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Probing the mechanisms of swelling of hydroxypropylmethylcellulose matrices

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Summary

Hydroxypropylmethylcellulose is often used as a component of sustained release matrix formulations. It is known that the swelling of HPMC results in the formation of a gel through which the drug slowly diffuses. It has been shown that HPMC compacts swell predominantly in the axial, rather than the radial, direction on exposure to water. Other workers have considered the possibility of applying impermeable coats to different aspects of HPMC compacts in order to alter drug release mechanism. The aim of this study was, given the axial rather than radial relaxation, to investigate whether the faces of cylindrical compacts of HPMC were of different nature to the edge. This was studied by coating the edges and faces of different compacts with paraffin, in order to prevent water access. The interpretation of the results would be different depending on the method of data presentation, with plots of normalised increases in height, diameter and area all suggesting a difference in properties between uncoated, edge coated and face coated tablets. However, if the areas were corrected for the paraffin coating, the plots of normalised area were found to tend towards being superimposed consequently, within experimental error, it can be concluded that the faces and edges of the HPMC compacts behaved in an identical manner. The axial relaxation must simply relate to the relief of stresses induced during compaction.

Introduction

Hydroxypropylmethylcellulose (HPMC) has received a lot of attention as a hydrophilic matrix for sustained release formulations. It is known that the mechanism by which drug release is slowed is by the rapid formation of the essentially hydrogel layer around the matrix (the core of which may remain dry, and glassy) following exposure to aqueous fluids (Alderman et al., 1984). The release of drugs (and in particular water soluble drugs) from the product will be controlled by the drug diffusion through the gel (e.g., Ford et al., 1991), and thus by the extent and nature of the swelling process. Colombo et al. (1990) have described a method by which the release from a swellable matrix (which contained HPMC as a major component) can be controlled by the application of impermeable coatings, giving rise to constant drug release rates. Colombo et al. (1990)

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applied impermeable coatings to either one or two faces of a cylindrical compact (of slab geometry), and monitored the effect on the swelling.

It has been noted previously (Colombo et al., 1990; and in our unpublished studies) that HPMC based compacts tend to swell predominantly in the axial, rather than the radial dimension. This type of behaviour is not exhibited by certain other hydrogel systems (unpublished data). The reason for such preferential swelling in one direction must be due to an orientation of molecules during compression. The issue which remains is whether the faces and edge of HPMC tablets have different properties, regarding water access and swelling. Colombo et al. (1990) considered drug release from formulations containing HPMC, and concluded that the drug release per unit area was identical for uncoated and face coated tablets. This observation does not preclude the possibility that the edges and faces of the tablets behave in different manners, as it may be that the swelling and release are dominated by water access through the edge (rather than the faces) of the tablet.

In the current study, tablets of HPMC (alone, without any other components) are investigated. The aim is to consider axial and radial relaxation during swelling, and to probe the effect of coating a) the faces and b) the edge of the cylindrical compacts. The aim is to investigate whether the orientation of the HPMC is such that the edge and faces are of different natures, or whether there is some other reason for the differential relaxation phenomena. As the swelling behaviour of such systems will be directly related to drug release mechanism, it is important to understand such behaviour.

Materials and Methods

Matrix preparation

Compacts were made from HPMC (Methocel K100 M, Colorcon, Orpington, U.K.), by weighing 500.0 mg and directly handfilling into the die of a Erweka single punch tabletting machine. The tablets were prepared by turning through the compression cycle by hand. The machine was adjusted to give tablets which would break under a force of 10–14 kg (although early experiments revealed that swelling was independent of tablet hardness over a range of breaking forces from as low as 2 to 14 kg). The diameter of the flat faced tablets was 9.0 mm and the height was 8.0 mm, giving an aspect ratio of 1.1 (calculated from diameter divided by the height).

Coating of tablets

Swelling experiments were undertaken on uncoated tablets, and on others after coating either the edge or the two faces of the cylinder. The coating was achieved by holding the tablet with forceps, and applying two consecutive coats of molten hard paraffin, with a small brush. With experience this process was standardised to produce tablets of uniform weight after coating.

Swelling experiments

Individually weighed tablets were allowed to swell, in a beaker containing approx. 100 ml of degassed distilled water. The tablet was held in place, under the surface of the water, by impaling it on a spike which was glued to the base of the beaker.

Numerous methods have been considered for the study of swelling tablet dimensions, these include, removal of the tablet and weighing, and occasional photography of the tablet against a calibrated graticule. In this work, we introduce the novel approach of using image analysis in order to monitor tablet swelling in situ. The image analysis approach allows regular accurate assessment of tablet dimensions with a non-invasive technique. The size measurements were made by constantly monitoring the swelling process with a video camera attached to a image analysis system (Seescan, U.K.). At defined time intervals (every 10 min) the image was measured, and the height and diameter (maximum dimensions) were recorded. The tablet was held edge on to a vertically mounted camera, with illumination from under the beaker. This allowed both height and diameter to be monitored simultaneously. Results are averages of swelling profiles for four different tablets.

Loss due to dissolution

HPMC is not a true hydrogel, as it is slowly dissolved in water, the extent of this dissolution was investigated. After 16 h in the water some of the 500 mg tablets were removed and dried. The mean final weight was 0.4419 g, which equates to approx. 11% dissolution of the HPMC, over a time scale considerably longer than the duration of the experiment. This small amount of dissolution has been ignored for the purposes of the discussion in this paper.

Results and Discussion

The normalised increase in diameter and height for uncoated, edge coated and face coated HPMC tablets are presented in Figs 1 and 2, respectively. It is apparent that the relaxation of compacts consisting of HPMC KI00M alone is predominantly axial. To demonstrate this point, the 500 mg compacts (which had an aspect ratio of 1.1, i.e., approximately equal lengths and diameters) were photographed during swelling. Fig. 3 is a photograph of such a compact after 8 h in pH 7.4 buffer, from which it is apparent that the aspect ratio has changed from 1.1 to approx. 0.6.

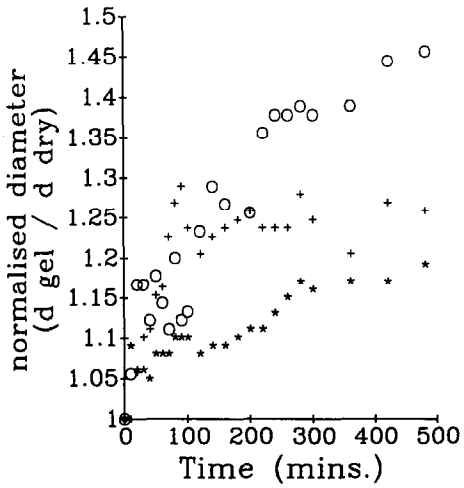

Fig. 1. Normalised diameter (calculated as the diameter of the gelled sample at time t, divided by the diameter of the dry sample) as a function of time. (○) Uncoated; (+) face coated; (*) edge coated.

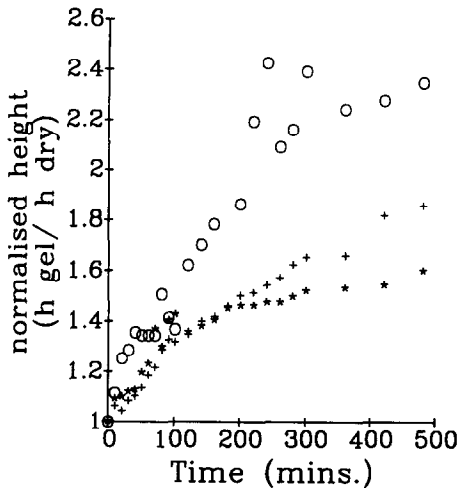

Fig. 2. Normalised height (calculated as the height of the gelled sample at time t, divided by the height of the dry sample) as a function of time. Symbols as for Fig. 1.

Peppas et al. (1992) investigated the swelling and release of tablets containing 35% HPMC, and found that the normalised height showed the greatest increase in cases where the edge was coated, followed by the uncoated, and then the face coated sample. The results presented here reveal that normalised height showed the greatest increase with the uncoated, followed by the face and then edge coated samples respectively. Peppas et al. (1992) reported no significant difference between the increases in normalised diameter for uncoated and edge coated tablets, the greatest increase being observed with the face coated

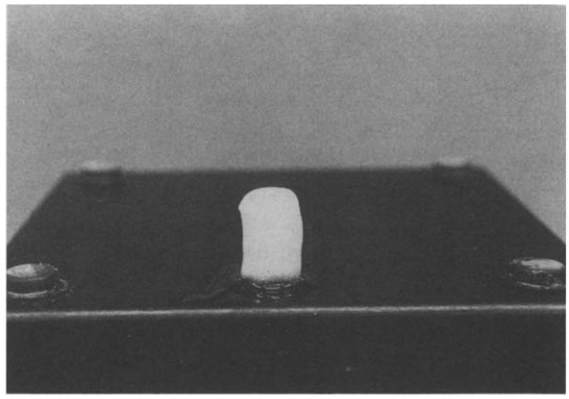

Fig. 3. Photomicrograph of HPMC tablet at time $t = 8$ h, showing the significant preferential axial swelling.

tablets. The conclusion of Peppas et al. (1992) was that coating the faces forced swelling to be radial, whilst coating the edges caused swelling to be axial. Such observations are dramatically different to the data presented here for the tablets of HPMC alone.

The changes in diameter (presented in a normalised fashion in Fig. 1) show that the uncoated and face coated tablets behave in a similar manner for about 200 min, after which the swelling of the face coated tablets is seen to slow significantly. The edge coated tablets are obviously physically restricted from swelling in this radial dimension, however, there is a gradual increase in diameter, such that the difference between face coated and edge coated tablet is small after about 300 min. It should be noted, however, that these increases in size are small, amounting to an increase in diameter of only about 2 mm in 500 min.

The major change for the HPMC compacts is observed as swelling in the axial direction. The data for normalised increases in height (Fig. 2) reveal that there are similar degrees of swelling for the face and edge coated tablets for the first 200 min, after which the edge coated tablets show slower axial swelling. The uncoated tablets swell faster than either of the coated tablets throughout the 500 minute experiment. It is interesting to note that the axial swelling process seems to fit to sequential zero order rate processes (e.g., for the edge coated sample a straight line is observed from 0 to 100 min, followed by a second from 100 to 200 min, and then a third after 200 min; a similar response is seen for the face coated tablets, except the second break point is at about 300 min, rather than 200 min).

Whilst the data for the radial swelling (Fig. 1) are not obviously zero order, they too reveal discrete breaks in the relaxation process. Even with the use of the image analysis system the data show a degree of spread, making the exact break points on the plots rather difficult to define, although they appear to be at approx. 100 and 300 min. At the present time we are unable to confirm whether the breaks in the plots have significance, or whether they are artifacts of measuring small changes in dimensions. Consequently, we make no attempt at any explanation in terms of physical significance of the different regions in the normalised dimensional plots (Figs 1 and 2).

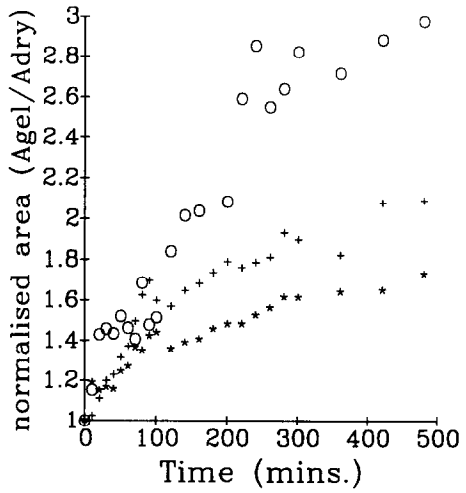

Fig. 4. Normalised area (calculated as the surface area of the gelled sample at time t, divided by the total surface area of the dry sample) as a function of time.

Colombo et al. (1990) have demonstrated that the release of drug from swelling systems is directly related to the increase in surface area during swelling. Colombo et al. (1990) and Peppas et al. (1992) have presented normalised area plots (area of the swollen system, divided by the area of the dry tablet) for swelling systems which have been partially coated. Such a normalised area plot is presented in Fig. 4. It can be seen that, especially after the first 100 min, the normalised area increased much more significantly for the uncoated than for the face coated, and for the face coated than for the edge coated. This finding is illogical, as the uncoated sample (if the results are truly normalised) should be either identical to, or the effective weighted mean of the edge coated and face coated tablets. An alternative normalised plot has been presented (Fig. 5), for which it has been assumed that the area of the paraffin coat is a constant region, to which water has no access; consequently the area of the paraffin coat has been subtracted from the area of both the dry and gelled systems. It can be seen

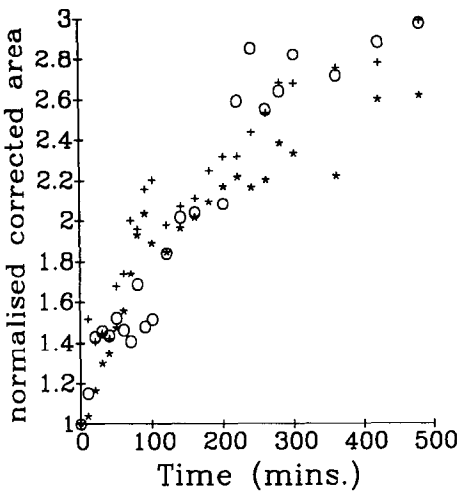

Fig. 5. Corrected normalised area (calculated as the surface area of the gelled sample at time t minus the area of the paraffin coat, divided by the surface area of the dry sample minus the area of the paraffin coat) as a function of time.

(Fig. 5) that the corrected results for the coated tablets, are now in much closer agreement with those obtained for the uncoated tablets. The minor (but largely insignificant) deviation after 300 min, of the face coated data, may be due to the failure of the approximation that the paraffin area is a constant inaccessible region.

It can be concluded from Fig. 5 that the faces and edge of the HPMC compact allow equal access to water. The preferential swelling in the axial direction must be due to the need for directional stresses, imposed in HPMC during tabletting, to relax. It follows that the area change in the swollen system is directly related to the area exposed to water access, and not related to whether the coating is positioned on the faces or edges of the tablet. This observation is different from that made by Peppas et al. (1992) for products with other components.

Peppas et al. (1992) calculated the dimensionality (d) of the swelling in tablets containing HPMC. The dimensionality was defined as the number of directions in which complete and unobstructed expansion occurs. Free unhindered expansion in dimensions of height, width and length would result in a value of $d = 3$. For systems which are inhibited in any way, the value of d must be less than 3, an extreme case being when swelling is limited to only x and y co-ordinates (and prevented in z), when d would equal 2.

Peppas et al. (1992) defined Q as the volume swelling ratio:

$$Q^{d/3} = V_{gel}/V_{dry} \equiv Q \tag{1}$$

and the swelling area:

$$Q^{(d-1)/3} = A_{gel}/A_{dry} \tag{2}$$

Consequently, the value of d can be obtained from a plot of $\ln(A_{gel}/A_{dry})$ as a function of $\ln Q$ (as the gradient $= (d-1)/3$).

For the formulation used by Peppas et al. (1992), the uncoated tablet had a value of $d = 2.91$, the face coated $d = 2.77$ and the edge coated $d = 2.89$. Thus, in each instance (including the uncoated tablet), swelling was not proceeding unhindered in all three dimensions, presumably due to the presence of other components in the tablet. The fact that the d values were close to 3 implied that all products were reasonable free to swell, and the fact that the d values did not differ greatly demonstrates that the coatings did not drastically alter the swelling dimensionality.

Calculation of d values for the HPMC compacts used in the current study yielded: uncoated $d = 3.00$, face coated $d = 3.02$, edge coated $d = 3.05$. The deviation of d above 3.0 must be due to error, but the results clearly indicate that the coatings do not influence the dimensionality of the swelling process. Such calculations provide an explanation for the data in Fig. 5, as the dimensionality remains equal to 3, the only factor that has changed is the original available surface area, which can be normalised. The dimensionality values calculated by Peppas et al. (1992) demonstrate that (for that particular formulated product) face coating produced a change in dimensionality that proved to be significant, whilst the edge coated sample behaved in a manner much more similar to the uncoated sample.

Acknowledgments

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