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RESEARCH PAPER

Effect of Polymer Hydration on the Kinetic Release of Drugs: A Study of Ibuprofen and Ketoprofen in HPMC Matrices

T. Salsa,[1,*] F. Veiga,[1] J. J. C. Teixeira-Dias,[2] and M. E. Pina[1]

[1]Laboratory of Pharmaceutical Technology, Faculty of Pharmacy, University of Coimbra, Coimbra, Portugal
[2]Department of Chemistry, University of Aveiro, Aveiro, Portugal

ABSTRACT

Samples of drug/hydroxypropylmethylcellulose (HPMC) mixtures and matrices (drug/HPMC mixtures plus excipients) were allowed to equilibrate in closed chambers with defined relative humidities (RHs). Their water uptake and drug release were evaluated by differential scanning calorimetry/thermogravimetric analysis and dissolution studies, respectively. Analysis of the thermal behaviors of the drug/HPMC mixtures and of the polymer alone, as functions of RH, leads to the conclusion that most of the hydration water is retained by the polymer, and points to the occurrence of different types of hydration water, from the strongly polymer-bound water molecules at RH values up to 81%, to the almost "free water" for RH values close to 100%. In addition, application of the Korsmeyer model to the dissolution results leads to the conclusion that the rate determining dissolution processes are predominantly of the fickian type.

Key Words: Ibuprofen; Ketoprofen; Polymer matrices; Hydration; Drug release.

INTRODUCTION

Polymer hydration plays an important role in the process of drug released from oral dosage matrix forms. During polymer dissolution, various phenomena occur, in accordance with several researchers.[1–5]

Because of a relatively low content in methoxyl groups, the Methocel K grade of hydroxypropylmethylcellulose (HPMC) hydrates quickly, a relevant feature for its application in controlled-release matrices.[3] Various studies on the hydration of HPMC matrices have been carried out by different authors.[1,6–16]

*Correspondence: T. Salsa, Laboratory of Pharmaceutical Technology, Faculty of Pharmacy, University of Coimbra, P-3000 Coimbra, Portugal; E-mail: tsalsa@mepha.pt.

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Despite the number of previous papers assessing the performance of HPMC matrices on the controlled release of drugs, the main objective of the present study is to clarify the effect of polymer hydration and its relationship on the kinetics modulation of the controlled release of drugs.

MATERIALS AND METHODS

Reagents, Matrices, and Tablets

HPMC (Methocel™ K 15M) was obtained from Colorcon (Bougival, France). Ibuprofen was kindly offered by Knoll Pharma Chemicals (Nottingham, UK), and ketoprofen was supplied by Sigma-Aldrich Química, S. A. (Madrid, Spain). Magnesium stearate, lactose, and talc of reagent grade were supplied by Merck.

The matrices were prepared with 200 mg of drug (ibuprofen or ketoprofen), 70 mg of HPMC, 71 mg of lactose (diluent), 6 mg of talc, and 3 mg of magnesium stearate (lubricants). The amounts of HPMC and lactose in these formulations were optimized by dissolution studies; several formulations containing different quantities of HPMC were prepared to obtain controlled-release matrix tablets, and the best formulations were those with 70 mg of polymer.[17]

The drug, HPMC, and lactose were passed through a 100-mesh sieve and thoroughly mixed in a blender for 15 min. Lubricants were sieved by aperture diameter net of 500 mesh, added to the previous mix, and blended again for 5 min, in accordance with those described in previous investigations.[18] All matrices (total mass of 350 mg) were obtained with flat punches of 10 mm diameter and a 5T pression in a Speca Press (hydraulic press).

Samples at Defined Relative Humidity

Samples of drug/HPMC mixtures and drug/HPMC mixtures plus excipients were allowed to equilibrate, for 7 days, in closed chambers of defined relative humidities (RHs) obtained from water vapor (RH 100%) and vapor of saturated solutions of $CuSO_4$ (RH 98%), $(NH_4)_2SO_4$ (RH 81%), $NaNO_2$ (RH 66%), $NaHSO_4$ (RH 52%), $CaCl_2$ (RH 32%), and anhydrous silica (RH 0%).[19] The samples were studied by differential scanning calorimetry (DSC)/thermogravimetric analysis (TGA) and the matrices by the dissolution procedure.

Methods

The DSC/TGA measurements were performed using a STA 1500H-Rheometric instrument, with a heat flow rate of $10^{\circ}C\,min^{-1}$ in an inert atmosphere. Samples were placed in a platinum balance.

Samples were analyzed for their water content determined by weight loss from thermic dehydration that, in turn, occurred during recording of the thermograms.

Dissolution studies were carried out in accordance with the paddle method described in U.S. Pharmacopeia 23[20] and in the European Pharmacopeia 97,[21] using the automatic procedure with a Hanson Research 72 model and a Shimadzu UV 1603 spectrophotometer. Samples were analyzed every 2 min for 960 min. The water bath was kept at 37°C, with a paddle speed of 100 rpm. The dissolution medium was 1,000 mL of phosphate buffer (pH 7.2).[20] Samples were analyzed at 264 nm and 320 nm for the ibuprofen and ketoprofen samples, respectively.[22]

RESULTS

HPMC at Defined RHs

During HPMC hydration, for RH values greater than 80%, a structural macroscopic change was observed, as the polymer ceased to be a solid and became a gel.

Figure 1a shows the thermogram and the DSC results for an HPMC sample at RH 98%. During this TGA, the polymer lost ca. 38% in weight from thermic dehydration (Fig. 1b). This endothermic event occurs at a DSC minimum of ca. 72°C. Figure 1c plots the dehydration temperatures that correspond to the minimum values of the DSC signals vs. RH, for HPMC samples. The first four points refer to RHs up to 66% and show an approximately constant temperature around 72°C for the DSC signal. In turn, the RH values from 66% up to 98% exhibit a linear increase in the DSC minimum value up to ca. 92°C, followed by a very steep increase from RH 98% to RH 100%. At the latter RH value, the DSC signal occurs at roughly 120°C. These results suggest that, for RH values up to 66%, most of the water retained by the polymer should be bound to the polymer by relatively strong hydrogen bonds to withstand temperatures up to 72°C, whereas the additional water retained

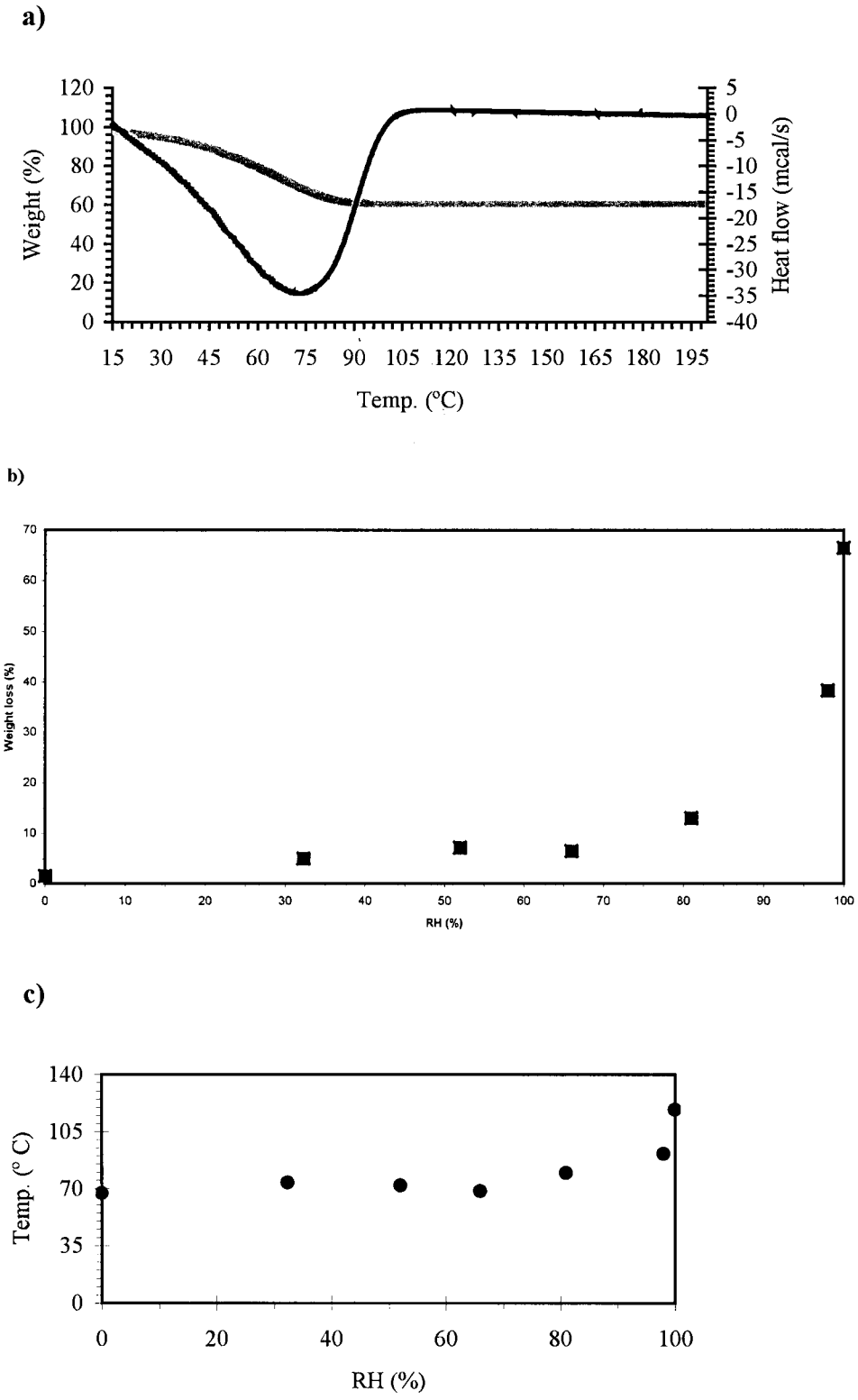

Figure 1. (a) DSC/TGA results for an HPMC sample at RH = 98%; (b) weight loss of HPMC samples during thermogram, as a function of RH; (c) temperature corresponding to the minimum of the DSC signal as a function of RH, for HPMC samples (number of assays = 5).

between RH 98% and RH 100% should be mostly "free water."

Thermal Behavior of Drug/HPMC Mixtures

Figure 2 shows the DSC/TGA curves for ketoprofen/HPMC (Fig. 2a) and ibuprofen/HPMC (Fig. 2b) mixtures, both at RH 66%.

As seen from Fig. 2a (ketoprofen/HPMC mixture), only two thermal events, both of them endothermic, occur in the scanned temperature region between room temperature and 120°C: one, whose broad and relatively weak DSC curve has a minimum at around 45°C, is accompanied by a small decrease in weight (ca. 1.2%) as given by the TGA curve; the other one, which is a relatively sharp DSC signal, is not followed by a variation in weight in the TGA curve, thus pointing to a phase transition in the ketoprofen/HPMC mixture, most likely the ketoprofen melting at ca. 92°C, in accordance with the DSC curve for ketoprofen alone. The thermal behavior of the ibuprofen/HPMC mixture is shown in Fig. 2b and exhibits two thermal events from room temperature up to 120°C. The first one occurs from room temperature up to ca. 60°C and is accompanied by a weight loss of 1.3%, thus pointing to the thermic dehydration of the ibuprofen/HPMC mixture. The second thermal event is composed of two signals at approximately 72°C and 76°C. The proximity of these temperatures suggests the occurrence of phase transitions for distinct forms of ibuprofen. The possibility of rotational isomerism in the $(H_3C)_2CHCH_2$— moiety bound to the ibuprofen phenyl fragment should not be excluded.

The water content for the drug/HPMC mixtures raised above 2% (w/w) only for RHs greater than 81%. Above this RH value, a distinct behavior was observed for ibuprofen/HMPC and ketoprofen/HPMC matrices. The water content of the ibuprofen/HMPC samples increased up to 10–15% for RH between 81% and 98%, and raised steeply to ca. 48% of water for RH between 98% and 100%. In turn, ketoprofen/HMPC samples increased their water content up to ca. 49% for RH between 81% and 98%, and raised from this value up to 55% of water for RH between 98% and 100%.

Both the drug/HPMC mixtures and the HPMC alone (Fig. 1b) show the same general variation for their water content as a function of RH. However, the water content for the polymer alone exhibit, for the same humidities, slightly higher values than for the mixtures.

Dissolution Studies

Dissolution studies have been performed to assess the influence of hydration on the release mechanism of ibuprofen and ketoprofen from HPMC matrices. In these dissolution studies, the released drug was plotted against time for assays prepared at defined RH values as described in Methods.

Figure 3 shows dissolution plots of ketoprofen released from compressed mixtures at two defined RH values (66% and 100%), a blend of HPMC and drug (Fig. 3a), and a blend of HPMC/drug and excipients (Fig. 3b). The corresponding figures for ibuprofen are Fig. 4a and 4b. The same general trend, observed for all the recorded RH values, emerges from these results: as RH increases, the amount of released drug increase. Differences between ketoprofen and ibuprofen regarding the amounts of released drug are probably because of the differences in water solubility for the drugs.

To obtain additional insight into these results, we have applied the Korsmeyer model[23] in its logarithmic form.

Having determined the n value for all the RH values and for all types of samples (matrices without and with excipients) considered in this work, a value $n = 0.5$ was predominantly found, indicating a fickian diffusion rate determining process.

DISCUSSION

In summary, the following general conclusions can be drawn from the previously described results. Comparison of the water content of drug/HPMC mixtures and HPMC samples as functions of RH leads to the conclusion that the polymer is responsible for retaining most of the hydration water. In fact, for the same humidities, the water content for the polymer alone reaches slightly higher values than for the mixtures, suggesting that the presence of the predominantly hydrophobic and less water-soluble drugs has the effect of disrupting the water hydrogen bond network of the polymer, thus diminishing the amount of hydration water.

Quantitatively distinct behaviors were observed between ketoprofen/HPMC and ibuprofen/HPMC samples for RH values greater than 81%. In this regard, it is interesting to point out that ketoprofen/HPMC samples display hydration water contents larger than ibuprofen/HPMC samples. This behavior is consistent with a larger polarity of the ketoprofen

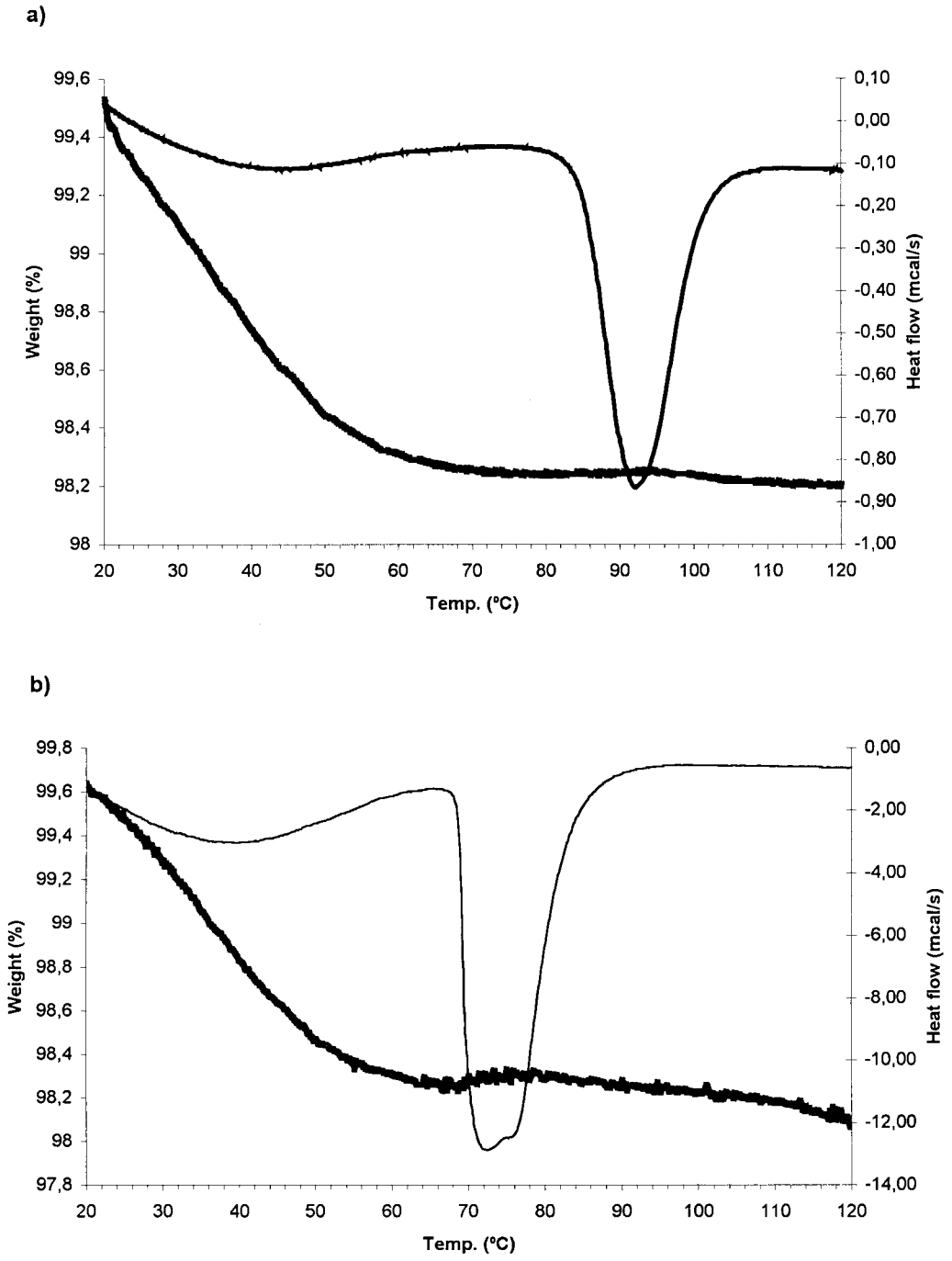

Figure 2. DSC and TG results for samples prepared at RH = 66%. (a) Ketoprofen/HPMC mixture. Weight loss from dehydration during TGA corresponds to 1.2% (w/w). (b) Ibuprofen/HPMC mixture. Weight loss from dehydration during TGA corresponds to 1.3% (w/w).

molecules because of the presence of their carbonyl group which, in turn, might act as a hydrogen bond acceptor group. In addition, the presence of the $(H_3C)_2CHCH_2$– moiety in ibuprofen will certainly contribute to a greater hydrophobic character of these molecules.

The experimental observation of distinct RH domains, both for the water content and the DSC

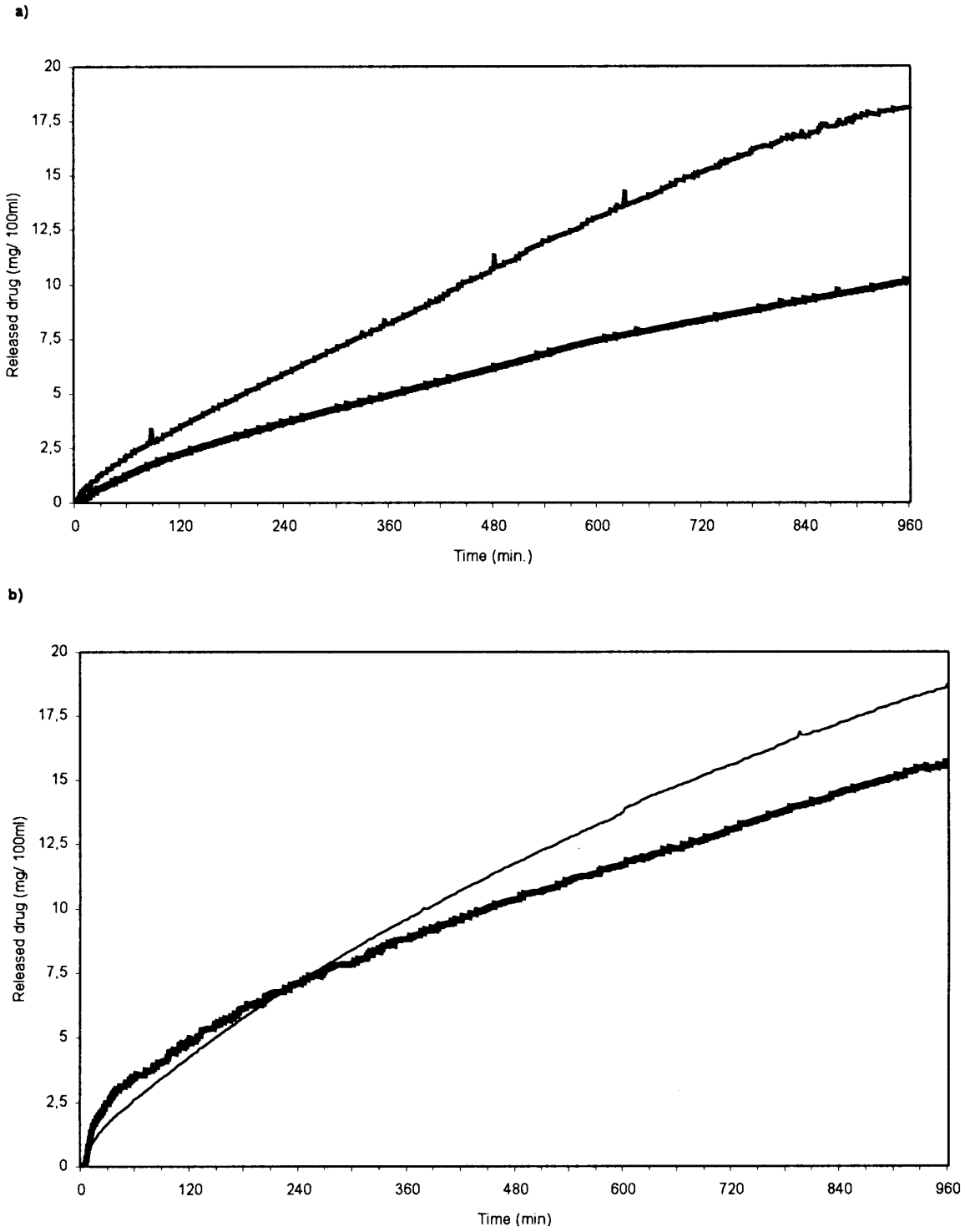

Figure 3. Kinetics of ketoprofen release at two distinct RH values [66% (——) and 100% (——)] by dissolution studies. (a) From matrix tablets without excipients. (b) From matrix tablets with excipients.

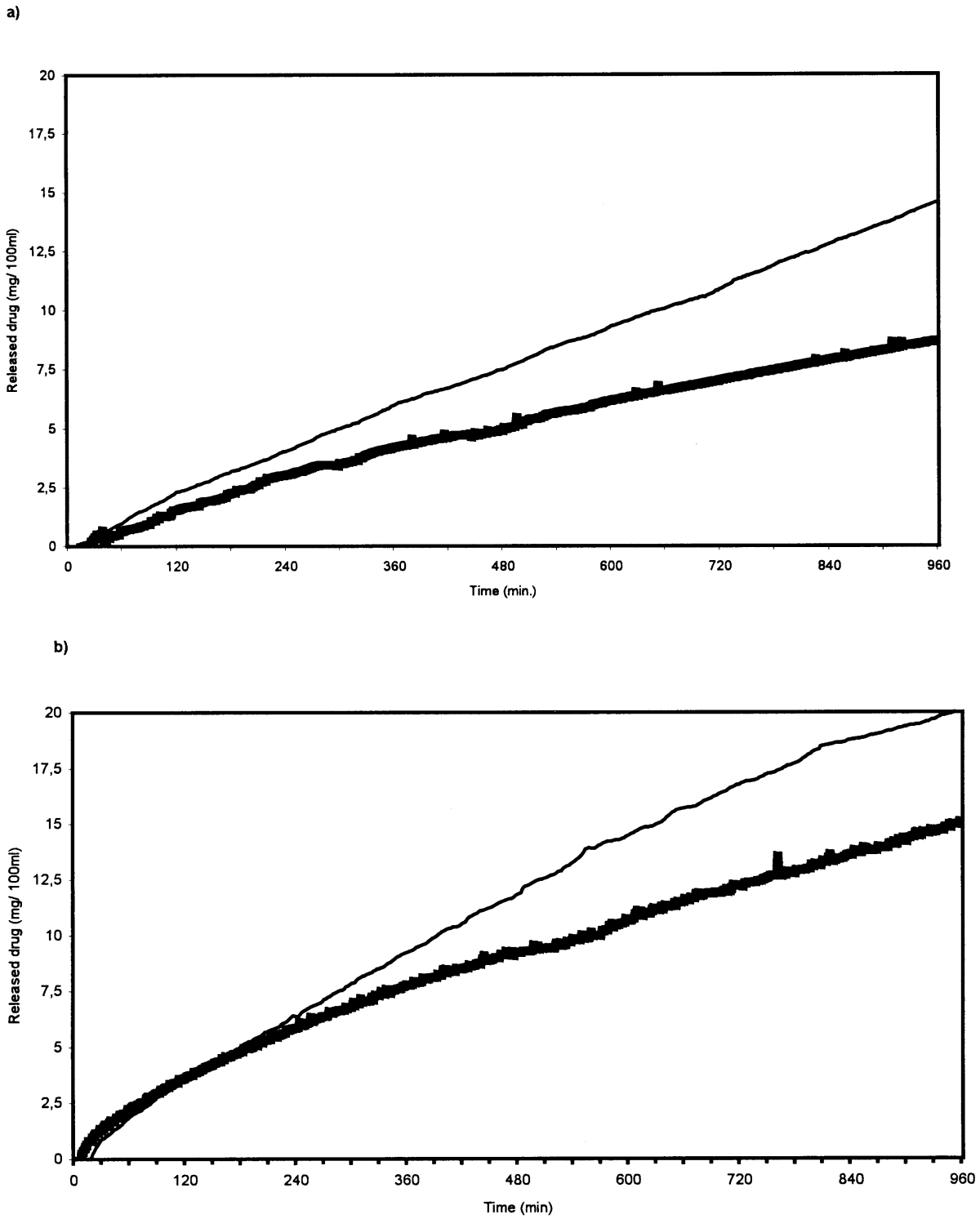

Figure 4. Kinetics of ibuprofen release at two distinct RH values [66% (——) and 100% (——)] by dissolution studies). (a) From matrix tablets without excipients. (b) From matrix tablets with excipients.

minimum temperature as a function of RH, leads to the conclusion that different types of hydration water might occur, as follows:

- Up to 66% RH: the hydration water should be probably made of individual water molecules bound through relatively strong water—polymer hydrogen bonds, mostly to the polymer.
- From 66% up to 81% RH: the hydration water molecules should be part of a moderately strong network of water—polymer and water—water hydrogen bonds.
- For RH values from 81% up to 98%: the hydration water becomes additionally bound to ketoprofen and ibuprofen molecules, most likely by interactions of the hydrogen bond type to the polar groups of these molecules. In fact, in this range of humidities, distinct hydration water contents were observed for the ketoprofen/HPMC and ibuprofen/HPMC mixtures, suggesting a role played by the drug molecules in the mixtures.
- In the short range of RH values between 98% and 100%: hydration water should be mostly "free water," with physical and thermodynamic characteristics resembling those of bulk water.

The Korsmeyer model applied to the results of the dissolution experiments carried out in the present study points to a predominantly fickian rate-determining diffusion process. In particular, the observation of this general trend, especially for RH values greater than 66%, may point to the importance of an almost "continuous" hydrogen bond network, for such a diffusion rate type of process. Moreover, these results stress the major role played by the HPMC polymer in building this network.

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REFERENCES

1. Alderman, D.A. A review of cellulose ethers in hydrophilic matrices for oral controlled-release dosage forms. Int. J. Pharm. Tech. Prod. Mfr. **1984**, *5* (3), 1–9.
2. Bowstra, J.A.; Junginger H.E. Hydrogels. In *Encyclopedia of Pharmaceutical Technology*; Swarbrick, J., Boylan, J.C., Eds.; Marcel Dekker: New York, 1993; Vol. 7, 441–465.
3. Kumar, V.; Banker, G.S. Chemically-modified cellulosic polymers. Drug Dev. Ind. Pharm. **1993**, *19* (1/2), 1–31.
4. Skoug, J.W.; Mikelsons, M.V.; Vigneron, C.N.; Stemm, N.L. Qualitative evaluation of the mechanism of release of matrix sustained release dosage forms by measurement of polymer release. J. Control. Rel. **1993**, *27*, 227–245.
5. Swarbrick, J. Advances in controlled drug delivery. S.T.P. Pharma Pratiques **1996**, *6*, 53–56.
6. Kararli, T.T.; Catalano, T. Stabilization of misoprostol with hydroxypropyl-methylcellulose (HPMC) against degradation by water. Pharm. Res. **1990**, *7* (1), 1186–1189.
7. Mitchell, K.; Ford, J.L.; Armstrong, D.J.; Elliot, P.N.C.; Rostron, C.; Hogan, J.E. The influence of the particle size of hydroxypropylmethylcellulose K 15M on its hydration and performance in matrix tablets. Int. J. Pharm. **1993**, *100*, 175–179.
8. Rajabi-Siahboomi, A.R.; Bowell, R.W.; Mansfield, P.; Davies, M.C.; Melia, C.D. HPMC hydrophilic matrix systems: effect of degree of substitution on swelling behaviour and water mobility. J. Pharm. Pharmacol. **1993**, *45* (Suppl. 2), 1110.
9. Rajabi-Siahboomi, A.R.; Bowell, R.W.; Mansfield, P.; Henderson, A.; Davies, M.C.; Melia, C.D. Structure and behaviour in hydrophilic matrix sustained release dosage forms: 2. NMR-imaging studies of dimensional changes in the gel layer and core of HPMC tablets undergoing hydration. J. Control. Rel. **1994**, *31*, 121–128.
10. Rajabi-Siahboomi, A.R. Slow release hydrophilic matrix systems: Investigation of the interactions between water and hydroxypropylmethylcellulose. Proceed. Int. Symp. Control. Rel. Bioact. Mater. **1998**, *25*, #133.
11. McCrystal, C.B.; Ford, J.L.; Rajabi-Siahboomi, A.R. Water distribution studies within cellulose ethers using differential scanning calorimetry. 1. Effect of polymer molecular weight and drug addition. J. Pharm. Sci. **1999**, *88*, 792–796.
12. McCrystal, C.B.; Ford, J.L.; Rajabi-Siahboomi, A.R. Water distribution studies within cellulose ethers using differential scanning calorimetry. 2.

Effect of polymer substitution type and drug addition. J. Pharm. Sci. **1999**, *88*, 797–801.
13. Nokhodchi, A.; Ford, J.L.; Rubinstein, M.H. Studies on the interaction between water and (hydroxypropyl)methylcellulose. J. Pharm. Sci. **1997**, *86*, 608–615.
14. Mitchell, K.; Ford, J.L.; Armstrong, D.J.; Elliot, P.N.C.; Rostron, C.; Hogan, J. E. The influence of substitution type on the performance of methylcellulose and hydroxypropylmethylcellulose in gels and matrices. Int. J. Pharm. **1993**, *100*, 143–154.
15. Joshi, H.N.; Wilson, T.D. Calorimetric studies of dissolution of hydroxypropylmethylcellulose E5 (HPMC E5) in water. J. Pharm. Sci. **1993**, *82* (10), 1033–1038.
16. Wan, L.C.S.; Heng, P.W.S.; Wong, L.F. Relationship between swelling and drug release in a hydrophilic matrix. Drug Dev. Ind. Pharm. **1993**, *19* (10), 1201–1210.
17. Salsa, T.; Veiga, F.; Teixeira-Dias, J.J.C.; Pina, M.E. Hydroxypropylmethylcellulose as a polymer for oral controlled-release dosage forms. IV Congreso Nacional de la Asociacion Española de Docentes de Farmacia Galénica **1999**, 113–114.
18. Veiga, F.; Salsa, T.; Pina, M.E. Influence of technological variables on the release of theophylline from hydrophilic matrix tablets. Drug Dev. Ind. Pharm. **1997**, *23* (6), 547–551.
19. Weast, R.C.; Astle, M.J. *Handbook of Chemistry and Physics*; CRC Press Inc.: Florida, 1980.
20. *US Pharmacopeia 23*, US Pharmacopeial Convention: Rockville, MD, 1995.
21. *European Pharmacopeia*, 3rd Ed. Council of Europe, 1997; pp. 128.
22. Bosanquet, A.G.; Betteridge, R.F. Comparison of dissolution rates of ibuprofen tablets. Int. J. Pharm. Practice **1993**, *2*, 114–116.
23. Korsmeyer, R.W.; Gurny, R.; Doelker, E.; Buri, P.; Peppas, N.A. Mechanisms of solute release from porous hydrophilic polymers. Int. J. Pharm. **1983**, *72*, 25–35.