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Structure and behaviour of hydrophilic matrix sustained release dosage forms: 1. The origin and mechanism of formation of gas bubbles in the hydrated surface layer

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Summary

Gas bubbles are an important feature of the surface hydrated layer of hydrophilic matrix tablets in that they may significantly influence the performance of these dosage forms. Cryogenic SEM studies on the hydrated layer provide direct visual evidence for the origin and mechanism of formation of these bubbles. Air within the voids of the dry tablet core is observed to be progressively entrapped by swelling polymer particles within a partially hydrated region at the core/pseudogel interface, giving rise to discrete air pockets within the pseudogel layer.

Hydrophilic matrix (HM) dosage forms sustain drug release by the rapid formation of a hydrated surface pseudogel layer, which then acts as a diffusional barrier to further liquid ingress and to the outgress of dissolved solutes. Although outwardly simple, drug release from HM systems is a complex phenomenon resulting from the interplay of many different physicochemical processes (Melia, 1991). In particular, the formation and physical properties of the hydrated surface barrier are an important determinant of subsequent behaviour and drug release performance. Previous cryogenic SEM studies have provided evidence that polymer hydration and swelling within different regions of the pseudogel layer may be limited by restricted space and water availability, resulting in a non-homogenous hydration structure within the hydrated layer (Melia et al., 1990).

Gas bubbles form an important structural feature of the hydrated surface layer (Rajabi-Siahboomi et al., 1992). They may affect the drug release kinetics and also be responsible for the bouyancy of these systems in vitro and in vivo. Korsmeyer et al. (1983) reported that release of potassium chloride from hydroxypropylmethyl cellulose (HPMC) matrices was shifted towards a zero-order time-profile in the presence of gas

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bubbles, in contrast with the linear square root of time kinetics observed for an evacuated tablet. Drug release rate was roughly proportional to the tablet void volume. These workers therefore postulated that air entrapped within the tablet during compression was released into the pseudogel and slowed release by acting as an additional barrier to solute transport. Potassium chloride is a highly soluble drug which appears to be released primarily by diffusion through the pseudogel layer (Salomon et al., 1979), and the presence of large numbers of bubbles would provide an increase in diffusional pathlength and thereby modify the release profile. This effect has been deliberately exploited by Hashim and Li Wan Po (1987) who have incorporated effervescent mixtures into HM tablets in order to produce dosage forms with zero-order release kinetics.

In this present work, freeze-fracture SEM studies have been undertaken on two types of hydrophilic matrices with the aim of confirming the origin and mechanism of formation of gas bubbles within the pseudogel layer.

Matrix preparation: Tablets containing two different HM carrier polymers were prepared by direct compression at compaction pressures within the ascending portion of the hardness:compression profile. 5 mm flat-faced tablets of HPMC (Methocel K4M: 63–90 μm particle size) were prepared at 1.2–1.4 kN (4–6 kg hardness) and hydrated in deaerated distilled water in USP dissolution apparatus 1 at 37°C and 100 rpm. 11 mm flat-faced tablets of xanthan gum (Keltrol TF: whole material, < 90 μm particle size) were prepared at 12–14 kN (7–9 kg hardness) and hydrated in degassed simulated intestinal fluid USP pH 7.5 ± 0.1 under the same conditions.

Cryogenic scanning electron microscopy: After 1 h, the hydrated tablets were carefully removed from the dissolution vessel, rapidly frozen in nitrogen slush (-210°C) and transferred to the

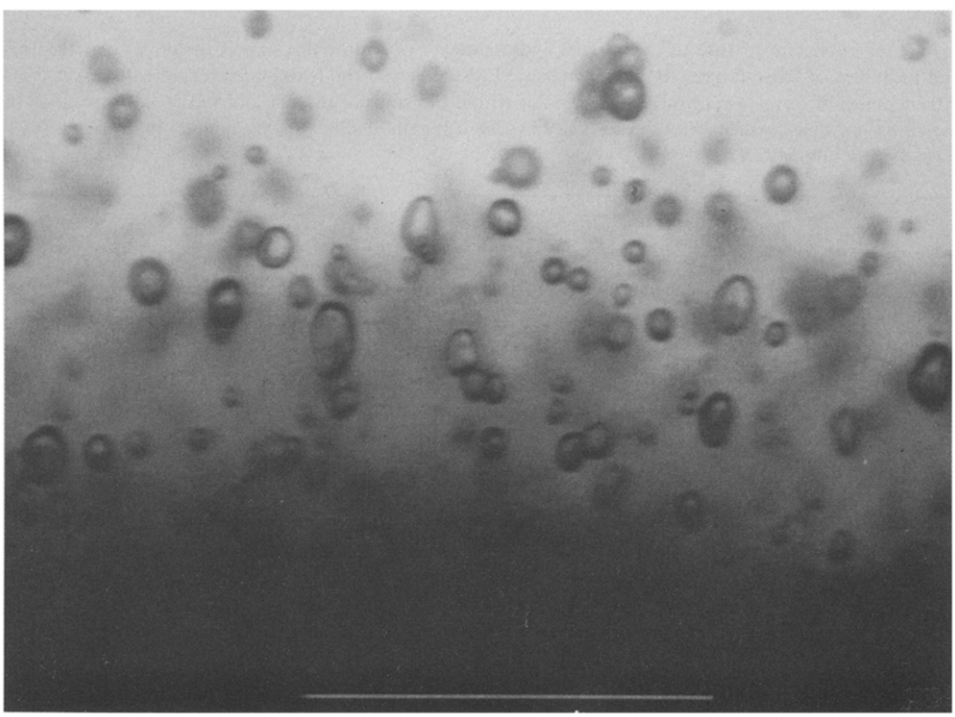

Fig. 1. Optical micrograph of a hydrated xanthan tablet under transmitted light showing the accumulation of gas bubbles in the pseudogel region adjacent to the core (scale bar = 0.5 mm).

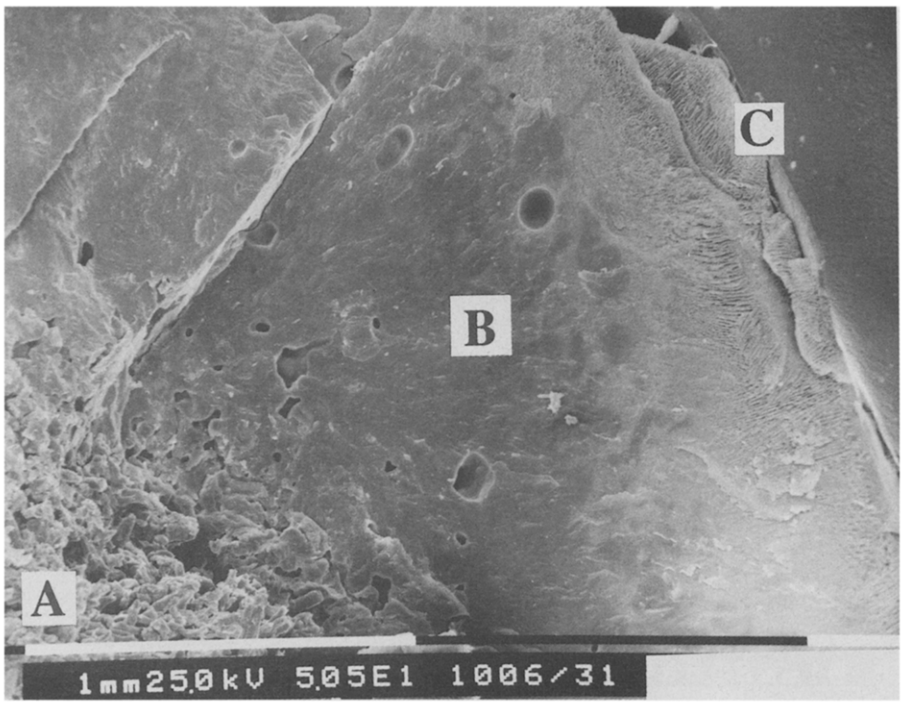

Fig. 2. Freeze-fracture SEM micrograph across the surface hydrated pseudogel layer of a HPMC tablet after 1 h hydration (×50). (A) Tablet core, (B) pseudogel layer, (C) tablet edge.

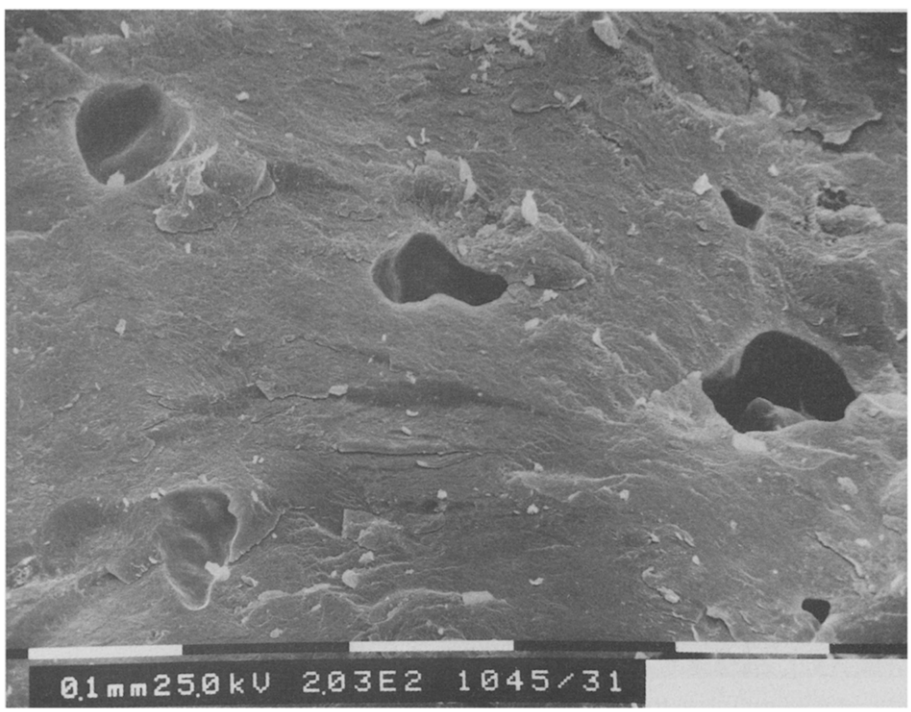

Fig. 3. Discrete cavities within the body of the gel in an HPMC tablet after 1 h hydration (×200).

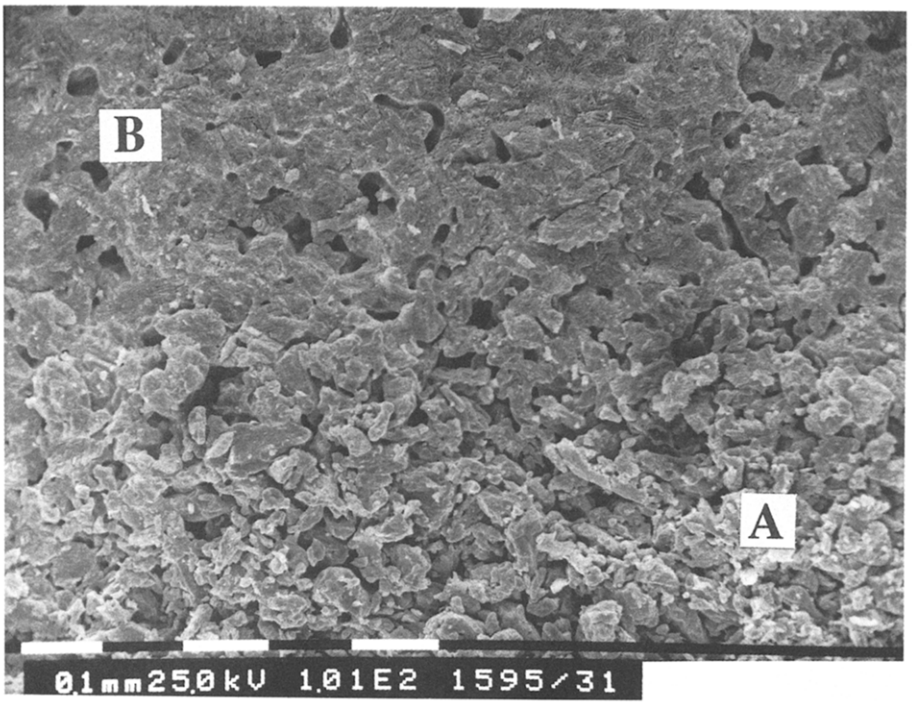

Fig. 4. The core/pseudogel boundary region of a xanthan tablet after 1 h hydration (×100). (A) Tablet core, (B) pseudogel layer.

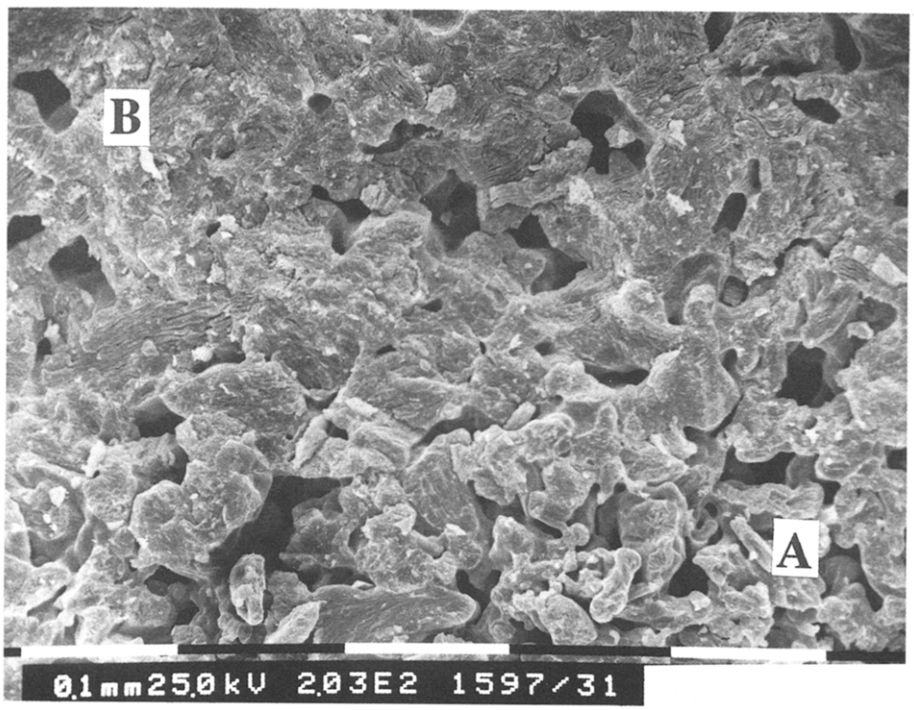

Fig. 5. The transition between partially hydrated particles and gel within the core/pseudogel boundary region of a xanthan tablet after 1 h hydration (×200). (A) Partially hydrated region, (B) pseudogel.

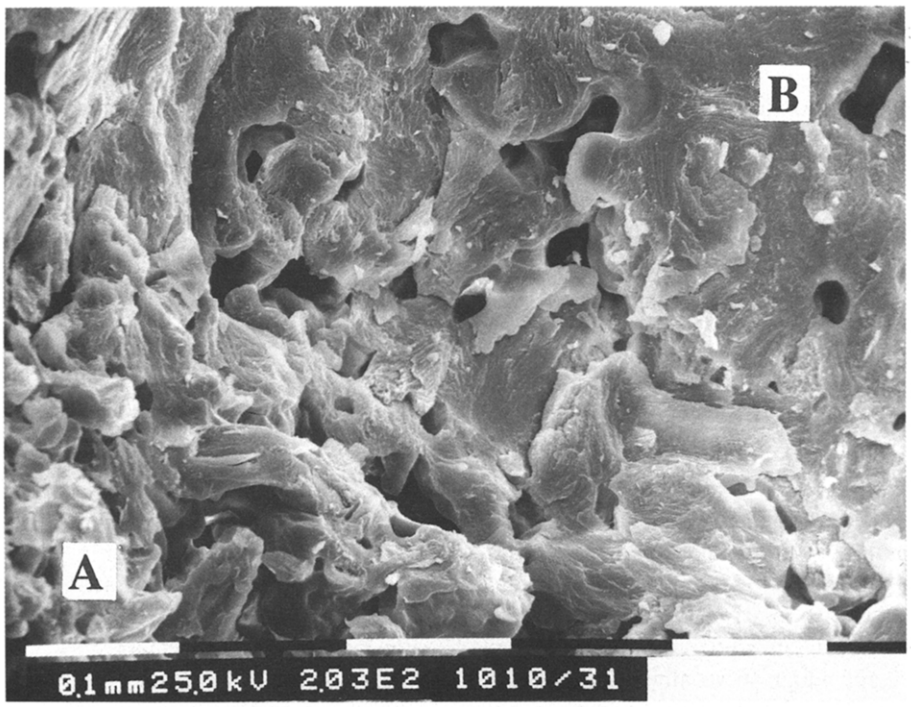

Fig. 6. The transition between partially hydrated particles and gel at the core/pseudogel boundary region of an HPMC tablet after 1 h hydration (×200). (A) Partially hydrated region, (B) pseudogel.

Fig. 7. Detail showing entrapment of air voids at the core/pseudogel boundary region of an HPMC tablet after 1 h hydration (×500).

cold stage (−180°C) of the cryopreparation chamber (Hexland CT1000 cryotrans). An area of undamaged surface was chosen and was freeze-fractured using a cold knife. The specimen was then etched under vacuum at −80°C, gold coated and transferred to the cold stage (−180°C) of the electron microscope (Philips SEM 505). Electron micrographs were obtained at an accelerating voltage of 25 kV.

Optical microscopy: Optical microscopy was undertaken using a Chou 4722 CCD camera fitted with a 1:14/9 lens on a dry xanthan matrix sandwiched between two glass faces of a thermostatically controlled chamber, and hydrated from the edge with degassed simulated intestinal fluid USP at 37°C.

After 1 h hydration a dense layer of gas bubbles was observable to the naked eye within the inner part of the pseudogel layer in both the xanthan and HPMC matrices. Optical micrographs (Fig. 1) clearly showed gas bubbles within the hydrated layer which were almost exclusively located within 0.5 mm of the core/gel interface. The absence of gas bubbles in the outer regions of the hydrated layer suggest that either they escape from this region or sufficient medium is present to dissolve them. Fig. 2 shows a typical low-magnification SEM micrograph of a freeze fracture surface across the pseudogel layer after 1 h tablet hydration. Discrete cavities are visible, again with the majority occurring within 0.5 mm of the core (Fig. 3).

The core/gel boundary is shown in more detail in Figs 4–8. Discrete polymer particles can be seen within the core with void air spaces interspersed between them (Fig. 4). Micrographs taken at higher magnifications reveal that between the core and the continuously hydrated pseudogel, there is an intermediate region where polymer particles are partially hydrated and undergoing swelling (Figs 5–8). Within this region, the swelling particles may be seen progressively entrapping void air as hydration proceeds, eventually forming discrete cavities.

The same mechanism of air entrapment may be seen in matrices prepared from both polymer

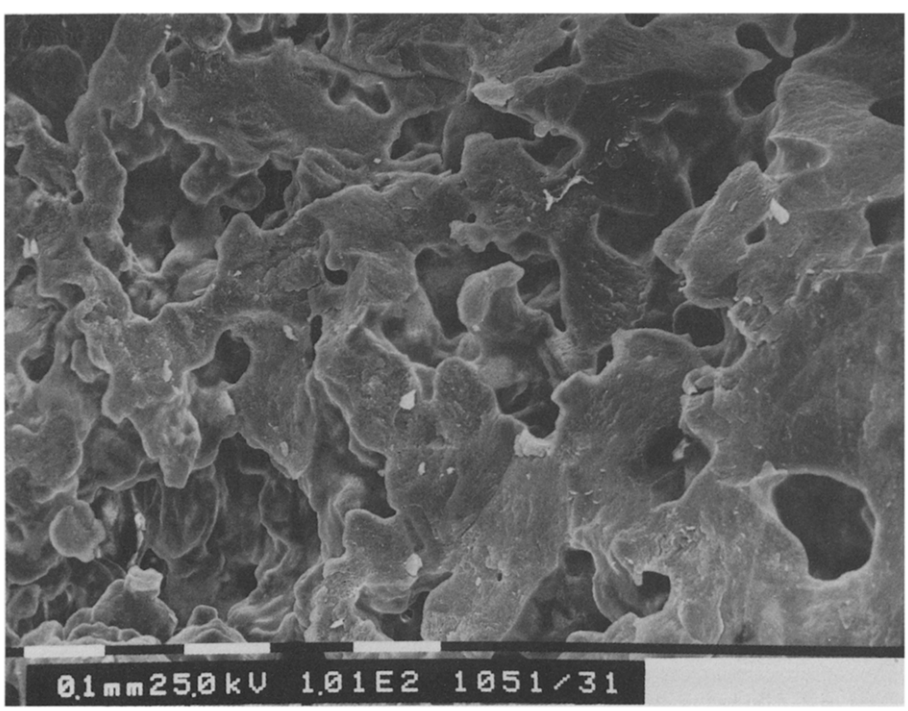

Fig. 8. The region of partially hydrated fibres at the core/pseudogel boundary of an HPMC tablet after hydration for 6.5 h (×100).

types, despite differences in particle morphology between the xanthan gum, which has a granular particle shape (Fig. 5) and HPMC, which has a fibrous morphology (Figs 6 and 7). After prolonged hydration (6.5 h), the partially hydrated region at the core/gel boundary is more extensive and the swelling and entrapment process even more evident (Fig. 8).

These results provide direct visual evidence that air bubbles in the gel layer do indeed originate from void air spaces within the core, confirming the postulation made from the indirect evidence of Korsmeyer et al. They are formed during the swelling of polymer particles within an area of intermediate hydration at the core/gel boundary.

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