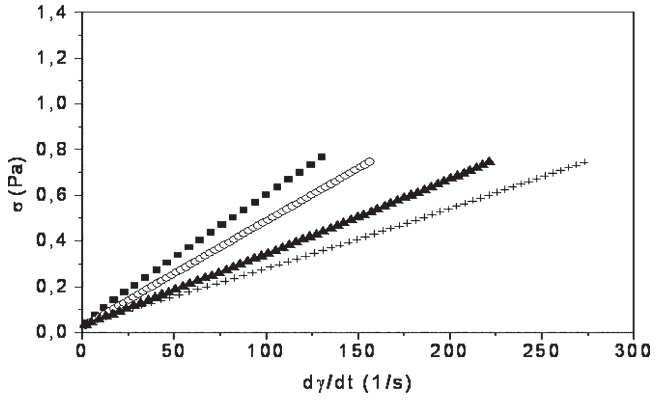


Figure 3. Rheogram of formulas prepared with sodium carboxymethylcellulose/Avicelat 1.0% (■), 0.75% (○), 0.5% (▲) and 0.25% (×).

Table 2. Viscosity of Formulas with Newtonian Behavior

thickener	η (Pa·s)
Carbopol	
0.25%	0.01367
0.5%	0.01621
0.75%	0.01797
carboxymethylcellulose and Avicel 1.0%	
0.25%	0.00259
0.5%	0.00322
0.75%	0.00461
1.0%	0.00557
xanthan gum	
0.25%	0.00348

because it corresponds to the pH in the proximal portion of the small intestine, where the drug is absorbed after oral administration.

The membranes were 47 mm in diameter and 0.45 μm in pore size. We tested membranes made of methylcellulose (Teknokroma, Sant Cugat del Valles, Barcelona, Spain), nylon (Waters Corporation, Barcelona, Spain) and polysulfone (Pall Corporation, East Hills, NY, USA). Methylcellulose membranes offered the least resistance to diffusion of the active principle, so they were used for diffusion studies.

■ RESULTS AND DISCUSSION

Rheological Behavior. *Viscosimetry.* We used a stepped stress sweep to observe changes in viscosity (η) and stress (σ)

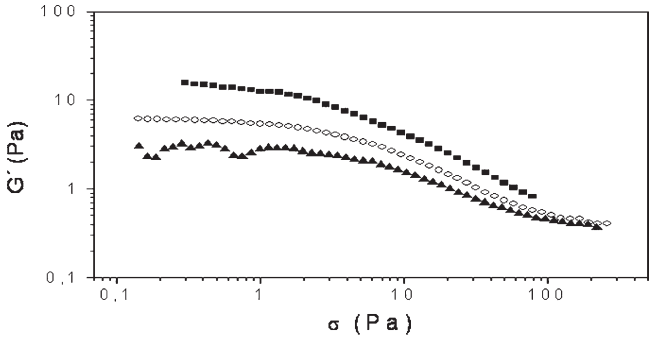


Figure 4. Zone of linear viscoelastic response in formulas prepared with xanthan gum at 1.0% (■), 0.75% (○) and 0.5% (▲).

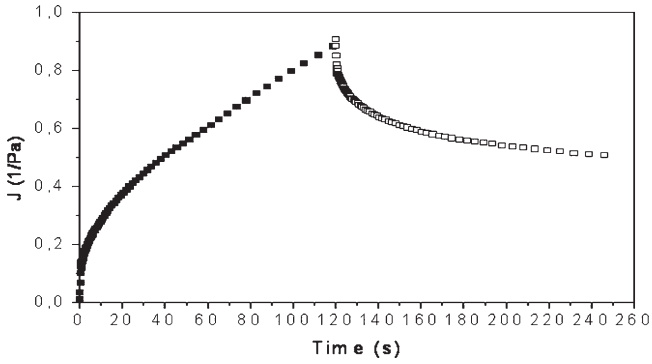


Figure 5. Creep-recovery of the suspension with xanthan gum at 1.0%.

with shear rate ($d\gamma/dt$). As seen in Figures 1, 2 and 3, all formulas showed Newtonian behavior except when the highest concentration of Carbopol was used (Figure 1), and when xanthan gum was used at a concentration of 0.5% or higher (Figure 2). Newtonian behavior is a feature of fluids that behave according to Newton's law, i.e., in which shear stress is directly proportional to shear rate, such that viscosity is constant and flow curves or rheograms yield a straight line with its intercept at the origin. Viscosity is given by the slope of the line or the tangent of the angle it forms with the abscissa.

The findings for viscosity in the different formulas with Newtonian behavior (Table 2) show that the formulas containing 1.0% sodium carboxymethylcellulose and Avicel or 0.25% xanthan gum had the lowest viscosities. Formulas with 1.0% Carbopol or 0.5% xanthan gum showed pseudoplastic behavior (Figures 1 and 2). Many colloidal systems, especially polymer solutions and solid/liquid flocculated systems,[17] become more fluid when agitated, a behavior termed pseudoplasticity. This is an example of non-Newtonian behavior resulting from the decrease in viscosity as shear rate increases. Shear rate in these samples increased more rapidly than shear stress, producing a concave flow curve that curved upward from the abscissa.

Suspensions with 0.75% and 1.0% xanthan gum showed plastic behavior (Figure 2). This type of behavior appears when the concentration of the suspension is high enough for particles to agglomerate and form bridges throughout the volume of the suspension, i.e., a three-dimensional network that imparts shear-thinning behavior.[18] When these systems are at rest, cohesive forces give them the characteristics of a solid, but above a ceratin threshold value the bonds are broken and the system behaves as a fluid. This threshold is known as the yield stress (σ_0). According

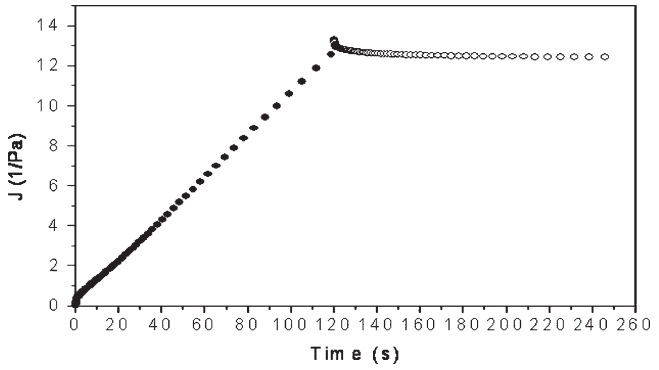


Figure 6. Creep-recovery of the suspension with xanthan gum at 0.75%.

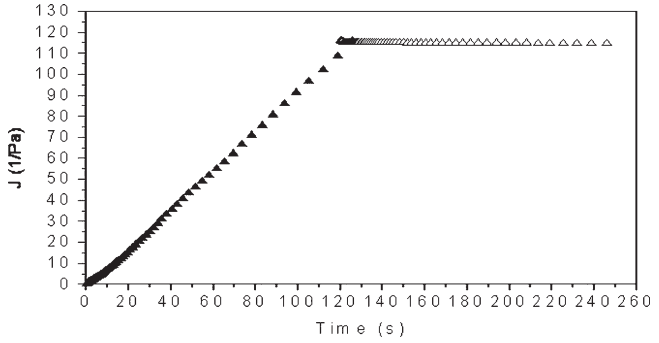


Figure 7. Creep-recovery of the suspension with xanthan gum at 0.5%.

to the criterion we used to determine yield stress, samples were considered to display flow when they reached maximum viscosity. The results for suspensions that showed plastic behavior were 1.164 Pa for formulas with the highest concentration of xanthan gum, and 0.939 Pa for suspensions with 0.75% xanthan gum. We can therefore say that yield stress and hence plasticity increased with concentration of the thickener.

Oscillometry. Although the formula containing 1.0% Carbopol showed pseudoplastic behavior, no linear viscoelastic region could be identified, and oscillometric assays were thus not done. As a result only the formulas that contained 0.5% and 1.0% xanthan gum were assayed by oscillometry.

As seen in Figure 4, at low shear stress values we found linear viscoelastic responses: the elastic modulus (G') was essentially unchanged with time. These results show that the elastic modulus increased with the concentration of xanthan gum in the formulas (Figure 4). This translated as greater structural stability, and corroborated the viscometric findings reported above. In all samples the elastic modulus (G') was greater than the loss modulus (G''), i.e., elastic (solidlike) behavior predominated over viscous (fluidlike) behavior.

Creep-Recovery. Figures 5 and 6 show that, at concentrations of thickener of 0.5% and higher, the suspensions showed some degree of recovery owing to their elastic nature. In contrast, formulas with lower concentrations of thickener showed poor recovery (Figure 7)

In Vitro Release Studies. Because each formula exhibited a different type of rheological behavior, we selected the formula with the highest concentration of each of the three thickeners. This approach yielded data on the influence of each type of rheology on the drug's release profile. To each formula we added 2406 μg of morphine hydrochloride. Then at fixed intervals we withdrew

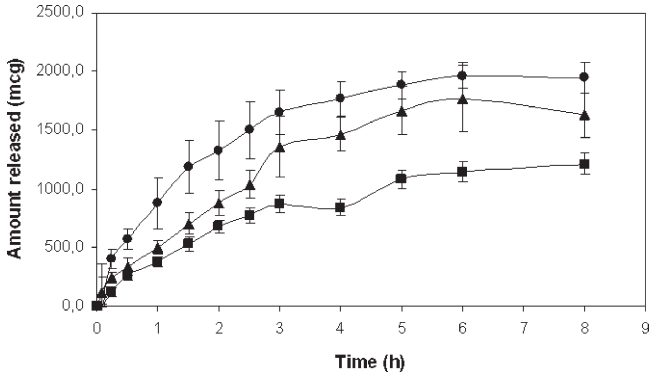


Figure 8. Amount of morphine in the receptor cell, released from formulas with xanthan gum at 1.0% (■), Carbopol at 1.0% (▲) and sodium carboxymethylcellulose at 1.0% (●).

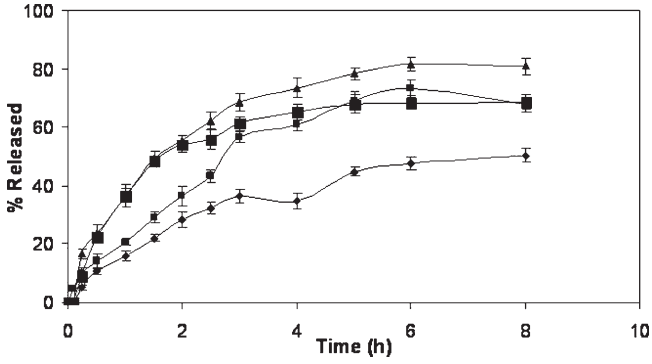


Figure 9. Percentage of morphine released from formulas with xanthan gum at 1.0%(◆), Carbopol at 1.0% (small ■) and sodium carboxymethylcellulose at 1.0% (▲), compared to the suspension without thickener (large ■).

400 μL samples from the receptor chamber and replaced the sample volume with the same volume of receptor solution. The amount of drug in the sample was estimated electrophoretically, and this amount was adjusted for the number of previous samples. Each assay was run in quadruplicate. Duration of the assay was 8 h; we used this cutoff time because we assumed that the formulas would not remain in the human digestive tract for more than 8 h.

It should be recalled that some ingredients in the formulas we tested may be soluble in the buffer and, like morphine, may cross the Franz cell membrane. When we tested a control formula lacking the active drug, we found that some components crossed the membrane and contributed to absorbance of the samples at 285 nm. However, their contribution was constant throughout the observation period, making appropriate correction to calculate the amount of morphine released in each assay straightforward. All samples were also analyzed spectrophotometrically to measure the amount of active principle released.

As shown in Figure 8, during the first hour of the release assay all three formulas showed similar behavior, although release was slightly faster from the formula containing 1.0% sodium carboxymethylcellulose. However, after 2 h release was clearly slowest from the formula that contained 1.0% xanthan gum. At the end of the 8 h observation period the amount of morphine hydrochloride released from this formula was significantly less than from the 1.0% Carbopol and 1.0% sodium carboxymethylcellulose

Table 3. Akaike Discriminatory Criterion Values for Formula with Each Thickener and Type of Kinetics

formulas	zero-order	single-order	square root	cube root
xanthan gum 1.0%	64.62 ± 3.49	47.56 ± 0.57	61.89 ± 0.28	37.64 ± 3.49
Carbopol 1.0%	61.26 ± 0.92	45.85 ± 0.74	61.47 ± 0.32	37.25 ± 0.66
carboxymethylcellulose + Avicel 1.0%	61.04 ± 0.70	47.67 ± 0.68	62.48 ± 0.39	39.18 ± 1.24

formulas. The active principle was released most rapidly from the latter formula.

Figure 9 compares the percentages of active principle released from formulas containing different thickeners and from the control formula with no thickener. These results provide reliable data on the influence of each thickener on drug release. The 1.0% xanthan gum formulation showed the slowest release: after 8 h only 50% of the dose of the active principle was detectable in the receiver chamber. This result was not surprising given that viscometric studies had shown this thickener to yield the highest viscosity. Earlier studied also found that higher viscosities delayed drug release.[19−21]

During the first 3 h, drug release from the 1.0% Carbopol formula was more gradual than from the suspension prepared without thickener. However, after this period the rate of release was similar to that from the suspension prepared without thickener, so that at the end of the study period both formulas had released 67% of the initial dose. Sodium carboxymethylcellulose at 1.0% did not affect the release rate from ethylcellulose microparticles during the first 2 h, but after this period it substantially increased the release of morphine hydrochloride. After 8 h we found that this formula had released 81% of the initial dose, a figure much higher than the percentage of active principle released from the suspension prepared with no thickener. This behavior probably reflects the water-soluble nature of sodium carboxymethylcellulose. This would lead to an increase in osmotic strength in the medium, which in turn would favor dissolution of the drug from the microspheres and enhance drug release. Our findings confirm earlier reports that water-soluble excipients increased dissolution rates.[22]

Release Kinetics. When the intrinsic mechanism of release is unknown for a given formula, mathematical models can be tested to choose the one which most reliably explains the release kinetics. We fitted the experimental data to several models and then used the Akaike information criterion (AIC)[22] to find the function that best explained the drug release process by calculating $AIC = n \ln SSQ + 2p$ where n is the number of pairs of experimental data, SSQ is the residual sum of the squares, and p is the number of parameters in the fitting function. The model that best fit the data was that with the lowest AIC. Table 3 shows the AIC values for the different formulations. All three formulations followed cube root kinetics. According to the laws of geometry, this type of kinetics is found when drug particles are spherical or when the sample contains a surfactant that forms micelles in the solution.[23] In our samples the ethylcellulose microparticles used to encapsulate morphine hydrochloride were in fact spherical, and we thus assume that cube root kinetics was the function that best described drug release.

CONCLUSIONS

The most suitable formula of those compared here was the one that contained 1.0% Carbopol as the thickener. Its pseudoplastic behavior favored stability during storage and made appropriate dosaging possible because the suspension was readily redispersed by shaking. This thickener at a concentration of 1.0% did not interfere with drug release from the ethylcellulose microparticles, and did not modify the expected release kinetics.

AUTHOR INFORMATION

Corresponding Author

*Departamento de Farmacia y Tecnología Farmacéutica, Facultad de Farmacia, Campus de Cartuja, Universidad de Granada, 18071 Granada, Spain. Tel: +34 958 243904. E-mail: adolfina@ugr.es.

ACKNOWLEDGMENT

Part of this work was supported by the Spanish Ministry of Education and Science and by FEDER funds through Project MAT 2005-07746-C02-02 02, and by Project FQM 410 (Proyecto de Excelencia). We thank K. Shashok for translating parts of the manuscript into English.

REFERENCES

(1) Moffat, A. C., et al. , Eds. *Clarke's isolation and identification of drugs*, 2nd ed.; The Pharmaceutical Press: London, 1986.

(2) Kotb, H. I.; El-Kady, S. A.; Emara, S. E.; Fouad, E. A.; El-Kabsh, M. Y. Pharmacokinetics of controlled release morphine (MST) in patients with liver carcinoma. *Br. J. Anaesth.* **2005**, *94* (1), 99–109.

(3) Volles, D. F.; McGory, R. Pharmacokinetic considerations. *Crit. Care Clin.* **1999**, *15* (1), 55–75.

(4) Bhat, R.; Chari, G.; Gulati, A.; Aldana, O.; Velamati, R.; Bhargava, H. Pharmacokinetics of a single dose of morphine in preterm infants during the first week of live. *J. Pediatr.* **1990**, *117* (3), 477–481.

(5) Ponce, L. M.; Oviedo, L. A.; Aiache., J. M. Análisis del efecto del pH en la cinética de liberación de la teofilina en un medicamento de liberación programada: Parte I. Microgránulos encapsulados recubiertos con goma laca. *Rev. Colomb. Cienc. Quim.-Farm.* **2005**, *34*, 126–139.

(6) Guo, X.; Zhang, L.; Oian, Y.; Zhou, J. Effect of composition on the formation of poly (dl-lactide) microspheres for drug delivery systems: Mesoscale simulations. *Chem. Eng. J.* **2007**, *131*, 195–201.

(7) Arias, J. L.; Gallardo, V.; Ruiz, M. A.; Delgado., A. V. Ftorafur loading and controlled release from poly (ethyl-2-cyanocrylate) and poly (butylcyanocrylate) nanospheres. *Int. J. Pharm.* **2004**, *337* (1−2), 195–201.

(8) Babu, V. R.; Sairam, M.; Hosamani, K. M.; Aminabjavi, T. M. Preparation of sodium alginate-methylcellulose blend microspheres for controlled release of nifedipine. *Carbohydr. Polym.* **2007**, *69* (2), 241–250.

(9) Whang, Q.; Dong, Z.; Du, Y.; Kennedy, F. Controlled release of ciprofloxacin hydrochloride from chitosan/polyethylene glycol blend films. *Carbohydr. Polym.* **2007**, *69* (2), 336–343.

(10) Lai, M. K.; Chang, C. Y.; Lien, Y. W.; Tsiang, R. C. Application of gold nanoparticles to microencapsulation of thioridazine. *J. Controlled Release* **2006**, *111* (3), 352–361.

(11) Morales, M. E.; Gallardo, V.; Calpena, A. C.; Doménech, J.; Ruiz, M. A. Comparative study of morphine diffusion from sustained release polymeric suspensions. *J. Controlled Release* **2004**, *95*, 75–81.

(12) Vanderhoff, J.W.; M. S. El-Aasser J. Ugelstad. US Patent 4,177,177, 1979.

(13) Matthews, B. A.; Rhodes, C. T. Use of the Derjaguin, Landau, Verwey and Overbeek theory to interpret pharmaceutical suspension stability. *J. Pharm. Sci.* **1970**, *59*, 521.

(14) Rudraraju, V. S.; Wyand, C. Rheological characterization of Microcrystalline cellulose/sodium carboxymethyl cellulose hydrogels using a controlled stress rheometer. Part I and II. *Int. J. Pharm.* **2005**, *292*, 53–61.

(15) Franz, T. J. Percutaneous absorption on the relevance of in vitro data. *J. Invest. Dermatol.* **1975**, *64* (3), 190–195.

(16) Kierstan, K. T.; Beeper, A. E.; Mitchell, J. C.; Hadgraft, J.; Raghavan, S. L.; Davis, A. F. UV-spectrophotometry study of membrane transport processes with a novel diffusion cell. *Int. J. Pharm.* **2001**, *229* (1−2), 87–94.

(17) Vasiljevic, D.; Parojcic, J.; Primorac, M.; Vuleta, G. An investigation into the characteristics and drug release properties of multiple w/o/w emulsion systems containing low concentration of lipophilic polymeric emulsifier. *Int. J. Pharm.* **2006**, *309*, 171–177.

(18) Nakamura, H.; Tachi, K Dynamics of shear-thinning suspensions of core-shell structured latex particles. *J. Colloid Interface Sci.* **2006**, *297* (1), 312–316.

(19) Luan, X.; Bodmeier, R. In situ forming microparticle system from controlled delivery of leurolide acetate: Influence of the formulation and processing parameters. *Eur. J. Pharm. Sci.* **2006**, *27* (2−3), 143–149.

(20) Fernández-Arévalo, M.; Alvarez-Fuentes, J.; Iruin, A.; Holgado, M. A. In Vitro Evaluation of a Morphine Polymeric Complex: Flowability Behavior and Dissolution Study. *AAPS PharmSciTech* **2004**, *5* (3), 1–7.

(21) Bonferoni, M. C.; Rossi, S.; Ferrari, F.; Stavik, E.; Pena-Romero, A.; Caramella, C. Factorial Análisis of the Influence of Dissolution Medium on Drug Release from Carrageenan-Diltiazem Complexes. *AAPS PharmSciTech* **2000**, *1* (2), E15.

(22) Khan, G. M.; Zhu, J. B. Ibuprofen release kinetics from controlled-release tablets granulated with aqueous polymeric dispersion of ethylcellulose II: Influence of several parameters and coexcipients. *J. Controlled Release* **1998**, *56*, 127–134.

(23) Berrozpe, J. D.; Delfina, J. M. P.; Lanao, J. M. *Biofarmacia y Farmacocinética II*; Síntesis: Madrid, 1998.