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Research paper

# Drug release from beads coated with an aqueous colloidal ethylcellulose dispersion, Aquacoat®, or an organic ethylcellulose solution

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**Abstract**

The objective was to investigate several factors (composition of the coating formulation, the type and pH of the release medium and curing conditions), which influence the drug release from beads coated with either the aqueous ethylcellulose dispersion, Aquacoat® or an organic ethylcellulose solution. The chlorpheniramine maleate release from Aquacoat®-coated beads was faster in pH 7.4 buffer than in 0.1 N HCl. Increasing the curing time and curing temperature decreased the drug release in pH 7.4 buffer but did not affect the release in 0.1 N HCl. In contrast, the drug release from beads coated with the ethanolic ethylcellulose solution was not affected by the curing step, the release medium or the addition of sodium lauryl sulfate. Scanning electron microscopy and contact angle measurements explained the release data. The differences in the drug release behavior of aqueous – and organic solvent – ethylcellulose – coated beads could be attributed to the differences in the film formation process. 

*Keywords:* Beads; Coalescence; Coating; Curing; Ethylcellulose; Film formation; Aqueous polymer dispersion; Pseudolatex; Sodium lauryl sulfate

## 1. Introduction

Ethylcellulose is a popular polymer used for the coating of solid dosage forms [1]. The polymer can be applied either as an organic solution or as an aqueous colloidal dispersion (pseudolatex). Because of safety and environmental considerations and a lower viscosity at the same solids content, aqueous ethylcellulose dispersions are preferred.

Film formation from organic polymer solutions is caused by the evaporation of the organic solvent initiating an increase of the polymer concentration. At higher polymer concentrations, an intermediate gel like stage is reached. Upon further evaporation of the solvent, a solvent free polymeric film is obtained. The film formation from aqueous colloidal polymer dispersions is more complex. During coating, water evaporates and the colloidal polymer particles coalesce into a film [2]. With ethylcellulose dispersions, plasticizers are required to reduce the minimum film formation temperature (MFT) below the coating temperature and to enhance the coalescence process.

Aquacoat® (30% w/w total solids) is an aqueous ethylcellulose pseudolatex stabilized with sodium lauryl sulfate and cetyl alcohol. It requires the addition of 20–30% (w/w) plasticizer based on the polymer. Two major problems have been observed with Aquacoat®-coated dosage forms, first a pH-dependent drug release with drugs being released faster in higher pH media than in simulated gastric juice [3–7] and second, changes in drug release profiles during storage (aging effects) [8,9].

The pH-dependent drug release, which was unexpected because of the non-ionic character of the cellulose ether, was either attributed to residual carboxylic acid groups in the ethylcellulose [3,6] or to the presence of the anionic surfactant, sodium lauryl sulfate, in the coating [4,10]. Heat-

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ing the coated pellets reduced [11] or eliminated the pH-dependent release [7].

The aging problem was attributed to the further gradual coalescence of the colloidal polymer particles during storage, whereby polymer chains in adjacent, not completely coalesced particles diffused across the particle boundaries, resulting in complete coalescence and a disappearance of the particle contours. The drug release generally decreased upon storage. A curing step (thermal treatment) at elevated temperatures above the MFT directly after the coating process has been recommended to accelerate the film formation process and to avoid stability problems [9,12–14]. Several studies have investigated the effect of curing on the drug release, with the most critical parameters being the curing temperature and time. Most of the time, the drug release decreased upon curing, however, with drugs having a high affinity for the ethylcellulose coating, like for example ibuprofen, an increase in drug release was seen because of diffusion of the drug into the coating [15]. No effect of curing on the drug release was seen with beads coated with another ethylcellulose dispersion, Surelease®, or an organic ethylcellulose solution [16].

The objective of this study was to investigate several factors influencing the drug release from beads coated with either an aqueous ethylcellulose dispersion (Aquacoat®) or an organic ethylcellulose solution. These factors include the composition of coating formulation (presence of surfactants), the type and pH of the release medium and post coating thermal treatment.

## 2. Materials and methods

### 2.1. Materials

The following chemicals were used as received: chlorpheniramine maleate (CPM; Thiemann Arzneimittel GmbH, Waltrop, Germany), Aquacoat® (FMC c/o Lehmann and Voss and Co., Hamburg, Germany), ethylcellulose (EC; grade N10 NF, Hercules GmbH, Düsseldorf, Germany), acetyltributyl citrate (Citroflex A-4; Morflex, Greensboro, NC, USA), sodium lauryl sulfate (SDS; supplied by Smithkline and Beecham, Worthing, UK), hydroxypropyl methylcellulose (Methocel® E5 Premium; Colorcon, Orpington, UK), polyethylene glycol 4000 (BASF, Ludwigshafen, Germany), non-pareil beads (Nupareil PG sugar spheres NF; 18-20 mesh, Hanns G. Werner, Tornesch, Germany). Ethanol was of reagent grade.

### 2.2. Preparation of coated beads

Chlorpheniramine maleate-loaded beads (12% w/w drug loading) were prepared by layering a drug-binder solution onto non-pareil beads using a fluidized bed coater (GPCG 1, Wurster insert, Glatt GmbH, Binzen, Germany). A solution of chlorpheniramine maleate (82 g) and polyethylene glycol 4000 (0.3 g) in 200 ml ethanol/water (60% v/v) was mixed with 30 g of an aqueous hydroxypropyl methylcellulose solution (10% w/v) and was sprayed onto non-pareil beads using the bottom spray mode. The process parameters are listed in Table 1. The layered beads were oven-dried (Heraeus T 6120, Hanau, Germany) at 40°C overnight to evaporate residual solvents.

Table 1

Process parameters for the chlorpheniramine maleate layering and the coating of the drug-layered beads

| Process parameter | CPM layering | Aqueous ethylcellulose dispersion, Aquacoat® | Organic ethylcellulose solution |
|---|---|---|---|
| Inlet temperature (°C) | 45 | 45–50 | 35 |
| Air volume ($m^3$/h) | 70–80 | 70–80 | 70–80 |
| Product temperature (°C) | 37–40 | 41–43 | 29–31 |
| Outlet temperature (°C) | 35–37 | 35–39 | 27–30 |
| Spray rate (g/min) | 3–11 | 2–10 | 3–7 |
| Atomization pressure (bar) | 1.8 | 1.8 | 1.8 |
| Nozzle diameter (mm) | 1.2 | 1.2 | 1.2 |

The drug-loaded beads were coated in a fluidized bed coater using the bottom spray mode (Glatt GPCG1; Wurster insert) with either a plasticized aqueous ethylcellulose dispersion (Aquacoat®) or an ethanolic solution of ethylcellulose. The aqueous polymer dispersion was plasticized with acetyltributyl citrate (20% w/w, based on the mass of the polymer) for 48 h prior to the coating step in order to achieve a good uptake of the lipophilic plasticizer by the colloidal polymer particles. The polymer content of the plasticized dispersion was then adjusted to 15% w/w by dilution with water. The organic coating formulation consisted of a solution of ethylcellulose (7% w/v) and acetyltributyl citrate (20% w/w, based on the mass of the polymer) in ethanol (96% v/v). Sodium lauryl sulfate was added to the organic polymer solution at the same concentration (5% w/w, based on the mass of ethylcellulose) as in Aquacoat®.

The final coating formulations were sprayed onto a mixture of drug-loaded and non-pareil beads (1:5 w/w, 600 g) to achieve a polymer weight gain of 10% w/w. The process parameters for the coating step are given in Table 1. Initially, the beads were coated at a slow spray rate (2–3 g/min for the first 10 min) in order to avoid overwetting of the pellets and drug migration into the film coating. After the coating process, the beads were further fluidized for 15 min (constant process parameters) in order to evaporate residual solvents in the coating prior to the curing step. The coated beads were cured at different temperatures (RT, 40°C, 50°C or 60°C) and for different time periods (1 h, 8 h or 24 h). The beads were then stored in closed, light-protected glass vials until further experimentation.

### 2.3. In vitro release studies

The USP XXIII rotating paddle method (VanKel 700, VK

650a, VanKel, Edison, NJ, USA; 37°C, 900 ml, 0.1 N HCl, 0.1 M pH 7.4 phosphate buffer USP XXIII or pH 7.5 borate buffer Ph. Eur. 1997, 100 rpm, $n = 3$) was used to study the drug release from coated beads. The samples (3 ml, not replaced) were withdrawn at predetermined time intervals by an autosampler (VK 800) and chlorpheniramine maleate was detected spectrophotometrically at 264 nm (0.1 N HCl) and 261 nm (0.1 M pH 7.4 phosphate buffer or pH 7.5 borate buffer) (UV-2101PC, Shimadzu Europa GmbH, Duisburg, Germany).

### 2.4. Contact angle measurements

The organic ethylcellulose solution or aqueous dispersion (same formulations as used for the coating) were cast into aluminum dishes (5 cm in diameter) and dried at 60°C for 24 h (aqueous dispersion) or at room temperature for 16 h (organic ethylcellulose solution). The dried organic cast films were kept for 3 days at 60°C to evaporate residual solvent. The films were cut and placed onto the adjustable platform of the contact angle goniometer (Krüss G1 Goniometer, Hamburg, Germany). Six microliters of either 0.1 N HCl or 0.1 M pH 7.4 phosphate buffer were applied onto the film using a microsyringe equipment. The contact angles were measured after 1 min and 2 min. At least six measurements were carried out for each formulation and time interval.

### 2.5. Scanning electron microscopy

The morphology of the surfaces of the coated beads were examined by scanning electron microscopy (SEM) before and after in vitro release studies. The dried samples were coated for 230 s under an argon atmosphere with gold-palladium (SCD 040, Balzers Union, Lichtenstein) and were then observed with a scanning electron microscope (PW 6703/SEM 515, Philips, Eindhoven, The Netherlands).

## 3. Results and discussion

In this study, the drug release from beads coated with either an aqueous colloidal dispersion, Aquacoat®, or an organic solution of ethylcellulose was compared with respect to curing, additives and dissolution media effects.

Strong curing and media effects were seen with beads coated with the aqueous polymer dispersion, Aquacoat® (Fig. 1). With uncured beads, the drug release was much faster in pH 7.4 buffer than in 0.1 N HCl. Since the drug, chlorpheniramine maleate, has a pH-independent solubility in the two media investigated, this difference in release profiles has been attributed to the surfactant, sodium lauryl sulfate, which is used in the aqueous dispersion to stabilize the colloidal polymer particles and therefore is also present in the dried coating [11]. The pellets were better wetted by the higher pH-dissolution medium because of the higher

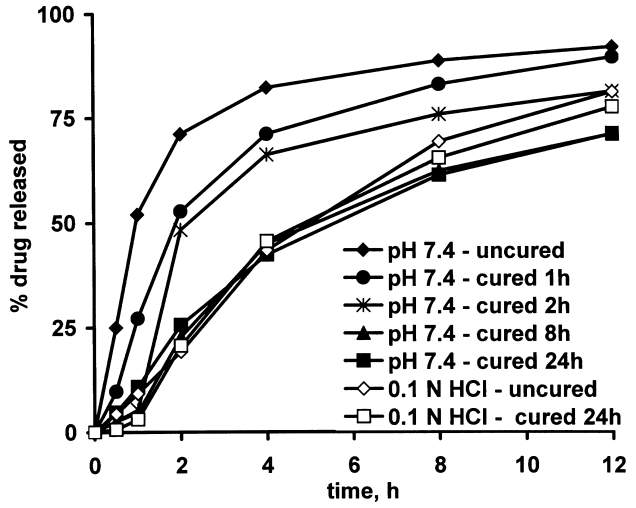


Fig. 1. Influence of curing time and release medium on the chlorpheniramine maleate release from Aquacoat®-coated beads (curing temperature = 60°C).

degree of dissociation of sodium lauryl sulfate, as was shown by contact angle measurements. Curing of the beads did not influence the drug release in 0.1 N HCl, even at a long curing time of 24 h. In contrast, the drug release decreased significantly with increased curing time for cured beads in pH 7.4 buffer and approached the release profiles in 0.1 N HCl (Fig. 1). A curing time of 8 h at 60°C appeared to be sufficient to achieve complete coalescence of the film. The film formation process was not completed after the coating step, resulting in a rapid release with the uncured beads; the curing then resulted in further coalescence of the polymer particles and a reduction in drug release.

The chlorpheniramine maleate release from uncured beads was not changed significantly by altering the buffer medium from phosphate to borate buffer of comparable pH value (Fig. 2). The drug release from beads cured for 24 h at 60°C also showed similar results. The type of ions present in the media did not contribute to the differences seen in the drug release pattern of Fig. 1. Similar drug release patterns were also obtained with distilled water and 0.1 N NaCl solution (Fig. 2).

To gain further information about the pH- and curing-dependent drug release, the drug release from beads coated with Aquacoat® was compared to the drug release from beads coated with organic ethylcellulose solutions. Sodium lauryl sulfate was not required for the coating with organic polymer solutions and coatings without the surfactant could therefore be prepared. The drug release from beads coated with the organic ethylcellulose solution was retarded and, in contrast to the beads coated with the aqueous ethylcellulose dispersion, was not affected by either the type of dissolution medium or curing (Fig. 3). The drug release profiles were similar to the release of cured beads coated with the aqueous polymer dispersion, except the lag phase was less visible. Curing did not affect the drug release because of the differ-

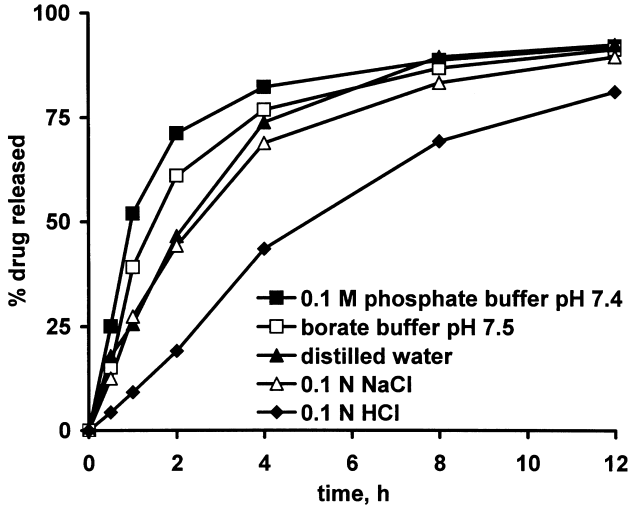


Fig. 2. Influence of type and pH of the release medium on the chlorpheniramine maleate release from uncured Aquacoat®-coated beads.

ent mechanism of film formation from organic polymer solutions when compared to the aqueous colloidal polymer dispersion. No coalescence and thus no post coating enhancement of the film formation was necessary. In addition, no dependence of the drug release on the release medium was obtained with organic ethylcellulose solutions.

A strong dependence of the contact angle on the pH of the release medium was observed with films prepared from the aqueous colloidal polymer dispersion because of the presence of sodium lauryl sulfate, while the contact angle for ethylcellulose films cast from organic polymer solutions was similar for both media (Table 2). The contact angle data correlated well with release data seen for the coated beads. The pseudolatex films were better wetted by the pH 7.4 buffer than by 0.1 N HCl. The contact angle of ethylcellulose-SDS films was smaller than of Aquacoat® films.

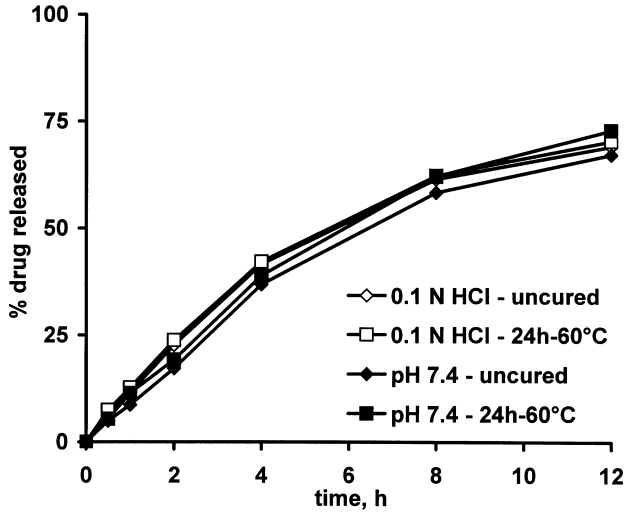


Fig. 3. Influence of curing conditions and release medium on the chlorpheniramine maleate release from beads coated with an organic ethylcellulose solution.

Table 2

Contact angles (±SD), of 0.1 N HCl or 0.1 M pH 7.4 phosphate buffer on films prepared from organic ethylcellulose solutions or Aquacoat®

| Film | 0.1 N HCl | | 0.1 M pH 7.4 buffer | |
|---|---|---|---|---|
| | 1 min | 2 min | 1 min | 2 min |
| Aquacoat® | 66.3 ± 2.0 | 65.8 ± 1.6 | 60.7 ± 1.7 | 46.3 ± 1.2 |
| Ethylcellulose | 66.2 ± 1.5 | 65.7 ± 1.7 | 64.7 ± 2.1 | 64.3 ± 1.7 |
| Ethylcellulose + SDS | 20.2 ± 1.2 | 17.7 ± 0.7 | 22.8 ± 1.0 | 17.8 ± 1.6 |

In addition to sodium lauryl sulfate, Aquacoat® also contains cetylalcohol as a low HLB-cosurfactant. Cetylalcohol and the different accessibility of sodium lauryl sulfate on the film surface could be responsible for the difference in contact angle.

Sodium lauryl sulfate was added to the ethanolic ethylcellulose solution in order to investigate its influence on the drug release in more detail. Sodium lauryl sulfate was used at the same level as in Aquacoat® (5% w/w, based on the mass of ethylcellulose). In contrast to the Aquacoat®-coated beads, the addition of sodium lauryl sulfate to the organic polymer solution did not affect the drug release in the two dissolution media of different pH (Fig. 4).

It can be concluded that the presence of sodium lauryl sulfate in ethylcellulose film coatings did not generally create a pH- or curing-dependent drug release. This dependent drug release was observed with beads coated with the aqueous colloidal polymer dispersion, Aquacoat®, but not with beads coated with the organic ethylcellulose solution. It could possibly be explained with the different mechanism of film formation. With coatings prepared from organic polymer solutions, sodium lauryl sulfate was distributed homogeneously in the ethylcellulose film, while with coatings prepared from the aqueous ethylcellulose dispersion, it was primarily present at the interface of the colloidal particles and was therefore not evenly distributed in the film. This is especially the case with not completely coalesced particles in uncured coatings. The pH 7.4 buffer will cause dissociation of sodium lauryl sulfate and rapid penetration of the dissolution medium through the not completely coalesced film. In 0.1 N HCl, sodium lauryl sulfate remained predominantly unionized, therefore not causing the rapid media penetration and drug release. During curing, a 'better' film is formed as the result of a further coalescence of the polymer particles and the pH-dependent differences in drug release were diminished.

Scanning electron micrographs of Aquacoat® – coated beads before and after in vitro release study are shown in Fig. 5. Smooth surfaces and no film defects were seen on uncured (Fig. 5A) and cured beads before in vitro release study. Large cracks were visible on uncured beads after release studies in pH 7.4 buffer (Fig. 5B), but not in 0.1 N HCl (Fig. 5C) or with cured beads in pH 7.4 buffer. These photographs confirmed the release data, namely a rapid release for uncured beads in pH 7.4 buffer (Fig. 1). Scanning

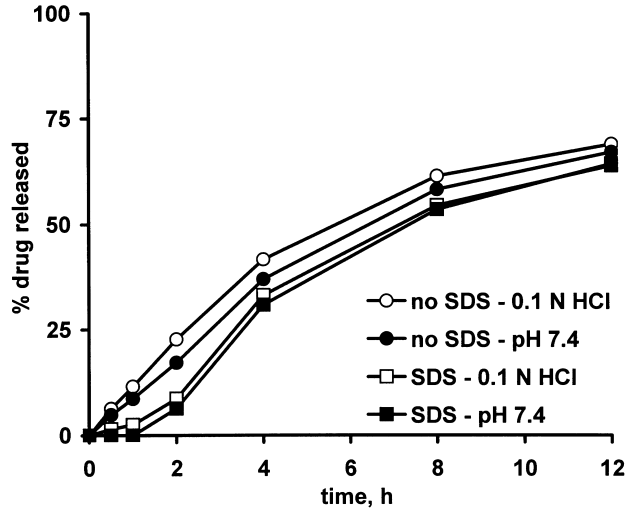


Fig. 4. Influence of sodium lauryl sulfate and release medium on the chlorpheniramine maleate release from uncured beads coated with an organic ethylcellulose solution.

electron micrographs taken from beads coated with an organic ethylcellulose solution did not show cracks regardless of the presence/absence of sodium lauryl sulfate, curing conditions or release medium (photographs not shown). This also confirmed the release data (Figs. 3 and 4), where no differences were seen.

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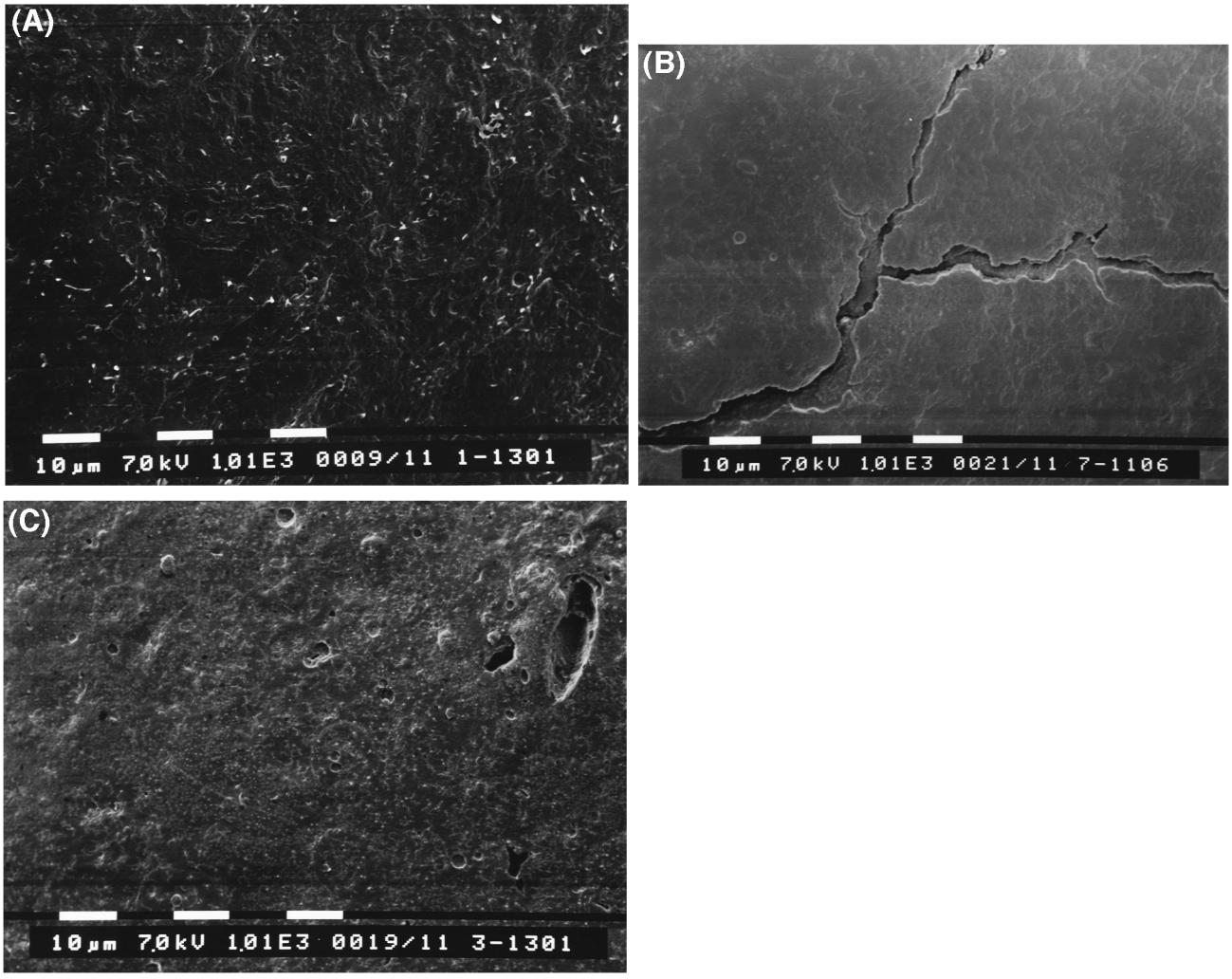


Fig. 5. Scanning electron micrographs of the surface of Aquacoat®-coated beads: (A) uncured beads, before dissolution studies, (B) uncured beads, 1 h release in pH 7.4 phosphate buffer, (C) uncured beads, 24 h release in 0.1 N HCl.

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