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The effects of casein on diclofenac release from hydroxypropylmethylcellulose (HPMC) compacts

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Abstract

The inclusion of casein, either as the acid or sodium salt form, was found to significantly modify the release of the acidic drug diclofenac from hydroxypropylmethycellulose (HPMC, Methocel grades K100LV and K15M)-based matrices. The presence of casein in diclofenac-K100LV matrices increased the drug release rate and rendered the release profile more linear. Furthermore, sodium caseinate appeared to retard the disintegrating tendency of the higher molecular weight HPMC-drug systems, apparently by enhancing the initial gel forming ability of these systems. Surprisingly, dissolution profiles of the salt and acid forms of the drug were similar when co-compressed with sodium caseinate, and addition of HPMC retarded release of both forms of drug to the same extent. Swelling and erosion experiments indicated that the presence of casein decreased the extent of medium uptake (swelling) of the matrices and accelerated the rate of erosion, while not altering the dissolution medium infiltration rate. Phase solubility analysis indicated that the solubility of the drug was also enhanced by sodium caseinate, consistent with complex formation between the drug and casein.

Keywords: Diclofenac; Sodium caseinate; HPMC Methocel; Dissolution; Erosion

1. Introduction

Caseins are a group of phosphoproteins comprised of four major caseins of average molecular weight (23,000 Da). They are widely used in food products for their nutritional and functional properties. They may also be used as excipients in pharmaceutical products (Rosen and Macheras, 1984; Millar and Corrigan, 1991, 1993; Corrigan and Heelan, 2001). Acid casein has a low aqueous solubility, while sodium caseinate is freely soluble except near its isoelectric point (pH 3.5–5). Previously, we reported that casein can modify drug dissolution from compacts, the magnitude of the effect being dependent on the drug loading, the form of casein, i.e. salt or free acid (Millar and Corrigan, 1993), and the processing method, e.g. freeze dried or physical mixture (Millar and Corrigan, 1991). The extent of the maximum enhancement in dissolution rate was dependent on the specific drug and values from 49- to 1.5-fold were observed for chlorothiazide and hydrochlorothiazide, respectively. These enhancements were related to both complexation of drug with casein, resulting in enhanced drug solubility and also solid state phase changes induced by processing. In contrast, compressed physical mixtures of ibuprofen with acid casein resulted in a significant retardation in drug dissolution compared to corresponding mixtures with sodium caseinate. These effects were attributed to microenviornmental pH changes and rheological changes at the drug–dissolution medium interface

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lowering the effective solubility and diffusivity of the acidic drug (Millar and Corrigan, 1993).

In this report, we have extended these studies of milk protein–drug composites to investigate the effect of both drug form, i.e. acid or sodium salt, together with the inclusion of hydroxypropylmethycellulose (HPMC) on drug release. The drug employed was diclofenac, both free acid and salt forms.

2. Materials and methods

2.1. Materials

Diclofenac acid was prepared by acidic precipitation from a solution of diclofenac sodium (Antigen Pharmaceuticals Ltd., Ireland), and after filtration the precipitate was washed with water and dried in an oven at 37 °C. Casein and sodium caseinate were supplied by the Irish Dairy Board. The HPMC samples employed were Methocel grades K100LV and K15M (Dow Chemical Company).

Diclofenac and excipient powders as supplied, in the required ratio by weight, were mixed using a glass mortar and pestle for 5 min and 200 mg samples compressed at 7000 kg in a 13 mm punch and die set.

2.2. Dissolution procedure

A 1000 ml volume of the dissolution medium, Sorensen phosphate buffer, pH 7.4, was added to the dissolution vessel, in the temperature-controlled water bath at 37 °C and stirred at 100 rpm using the paddle method (USP Apparatus 2, VanKel Industries Inc., New Jersey).

The diclofenac disc to be examined was weighed prior to immersion in the dissolution medium. Samples (2 ml) were removed after 10, 20, 30 and 60 min, respectively, then every hour for the next 4 h and finally every 2 h if the discs had not yet fully dissolved. Samples were filtered through a 0.45 μm filter and the first millilitre discarded. The remaining solution sample was retained for assay by HPLC according to the method of El-Sayed et al. (1988). All samples were replaced with 2 ml of fresh dissolution medium.

For weight gain and erosion studies, discs containing Methocel alone or Methocel plus excipient of weight 200 mg were compressed on the hydraulic press as described above. Discs were removed from the dissolution medium at predetermined intervals and weighed (Tahara et al., 1995). The discs were then dried in an oven at 37 °C until a constant dry weight was obtained. Studies were performed in triplicate.

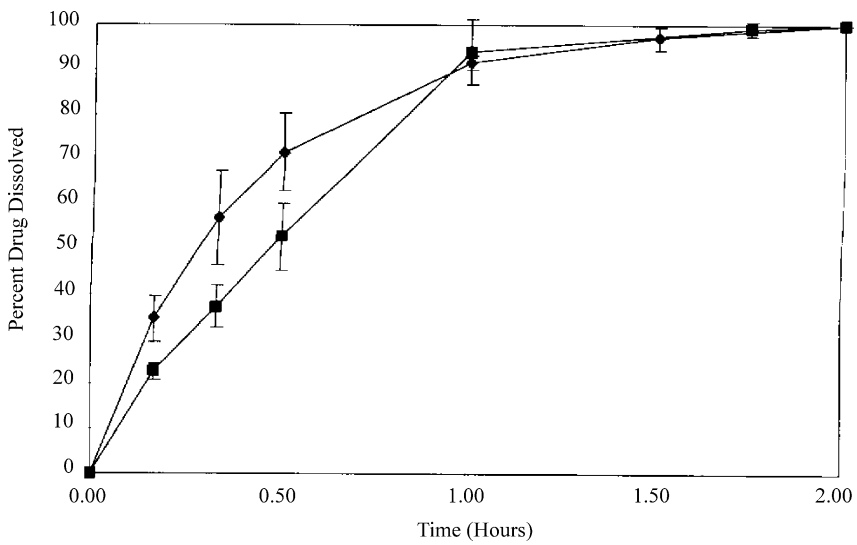

Fig. 1. The dissolution profile of discs (±S.D.) containing diclofenac sodium 100% (◆) and diclofenac sodium and sodium caseinate (50:50) (■).

2.3. Aqueous solubility

The saturated aqueous solubility of drug was measured using a modification of the method of Hamlin and Higuchi (1966). Excess drug, approximately three times that anticipated to be necessary to saturate the solvent, was added to 10 ml of the medium under investigation in a 10 ml glass ampoule. The ampoules were sealed and shaken in a water bath at 60 rpm and 37 °C. Ampoules were sampled at 24-h intervals for 72 h. A 5 ml sample of the saturated solution was removed and filtered through a 0.45 μm filter. An appropriate quantity of the filtrate was diluted immediately with the medium, preheated to 37 °C in order to avoid precipitation. The pH of the remaining filtrate was then measured. The diluted samples were assayed by ultraviolet spectroscopy at 276 nm. Solubilities were determined in triplicate.

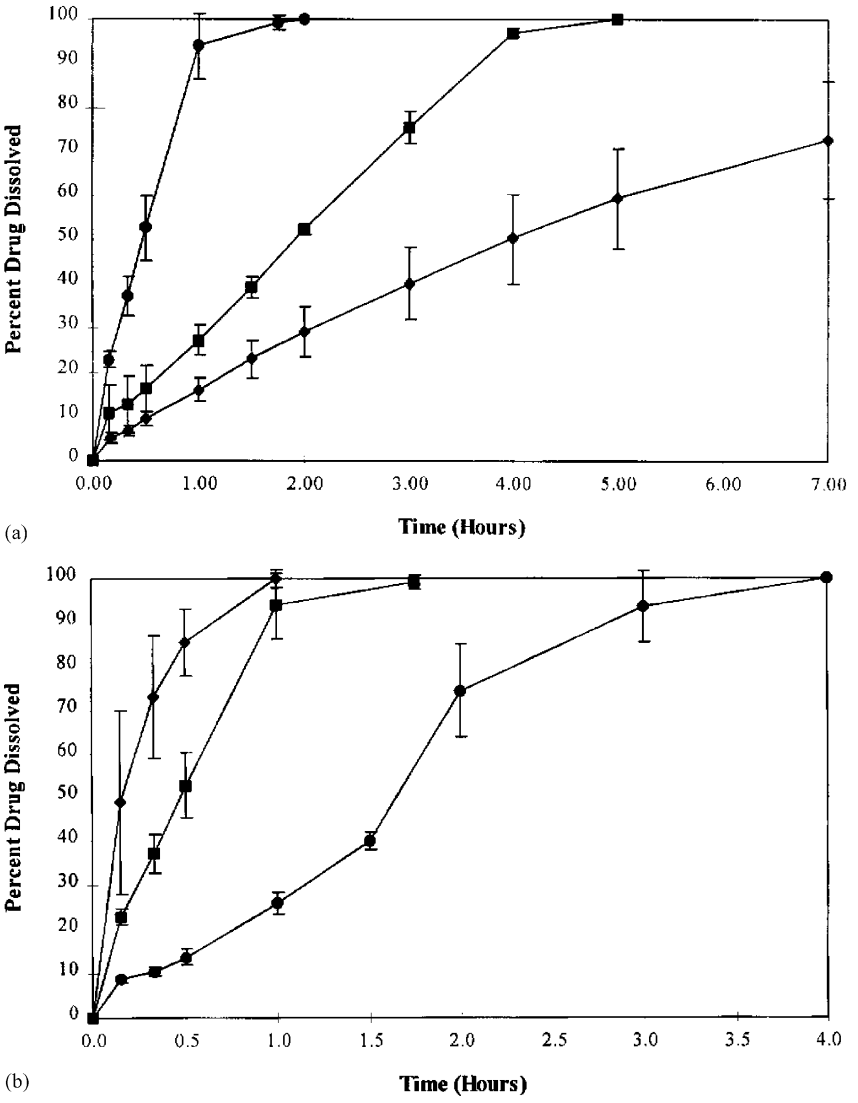

Fig. 2. The dissolution profile of discs (±S.D.) containing diclofenac sodium and (a) Methocel K100LV 50% (◆), sodium caseinate 50% (●) and sodium caseinate 25% with Methocel K100LV 25% (■) or (b) Methocel K15M 50% (◆), sodium caseinate 50% (■) and sodium caseinate 25% with Methocel K15M 25% (●).

3. Results and discussion

3.1. Drug release

Discs of 200 mg diclofenac sodium completely dissolved in phosphate buffer in 2 h, the profile fitting the exponential equation of Wagner (1969) better (coefficient of determination (CD); 0.999) than the cube root equations of Hixon and Crowell (1931) (CD; 0.991) or Ballard and Nelson (1962) (CD; 0.982). Compacts containing diclofenac sodium and sodium caseinate (50:50) dissolved at a slightly slower rate initially, resulting in a profile which was approximately linear for up to 90% drug dissolved (Fig. 1). Compression of diclofenac sodium with Methocel K100LV greatly retarded drug release such that ~50% drug was

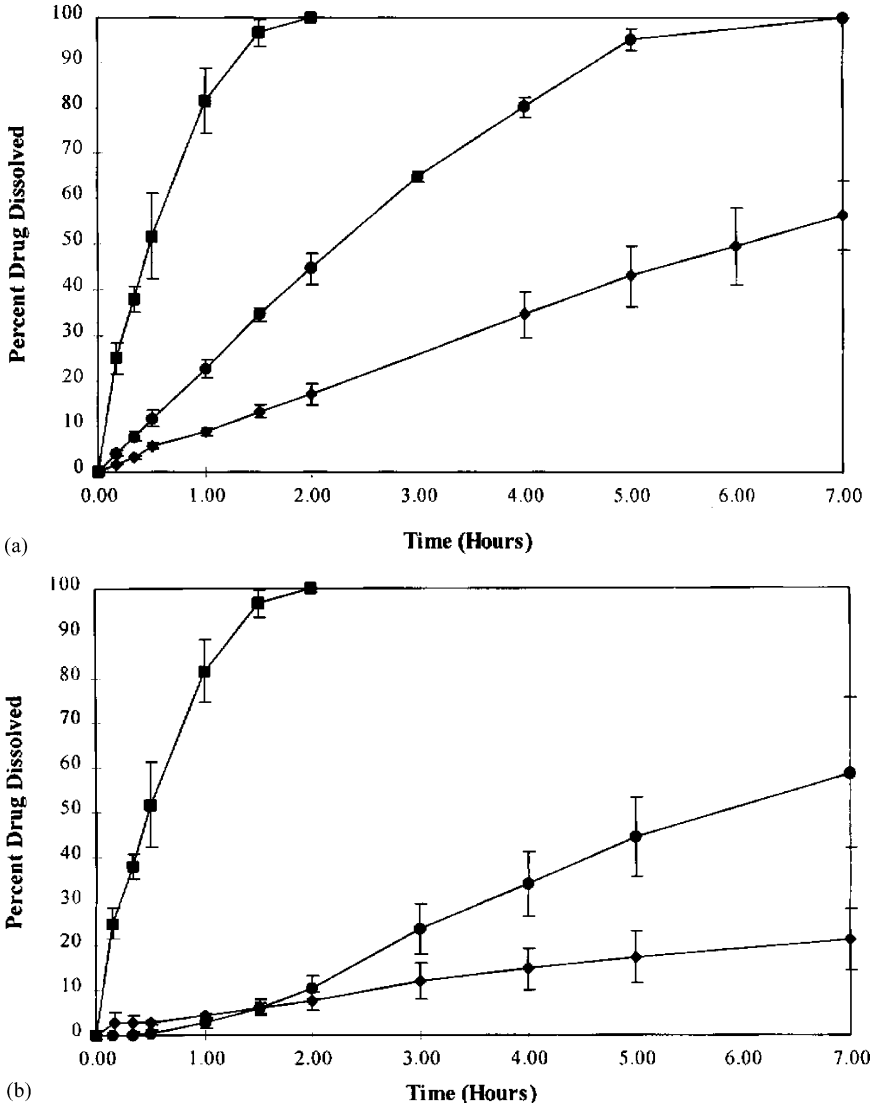

Fig. 3. The dissolution profile of discs (±S.D.) containing diclofenac acid and (a) Methocel K100LV 50% (◆), sodium caseinate 50% (■), sodium caseinate 25% with Methocel K100LV 25% (●) or (b) Methocel K15M 50% (◆), sodium caseinate 50% (■) and sodium caseinate 25% with Methocel K15M 25%(●).

dissolved in 5 h. In contrast, inclusion of sodium caseinate with the Methocel K100LV gave more rapid and more linear release than Methocel K100LV alone (Fig. 2a). Also included in Fig. 2a is the diclofenac release profile obtained in the presence of sodium caseinate alone. In contrast, when these experiments were repeated using the higher molecular weight polymer, Methocel K15M in place of Methocel K100LV, the HPMC-drug compact disintegrated giving rapid drug release. The inclusion of casein with the HPMC however retarded disintegration and prolonged the release of the drug (Fig. 2b).

Similar experiments were then carried out using the acid form of diclofenac rather than the sodium salt. The results obtained with Methocel K100LV are shown in Fig. 3a and are qualitatively similar to those obtained with the sodium salt. Use of the acid form of diclofenac resulted in slightly lower drug release rates. Diclofenac sodium was found to have a solubility of 10 mg/ml while the intrinsic solubility of diclofenac is ~1000-fold less (Ledwidge and Corrigan, 1998). Thus, surprisingly changing the drug form from the soluble salt to the much less soluble acid form did not dramatically alter drug release. When Methocel K100LV was replaced by the higher molecular weight grade K15M, release rates in all cases were slower than those observed with K100LV grade (Fig. 3b). Thus, the inclusion of sodium caseinate in HPMC matrix formulations enhances the release of the drug and reduces the tendency for matrix disintegration.

In the light of the similarity in dissolution of the acid and salt forms of the drug in the presence of sodium caseinate, the effect of casein on the dissolution of the acid and sodium salt forms of diclofenac in the absence of HPMC was also examined. Both sodium caseinate and acid casein were used. Drug release from systems containing acid casein dissolved about three to four times slower than those containing sodium caseinate, consistent with the different intrinsic dissolution rates of the two forms of casein (Millar and Corrigan, 1993). Irrespective of which form of drug was used, similar, quite linear dissolution profiles were obtained (Fig. 4). Thus, substitution of acid casein for sodium caseinate reduced the drug dissolution rate and release was independent of the form of drug used. It therefore seems likely that casein is exerting a local buffering effect (Millar and Corrigan, 1993) which dictates the rate of release of the drug and that this effect is also operative when the casein is included in HPMC matrices. Millar and Corrigan (1993) reported that the pH of concentrated sodium caseinate systems was 7.13 and that of acid casein 5.54.

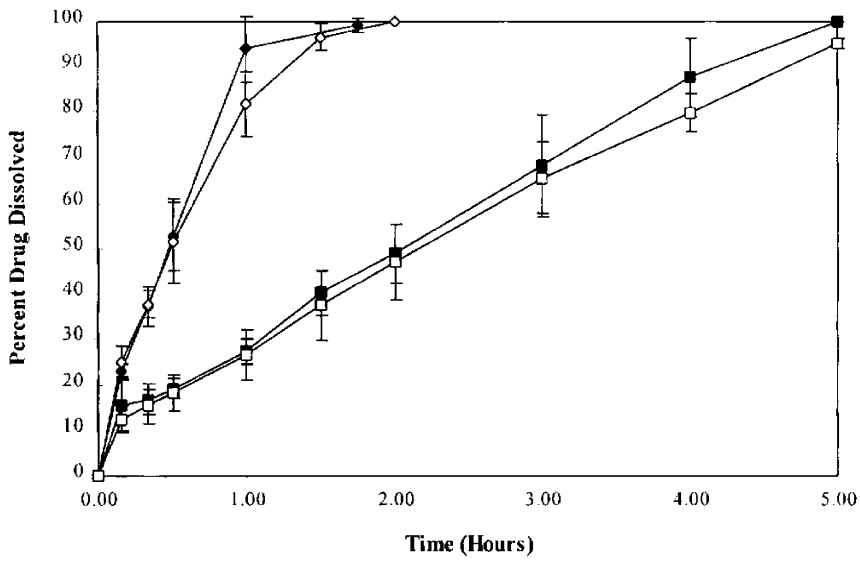

Fig. 4. The dissolution profile of discs (±S.D.) containing diclofenac sodium (closed symbols) and diclofenac acid (open symbols) with sodium caseinate 50% (◆) or acid casein 50% (■).

3.2. Weight gain and erosion

To better understand the effect of casein on HPMC matrices, the swelling and erosion of compacts of HPMC in the absence and presence of sodium caseinate was investigated. The effect of sodium caseinate on the swelling and erosion of Methocel K100LV:sodium caseinate (50:50), as reflected in the change in wet and dry weights, is shown in Fig. 5a. The wet weight profile for K100LV indicates that this polymer swells and erodes, the maximum weight gain of approximately sixfold occurred after 5–6 h and beyond this time erosion dominates. The presence of sodium caseinate is seen to reduce the overall extent of weight gain and to increase the rate of erosion of HPMC compacts. The enhanced erosion is consistent

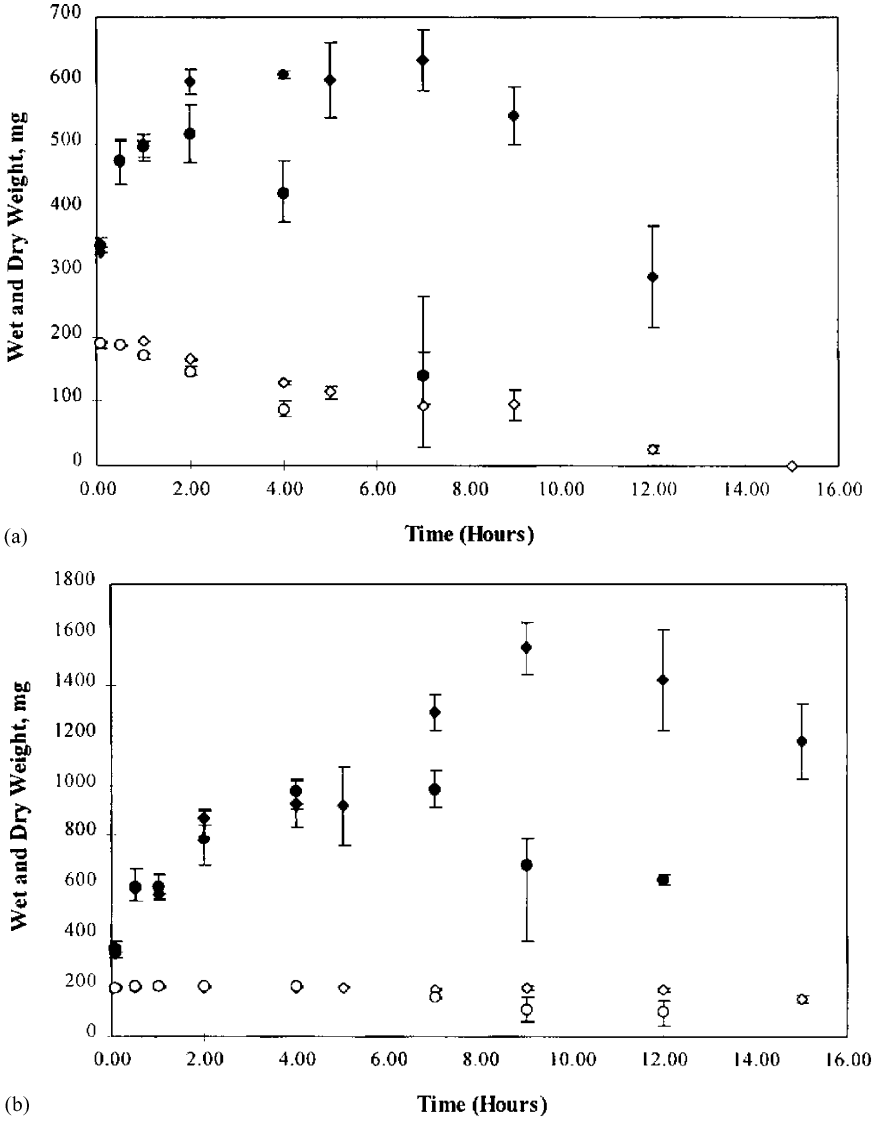

Fig. 5. Comparison of the weight gain (closed symbols) and erosion (open symbols) vs. time profiles of (a) Methocel K100LV discs (◆), Methocel K100LV:sodium caseinate (50:50) mixed discs (●) and (b) Methocel K15M discs (◆), Methocel K15M:sodium caseinate (50:50) mixed discs (●).

with the more rapid and more linear drug release observed. Similar effects are evident on inclusion of sodium caseinate with the more viscous HPMC Methocel K15M. The extent of swelling evident with this polymer is greater than that of Methocel K100LV and the rate of erosion is slower (Fig. 5b). In the absence of sodium caseinate little erosion was observed in the first 10 h.

Tahara et al. (1995) observed that the initial rate of medium infiltration into HPMC matrices is proportional to square root of time. Such plots for K100LV and K15M matrices, in the absence and presence of

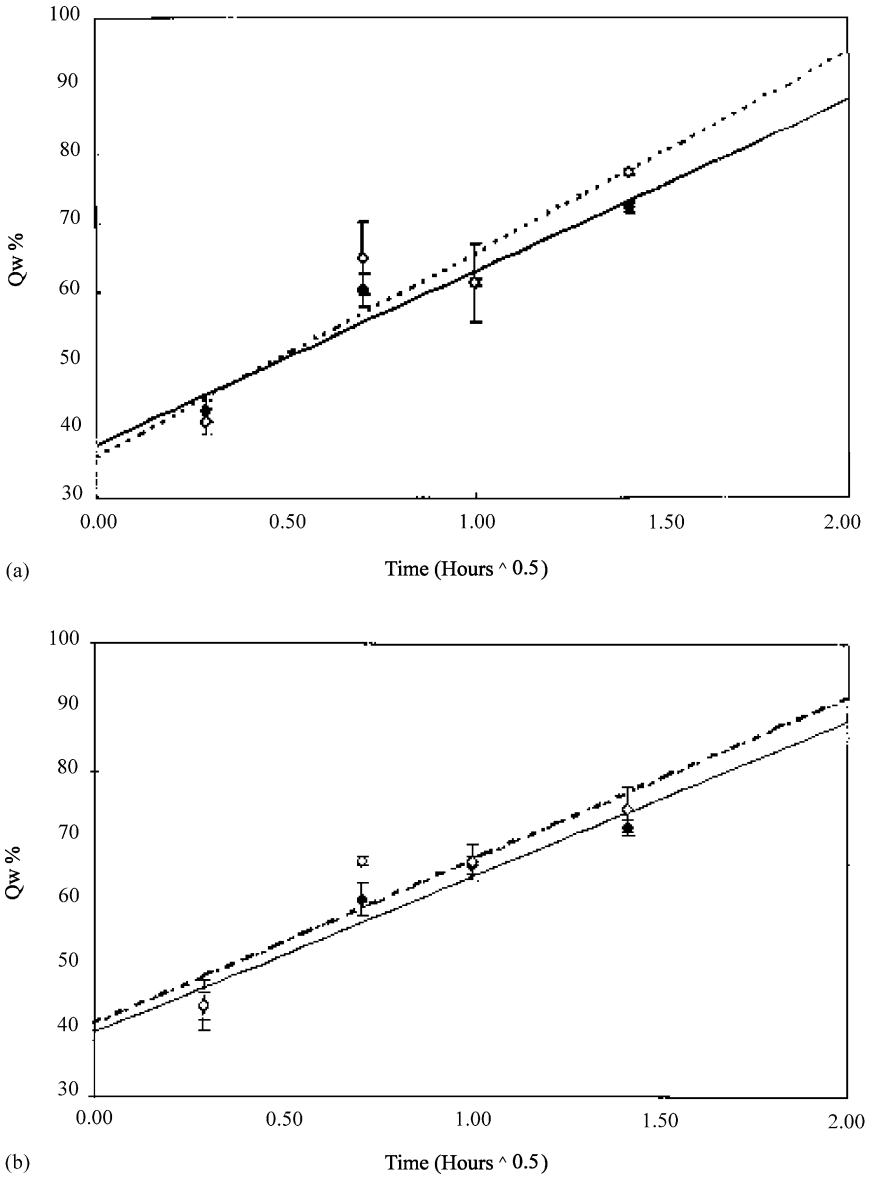

Fig. 6. Medium uptake (±S.D.) as a function of the square root of time of discs in the absence (0%) (a) and presence (b) of sodium caseinate 50% and either Methocel K100LV (closed symbols) or Methocel K15M (open symbols) where unbroken and broken lines represent the lines of best fit, respectively.

caseinate are shown in Fig. 6a and b, respectively, where medium uptake (Q_w%) is given by:

$$Q_w = 100\frac{(W_w - W_d)}{W_w}$$

where W_w and W_d are the wet and dry weights of the tablet, respectively. Similar infiltration rates were observed between the two polymers both in the presence and absence of sodium caseinate.

3.3. Solubility

As caseinates can form micelles and also complexes with drugs, the effect of sodium caseinate on the solubility of diclofenac sodium was examined. Sodium caseinate increased the solubility of the drug (C_s, mg/ml) in a relatively linear manner in the concentration range 1–50 mg/ml sodium caseinate (C_a, mg/ml) ($C_s = 12.7 \pm 0.23C_a$ with $R^2 = 0.976$), such that at a sodium caseinate concentration of 50 mg/ml a twofold increase in solubility is observed. This increase could not be explained in terms of a pH change. A similar increase in the solubility of ibuprofen was reported previously (Millar and Corrigan, 1993).

4. Conclusions

The presence of casein in diclofenac-Methocel K100LV matrices increased the drug release rate and rendered the release profile more linear. A number of mechanisms seem to be involved. Swelling and erosion experiments indicated that the presence of casein reduced the extent of swelling of HPMC matrices and accelerated the rate of erosion, while not altering the dissolution medium infiltration rate. Surprisingly, despite their large difference in solubility, dissolution profiles of the salt and acid forms of the drug were similar when co-compressed with sodium caseinate, and addition of HPMC retarded release of both forms of drug to the same extent. This similarity in dissolution rate of the acid and salt forms of drug may be explained by the reported ability of the caseins to exert a local buffering effect, the sodium caseinate giving a higher local pH, which dictates the rate of release of the drug (Millar and Corrigan, 1993). An additional factor is the more viscous and more rigid nature of acid casein gels formed at the liquid–solid interface. Furthermore, phase solubility analysis indicated soluble complex formation between the drug and casein. Sodium caseinate also appeared to retard the disintegrating tendency of some high molecular weight HPMC-drug systems, apparently by enhancing the initial gel forming ability of these systems.

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