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## Translocation of drug particles in HPMC matrix gel layer: effect of drug solubility and influence on release rate

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### Abstract

The aim of this work was to study the release mechanisms of drugs having different solubility (bufomedil pyridoxalphosphate 65%, sodium diclofenac 3.1%, nitrofurantoin 0.02% w/v,) from hydroxypropyl methylcellulose (HPMC) matrices by concomitantly studying swelling, diffusion and erosion fronts movement and drug delivery. The main goal was to clarify the role played by polymer swelling in drug transport. The results showed that the rate and amount of drug released from swellable matrices was dependent not only from drug dissolution and diffusion but also from solid drug translocation in the gel due to polymer swelling. In fact, as drug solubility decreased, the slower drug dissolution rate in the gel layer allowed drug particles to be transported close to the matrix erosion front. The presence of solid particles in the gel reduced the swelling and the entanglement of polymer chains and affected the resistance of gel towards erosion. As a consequence, the matrix became more erodible. The erosive delivery accelerated after the matrix had been completely transformed into the rubbery state, particularly when a considerable amount of solid drug particles remained in the gel phase. © 2001 Elsevier Science B.V. All rights reserved.

**Keywords:** Swelling; Translocation; Release mechanism; Drug solubility; Hydroxypropyl methylcellulose; Hydrophilic matrix

### 1. Introduction

Polymer swelling, drug dissolution and matrix erosion are the phenomena that determine drug release from swellable matrices, either on a macroscopic or on a molecular level [1–8]. The kinetics of these phenomena is effectively studied by the analysis of the movement of swelling, diffusion and erosion fronts inside the matrix. In particular, the swelling and erosion front positions define the gel layer thickness, which is considered the key factor in

drug release kinetics. Gel layer thickness behavior has been studied using imaging techniques or NMR spectroscopy [9,10].

The rate of drug release from swellable matrices depends on the drug concentration in the gel layer. For example, when swelling and erosion fronts synchronize their movements, the thickness of the gel layer remains constant and zero order release is achieved [11]. The possible presence in the gel of a diffusion front, namely the boundary between the solid and dissolved drug, can affect the drug transport [12]. Furthermore, the polymer swelling may displace particles in the gel layer due to expansion of the polymer chains [13,14]. We have also observed

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[15] that polymer swelling modifies the drug gradient in the gel. All these experimental observations support that, concomitantly with diffusion, polymer relaxation and matrix erosion contributes to drug release kinetics [16].

Therefore, given that in swellable matrices diffusive, polymer relaxation and erosive mechanisms can coexist, we decided to examine the relative importance of these phenomena in high viscosity hydroxypropyl methylcellulose (HPMC) matrices in dependence on drug solubility.

The aim of the work was to study the mechanisms of drug release by following the drug delivery of HPMC discs containing three drugs with solubility of 0.02, 3.1 and 65% w/v, respectively. In addition, the movement of swelling, diffusion and erosion fronts during drug release was investigated in radial swelling experiments. The main goal of this particular experimental set-up was to visualize the role played by polymer swelling in drug transport.

## 2. Materials and methods

Buflomedil pyridoxalphosphate (BPP, Lisapharma, Erba, Italy; MW 553.6; solubility in water at 37°C, 65% w/v), nitrofurantoin (NTF, Fabbrica Italiana Sintetici, Vicenza, Italy; MW 238.2; solubility in water at 37°C, 0.02% w/v) and sodium diclofenac (DCN, Lisapharma, Erba, Italy; MW 282.7; solubility in phosphate buffer solution pH 7.4 at 37°C, 3.1% w/v) were used as received. Particle size fraction between 125 and 180  $\mu\text{m}$  was employed.

Tablets containing 100 mg of drug were prepared by granulating 60 parts of the drug mixed with 32 parts of HPMC (Methocel K100M CR Premium, Colorcon, Orpington, UK). Five parts of poly(vinyl pyrrolidone) (Acef, Fiorenzuola d'Arda, Italy) dissolved in ethanol (10% solution w/v) were used as a binder. The granules were dried and then lubricated with 1 part of magnesium stearate (USP 24) and 2 parts of talc (USP 24). The mixtures were compressed to a thickness of  $3.3 \pm 0.1$  mm, using a reciprocating tableting machine (EKO Korsch, Berlin, Germany) equipped with flat face punches of 7 mm in diameter. The total weight of the matrices was 165 mg.

Drug release experiments were carried out using a

USP 24 Apparatus 2 (Esadissolver, Advanced Products, Milan, Italy) with paddle rotation of 100 rpm, in 1 liter of distilled water at 37°C for BPP and NTF and phosphate buffer solution at pH 7.4 (USP 24) for DCN. A mesh (3×3 cm, grid 0.1 cm) was placed on the bottom of the vessel in order to avoid matrix sticking. The amount of drug released was determined spectrophotometrically at 282 nm for BPP, 365 nm for NTF and 275 nm for DCN, respectively (Spectracompt 602, Advanced Products, Milan, Italy).

The swelling behavior of these matrices was studied using the special device previously reported [17]. The matrix bases were clamped between two transparent Plexiglas® discs (diameter 30 mm; thickness 5 mm) which permitted water uptake and drug release to take place only from the lateral side of the matrix. The assembled device was introduced into the vessel of the dissolution apparatus containing 1 liter of medium at 37°C. In order to reduce the boundary layer effects, a paddle agitation speed of 200 rpm, forcing a continuous device rotation at the bottom of the vessel, was selected. The swelling of the matrix base was video recorded through the transparent Plexiglass® and the photographs were analyzed using Image 1.49 software (NIH, Bethesda, USA) [18].

## 3. Results and discussion

The release profiles of three drugs from HPMC matrices are shown in Fig. 1. In the early time (<60% of drug released), BPP was released faster (60 mg in 3.1 h) than DCN (60 mg in 5 h) because of its higher solubility. Despite the slower initial release rate, DCN matrix completely released the drug in about 15 h. The first 20% of NTF were released at a significantly lower rate than BPP and DCN. However, after 6 h a sudden acceleration of the release rate of the remaining NTF assured the dose release in 24 h.

We calculated the delivery rates (Fig. 2) and observed that the matrices containing the less soluble DCN and NTF exhibited significant sudden increases in release rate after 4 and 6 h, respectively. In the case of NTF, this increase created a dual delivery profile in the cumulative release curve (see Fig. 1).

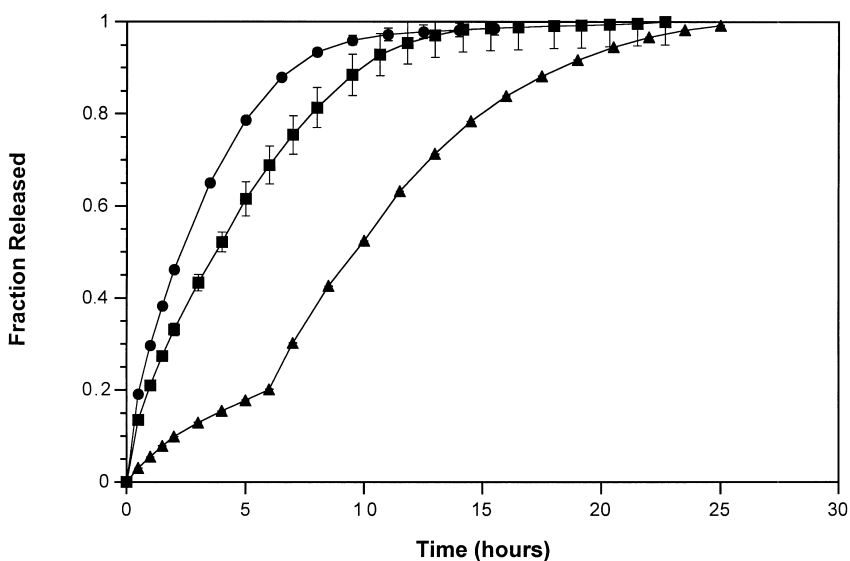


Fig. 1. Fraction of BPP (circle) DCN (square) and NTF (triangle) released as a function of time from HPMC matrices. The bars represent the standard error of the mean ( $n=3$ ).

The presence of the inflection point during erodible matrix delivery was explained as a combination of diffusion and erosion mechanism [19]. In short, the early time delivery rate of the three drugs proved to

be directly related to drug solubility, whereas in the late time delivery rate a sudden acceleration, very relevant for the less soluble NTF, was observed.

An acceleration in the release rate of a slightly

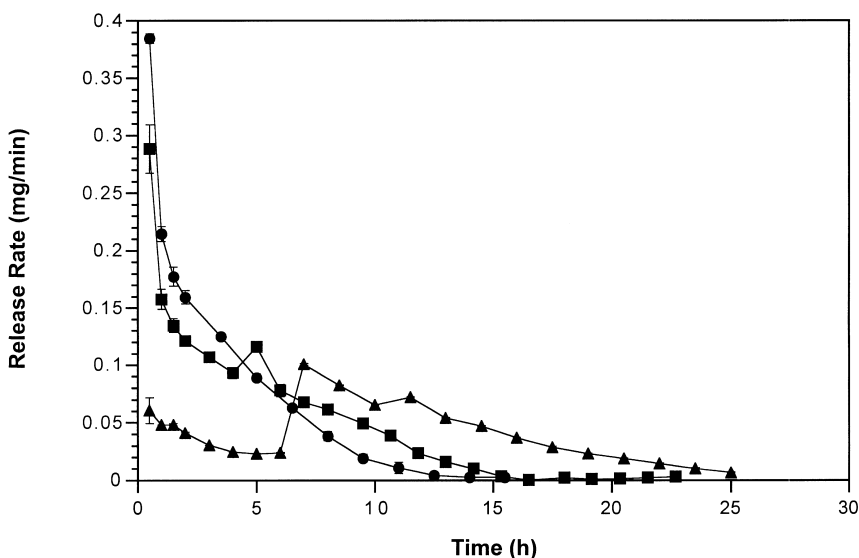


Fig. 2. Drug release rate from HPMC matrices containing BPP (circle) DCN (square) and NTF (triangle) as a function of time. The bars represent the standard error of the mean ( $n=3$ ).

soluble drug was recently observed in HPMC:PEO hydrochlorothiazide matrices once the liquid had saturated the core [20]. In DCN and NTF matrices we verified the complete hydration of glassy core after 4 and 6 h of dissolution, respectively, despite the presence in the gel of a significant amount of undissolved drug. Thus, the ‘dual’ delivery rate of DCN and NTF matrices was linked to the disappearance of the glassy core.

This phenomenon was also present, but kinetically less evident, in BPP matrices, since more than 70% of the drug had already been released by the time this matrix had been completely hydrated (approx. 3 h). Gehrke and Lee [21] described an increase in water absorption of glassy matrices, corresponding to the disappearance of the glassy core. This phenomenon was attributed to the presence of a glassy/rubbery front that rendered the matrix swelling anisotropic, since the glassy core could resist the swelling stresses. As the glassy core disappeared and the constraint was removed, a sudden increase in matrix area occurred, together with a decrease of diffusion path. This behavior in matrix swelling determined in our case the change in the rate of drug release, which became more and more important as the drug solubility decreased.

Erodible matrices typically show a similar dual release behavior [22]. Despite the fact of having studied swellable matrices made with a high viscosity type of polymer (Methocel<sup>®</sup> K100M), a certain degree of erosion was expected. Matrix erosion became evident in correspondence of the glassy core disappearance when all the matrices were dragged in the dissolution medium. In the case of BPP, erosion resulted irrelevant since the swollen BPP matrix disappeared long after the completion of drug delivery. In fact, the presence of drug exhausted gel could still be observed after 24 h. On the contrary, the DCN matrix underwent slow erosion leading to the complete dissolution in 24 h. Also the NTF matrix completely disappeared in 24 h.

From these experiments we concluded that drug release from the three matrices occurred with different mechanisms depending on their hydration level. In the matrix containing the soluble BPP, drug delivery was mainly diffusive, whereas in the matrix containing DCN the release was diffusive at early times and erosive at late times. In the matrix containing NTF, the drug was mainly released by

erosion, considered that at the disappearance of the glassy core only 20% of drug was released.

Matrix erosion became pronounced as the drug solubility decreased. We believe that the presence of undissolved particles of drug contributed to the tendency of the matrix to erode by affecting the gel strength. However, it is the disappearance of the glassy core that, while modifying the gelled matrix structure, made the late time delivery erosive.

To investigate further the relationship between drug dissolution, matrix swelling and release kinetics, swelling/release experiments were carried out by firmly clamping the matrices between two transparent discs for direct observation of the undergoing swelling. The positions where polymer transition and drug dissolution took place [12] were measured as a function of time, together with the amount of drug released.

The release profiles of the three swellable matrices clamped between the discs are shown in Fig. 3. In each case the release rate was significantly lower than that of the freely swellable matrices due to the reduction in the release surface available [17]. Moreover, the fact that the matrices were constrained by the Plexiglas<sup>®</sup> discs significantly affected the previously observed release acceleration in correspondence of the disappearance of the glassy core. This behavior was explained with the creation of internal anisotropic stresses due to the contact of the matrix with the Plexiglas<sup>®</sup> discs, which determined an one-dimensional swelling. Practically the Plexiglas<sup>®</sup> discs worked as a permanent “glassy core”. Photographs of the three matrices are shown in Fig. 4. At 24 h, the solid drug has disappeared from the BPP matrix, while a considerable part of the gel layer of the DCN and NTF matrices was still occupied by the undissolved drug. The NTF particles disrupted the continuity of the gel creating cracks indicative of a weak gel layer.

The movement of the fronts as a function of time is reported in Fig. 5. In all matrices the swelling front reached the center in about 10 h, with no evident dependence on drug solubility. The erosion front moved outwards until a plateau was reached. The rate and extent of this movement is reduced with the decrease of drug solubility. The presence of the two discs holding the matrix slowed the tendency of the matrix towards erosion [23].

The most interesting finding proved to be the

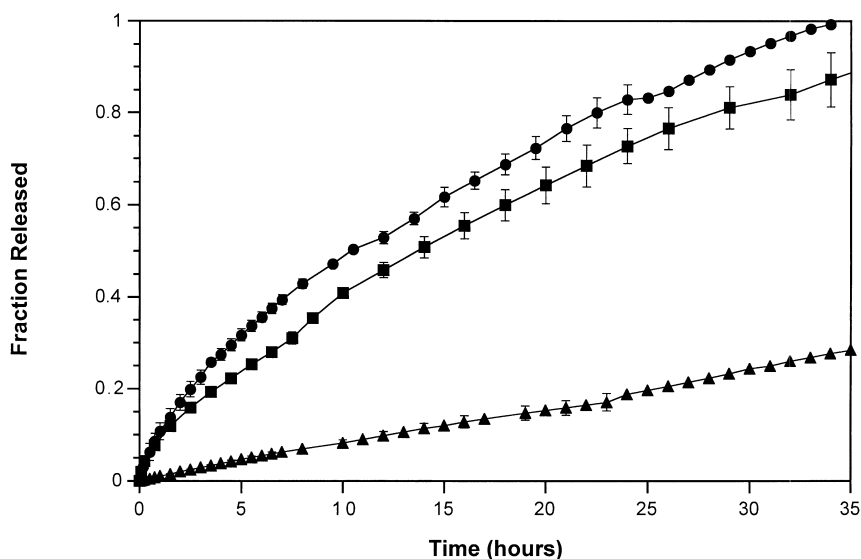


Fig. 3. Fraction of BPP (circle) DCN (square) and NTF (triangle) released as a function of time from HPMC matrices clamped between two Plexiglas® disks. The bars represent the standard error of the mean ( $n=3$ ).

movement of the diffusion front. This front, related to the dissolution rate of the drug in the gel layer, moved inwards in BPP matrix, reaching the matrix center in about 20 h. At this point, BPP in the matrix resulted completely dissolved. On the contrary, the diffusion front in the DCN and NTF matrices started moving outwards, beyond the original position. Such a diffusion front dynamics indicated the transport of solid drug particles in the gel layer, as a consequence of polymer swelling. In the NTF matrix the diffusion front moved very close to the erosion front and as a consequence, the dissolved drug gel layer thickness, which represents the drug diffusive pathway, was extremely thin. Thus, a high probability existed for drug solid particles to escape from the gel layer.

To summarize, the drug dissolution rate in the gel drastically changed the diffusion front movement. As the drug dissolution rate slowed down, there was an increased probability for the drug particles to be transported within the gel, reducing the thickness of the diffusive pathway. Since the presence of solid particles also affects the entanglement of polymer chains, thus increasing the fragility of the gel, erosion was favored.

An observation that becomes clear from the previous analysis of fractional release curves and diffusion front movement is that under certain conditions of drug solubility the ‘dual release’ process in

high viscosity HPMC matrices becomes evident after complete hydration of the glassy core. We have already discussed that this ‘dual release’ process is characterized by the low solubility of the drug. It may be associated with an unusual increase in the release rate due to ‘expulsion’ of non-soluble drug particles from the gel layer of the matrix. Indeed, expansion of the hydrophilic matrix leads to an immediate hydration of the adjacent drug particles, a hydration that is affected by drug solubility. Thus, in the case of a water-soluble drug such as BPP, the polymer chains expand by relaxation and ‘push’ molecules of the dissolved BPP. Even after the disappearance of the glassy core of the tablet, this process continues to be diffusion-controlled, as BPP molecules are already dissolved in the system. Fig. 1 shows that the BPP release curve is continuous and the associated drug release rate curve decreases monotonically with time.

However, in the case of a low solubility drug, drug particles remain in the vicinity of the swelling front. Then, they are ‘pushed’ towards the gel layer by a spring-like action of the macromolecular chains as these pass from the glassy to the rubbery (gel-like) state. Clearly, in the case of low solubility drugs, a particle displacement may be expected as a result of the significant relaxation of the macromolecular chains due to swelling. The overall phenomenon may

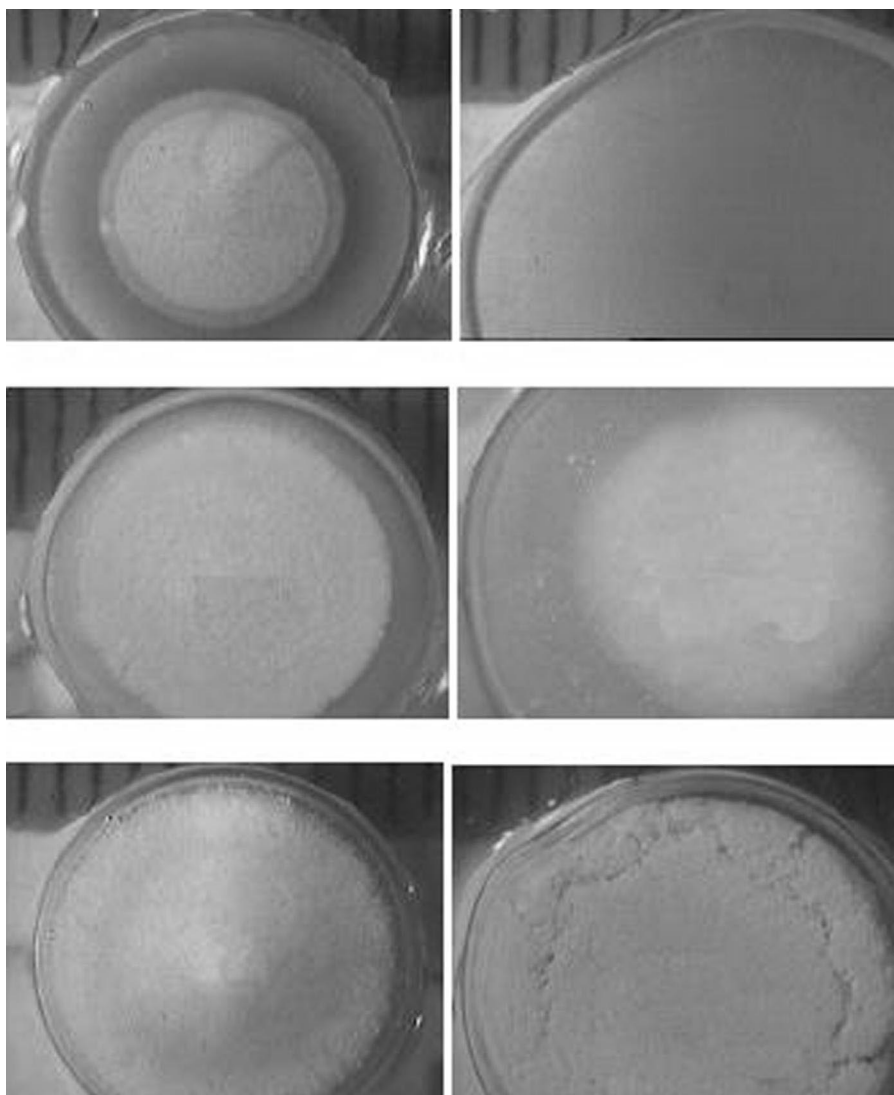


Fig. 4. Pictures of the base of HPMC matrices containing BPP (top) DCN (middle) and NTF (bottom) taken after 1 h (left column) and 24 h (right column).

be termed a ‘drug particle translocation’ process. In fact, Adler et al. [14] have already shown a clear translocation process of insoluble beads incorporated in swellable polymers. Drug particle translocation is more prominent the less soluble a drug is. Thus ‘pushing’ of the particles through the gel layer (which is very thin in the case of insoluble NTF, as shown in Fig. 5) leads to an exposure of the particles to water. Such an exposure assumes particular relevance when the gel layer becomes thinner and fragile

after the disappearance of glassy core. This is clearly shown in Figs. 1 and 2, which indicate an abrupt change in the rate of DCN and NTF release at 4 and 6 h, respectively, i.e. when the glassy core disappears.

#### 4. Conclusions

The two different swelling/release experiments

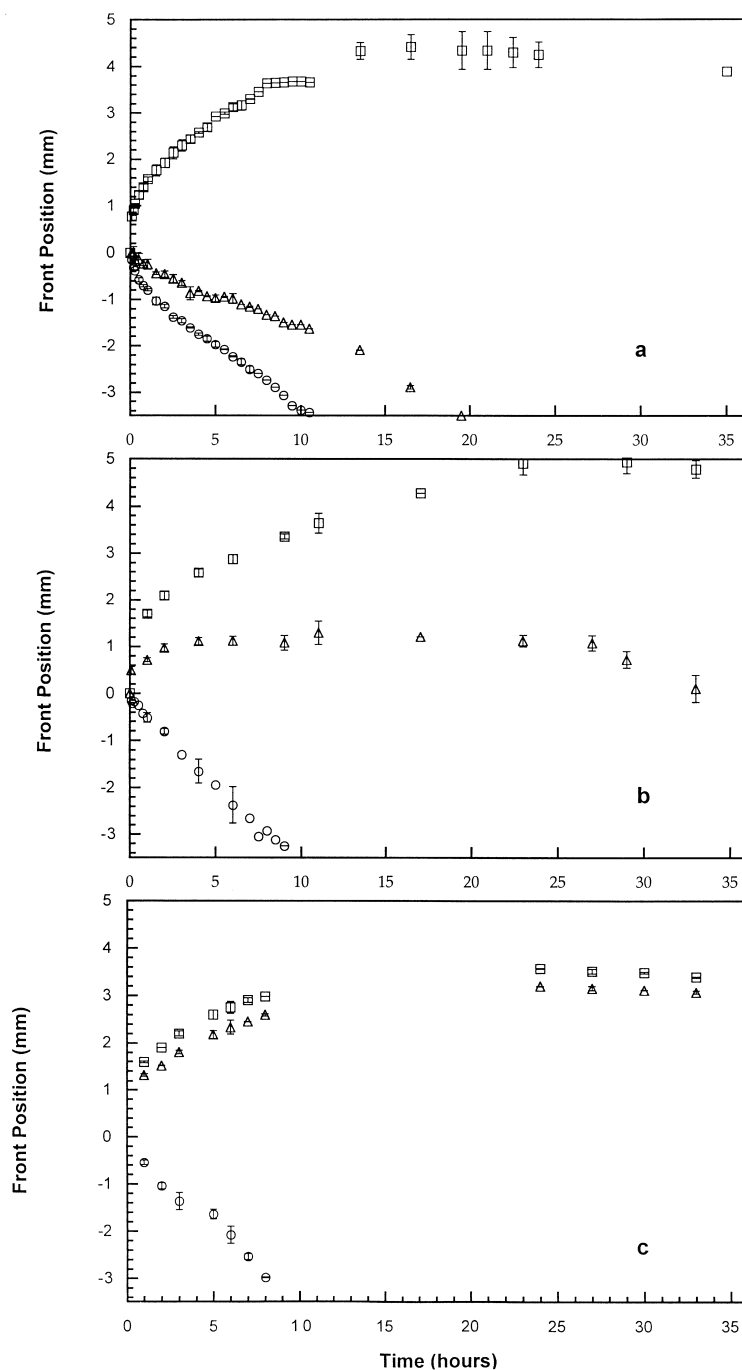


Fig. 5. Position of the swelling (circle), diffusion (triangle) and erosion front (square) as a function of time in HPMC matrices containing BPP (panel a), DCN (panel b) and NTF (panel c). The bars represent the standard error of the mean ( $n=3$ ).

have enabled us to conclude that the rate and amount of drug released from swellable matrices are dependent not only on drug dissolution and diffusion but it has also been demonstrated a solid drug transport in the gel.

As drug solubility decreases, the tendency of the matrix to erode increases, particularly after complete hydration of the matrix. We have shown that in swellable matrixes loaded with sparingly or slightly soluble drugs, solid drug particles can be transported within the gel layer by polymer swelling. Drug solubility in the gel layer, or better still the drug dissolution rate, is responsible for the transport of the drug close to the erosion front of the matrix. The presence of solid particles in the gel reduces the swelling and the entanglement of the polymer chains and affects the resistance of the gel to erosion. As a consequence, the matrix becomes more erodible. The erosive delivery accelerates after the matrix is completely transformed into the rubbery state, particularly when an important amount of solid drug particles remains in the gel phase. The relative importance of the diffusive and erosive contributions to drug transport depends on the drug solubility and geometry of the swellable matrix.

In high viscosity HPMC matrices, the drug release kinetics results from the combination of drug dissolution and relaxation transport in the gel layer. The drug solubility affects not only the drug dissolution in the gel but also the matrix erosion due to particle displacement.

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