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An investigation into the release of cefuroxime axetil from taste-masked stearic acid microspheres Part 1: The influence of the dissolution medium on the drug release profile and the physical integrity of the microspheres

H.J. Robson [a,1], D.Q.M. Craig [a,*], D. Deutsch [b]

[a] *Centre for Materials Science, The School of Pharmacy, 29-39 Brunswick Square, London WC1N 1AX, UK*
[b] *GlaxoWellcome Research and Development, Park Road, Ware, Herts SG12 0DP, UK*

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Abstract

The dissolution properties of stearic acid-coated cefuroxime axetil (SACA) systems have been studied with a view to investigating the effects of the dissolution medium on both the release rate and the physical integrity of the microspheres. The release from the spheres was found to be highly dependent on the media used, with systems in distilled water (pH 6.8) and pH 5.9 Sorensens modified buffer showing a relatively slow release which exhibited linearity with the square root of time, implying a diffusion process. The rate of release from systems in pH 7.0 and 8.0 buffer was considerably faster and did not follow simple diffusion kinetics. Examination of the microspheres after immersion in the various media indicated a change in the integrity of the spheres in those media which showed the most rapid release. This was particularly marked when the systems were dried in buffer, with disintegration seen in the higher pH systems. It is suggested that the release of the drug is dependent both on diffusion through the intact microspheres and changes in the physical integrity of the spheres as a result of a reaction with the surrounding medium.

Keywords: Cefuroxime axetil; Stearic acid microspheres; Taste

1. Introduction

It is well established that any medication which imparts an unpleasant taste is likely to result in poor compliance to a drug regimen (e.g. Dupuis, 1985; Aronson and Hardman, 1992; Behrens et al., 1992; Roy, 1994). This presents a particular problem in the case of infants and young children, as many drugs are presented as liquid formula-

* Corresponding author. Present address: The School of Pharmacy, The Queen's University of Belfast, 97 Lisburn Road, Belfast BT9 7BL, UK. Tel./fax: +44-1232-272129.
E-mail address: duncan.craig@qub.ac.uk (D.Q.M. Craig)
[1] Present address: GlaxoWellcome, Langley Court, South Eden Park Road, Beckenham, Kent BR3 3BS, UK.

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tions due to difficulties associated with conventional solid dosage forms. These include the need for fractional doses and the difficulty small infants may experience in swallowing relatively large, solid objects. A number of taste-masking approaches have been described in the literature (Roy, 1994): Over and above chemical modification of the drug (e.g. Gregory et al., 1990; Asaka et al., 1994), formulation approaches include the use of flavours (e.g. Hussein and Barcelon, 1991; Eby, 1992), lipid coating (e.g. Cherukuri and Chau, 1991; Shiozawa et al., 1993; Katsuragi and Kurihara, 1993), coating with hydrophilic materials (e.g. Block et al., 1990; Wheatley and Erkoboni, 1992; Roche and Reo, 1994), viscosity modification (e.g. Blase and Shaw, 1993), the use of ion exchange resins (e.g. Lu et al., 1991), the use of inclusion complexes with cyclodextrins (e.g. Motola et al., 1991) and emulsification approaches (Behrens et al., 1992). In all cases it is essential for the formulation, which is almost invariably administered as a liquid, to mask the taste of the drug in the vicinity of the taste buds while also allowing favourable release in the lower gastrointestinal tract. These dual requirements have led to the development of suitable taste-masking formulations remaining a particular difficulty.

In this investigation, the use of stearic acid microspheres as a means of taste-masking cefuroxime axetil is described, with particular emphasis placed on studying the factors and mechanisms pertaining to drug release. Cefuroxime is a second generation cephalosporin antibiotic which is marketed as a parenteral product (Zinacef™). On introduction the drug was reported to be active against a wide spectrum of bacteria, attributed to its stability towards β-lactamase-producing organisms (e.g. Ryan et al., 1976). However, as absorption via the oral route is minimal (Foord, 1976) an orally active prodrug was developed by substituting a 1-acetyloxyethyl ester group for sodium on the parent molecule. This substitution enhanced the lipid solubility and gastric stability of the molecule, thereby facilitating its oral absorption. Cefuroxime axetil itself has no antimicrobial activity. After oral administration, the ester is absorbed intact then rapidly hydrolysed by non-specific esterases in the internal mucosa and portal blood to produce cefuroxime which is then absorbed into the blood stream (Harding et al., 1984).

Cefuroxime axetil has been shown to be successful for the treatment of a variety of complaints such as bacterial infection of skin and soft tissue, uncomplicated gonococcal infections, and lower respiratory tract and urinary tract infections (e.g. Gooch et al., 1987; Baddour et al., 1989). However, administration to babies and young children was restricted due to only a tablet form being available. Prior to the development of the suspension formulation described below it was sometimes necessary to administer crushed tablets mixed with a suitable beverage (Ginsburg et al., 1985). Studies by St. Claire and Caudill (1989), St. Claire et al. (1988) showed crushed cefuroxime axetil tablets to be stable for at least 2 h when dispersed in several brands of fruit juice and chocolate milk then left at room temperature. This practice overcame some of the administration difficulties but a second problem became apparent. Cefuroxime axetil is known to have an unpleasant taste and this was exacerbated when the tablets were administered as an *ad hoc* suspension. There was, therefore, a need to develop a liquid form of the drug which masked its unpleasant taste.

In order to improve the palatability of the suspension, cefuroxime axetil is coated with stearic acid. This intermediate wax-coated product is known as stearic acid-coated cefuroxime axetil or SACA and is manufactured using a simple spray chilling process. The two materials are mixed together before being introduced into a stainless steel jacketed mixing vessel. The mix is heated to the liquid state, the mixing vessel pressurised and the material forced through an atomising nozzle into a large, cooled collection vessel. The droplets solidify producing spheres of stearic acid which contain the drug. Freeze fracture studies carried out by GlaxoWellcome have shown cefuroxime axetil to exist as several discreet particles within each sphere (data not shown). These microspheres are granulated with sucrose prior to the addition of flavour to produce the final product which, when reconstituted with water,

provides a sweetened and flavoured aqueous suspension of the drug which retains the drug until after ingestion. Trials of the suspension in children have shown a good tolerance of the medication, indicating that the unpleasant taste of the drug has been successfully masked (Powell et al., 1991; Shalit et al., 1994). In the UK, the suspension and tablet dosage forms of cefuroxime axetil are marketed as Zinnat™. However, the mechanisms by which the drug is released from the microspheres are still not fully understood.

In this investigation, the factors influencing the release of cefuroxime axetil from SACA have been investigated, with a view to elucidating the macroscopic (as opposed to molecular) mechanism by which drug release occurs. In particular, the influence of pH has been investigated with a view to gaining further insights into the likely behaviour of the spheres in the gastrointestinal tract. This has been carried out using a combination of dissolution studies and scanning electron microscopy (SEM).

2. Materials and methods

2.1. Materials

A single batch of cefuroxime axetil was used throughout the study which was obtained from GlaxoWellcome Operations, Ulverston, Cumbria and used as received. The drug was prepared using the spray drying protocol described by Crisp et al. (1989). Examination of the drug substance by SEM showed it to consist of hollow spheres $\sim 2-30$ μm in diameter (data not shown). A single batch of SACA was used throughout the study which was obtained from GlaxoWellcome Operations, Ulverston, Cumbria and was used as received. The material is an off-white, free flowing powder and is composed of solid, spherical particles with an approximate diameter of 40–100 μm. SACA is composed of 85% stearic acid and 15% cefuroxime axetil. Stearic acid BP/USP containing not less than 90% stearic (C18) and palmitic (C16) acid was used in the manufacture of the product. All buffers salts were obtained from BDH and buffer solutions were prepared according to the directions given in the Pharmaceutical Codex (1994). The pH of the distilled water used for the study was 6.8.

2.2. Methods

2.2.1. Dissolution studies

Dissolution studies were performed using a six station Pharma Test Type PTWS dissolution bath (Pharma Test Apparatebau GmbH, Hainbury, Germany) connected to a Philips PU 8620 UV/VIS/NIR spectrophotometer (Pye Unicam Ltd., Cambridge, UK). The complete dissolution process was automated using a Philips PU 8620 tablet dissolution monitoring system (Pye Unicam, Ltd., Cambridge, UK) connected to a PC. Each of the six dissolution vessels contained 900 ml of degassed dissolution medium maintained at 37 ± 0.5°C, and a paddle rotation speed of 100 rpm was used throughout the studies. For SACA the sample weight was ~ 150 mg and for cefuroxime axetil 22 mg.

Due to the hydrophobic nature of the stearic acid initial problems were encountered due to inadequate wetting of the material. In order to minimise this it was necessary to wet the material prior to transfer to the dissolution vessel. This was achieved by initially weighing the material into a clean, glass sample jar then adding 10 ml of pre-warmed buffer from the respective dissolution vessel. The jar was shaken vigorously to ensure adequate wetting of the material and its contents immediately tipped back into the vessel. A previously withdrawn second 10 ml aliquot of buffer was then used to rinse the jar and all washings were transferred into the vessel.

2.2.2. Scanning electron microscopy

Approximately 3 g of SACA were weighed into a sample pot and 10 ml of pre-warmed dissolution media were added. The pot was shaken, then its contents emptied into a single dissolution vessel containing 900 ml of the chosen dissolution media. A 1-h dissolution run was performed using a

Pharma Test PTWS dissolution bath which was held at 37 ± 0.5°C and used a paddle speed of 100 rpm.

At 10-min intervals a 10-ml aliquot of the dissolution media containing SACA was removed using a syringe. The liquid was transferred onto a Whatman filter paper placed on top of a buchner funnel. A continuous vacuum was applied in order to remove excess buffer and the material was washed using distilled water unless otherwise stated. The solid material was transferred onto a petri dish, placed into a Heraeus vacuum oven, and dried at 37°C under vacuum until constant weight was obtained. Dry SACA which had not been in contact with the dissolution media were subjected to the same drying protocol and material which had been kept at room temperature were used as controls.

The dry powder samples were adhered to a SEM stub using carbon impregnated disks. The disk was divided into several segments, one per sample, and excess powder was removed using a can of compressed air. It was then transferred to a sputter coater and coated with gold for 2 min at 20 mA. Microscopic examination was carried out using a Phillips XL20 SEM (Phillips Electron Optics, Eindhoven, Netherlands).

3. Results and discussion

3.1. Dissolution studies

Fig. 1 shows the dissolution profiles for cefuroxime axetil and SACA in Sorensens pH 7.0 buffer and distilled water. In both media, the drug showed a rapid release (in excess of 90% within the first few minutes). However, complete dissolution was not observed, with the profiles remaining level up to and beyond one hour following the initial release. This was ascribed to the poor wetting of the drug, leading to the possibility of adsorption and flotation effects.

Markedly different profiles were seen for the SACA samples. The percentage drug release in pH 7.0 buffer at 30 minutes was found to be 71%. After 4 h, 90% of the drug had been released and runs were not continued after this point due to the absence of any further change. This may again be a result of wetting effects or alternatively may reflect entrapment of the drug within the microspheres. The samples in distilled water showed considerably slower release, with only 32% being attained after 4 h. Clearly, therefore, the release of the drug is slowed by incorporation into the stearic acid microspheres, as may be expected.

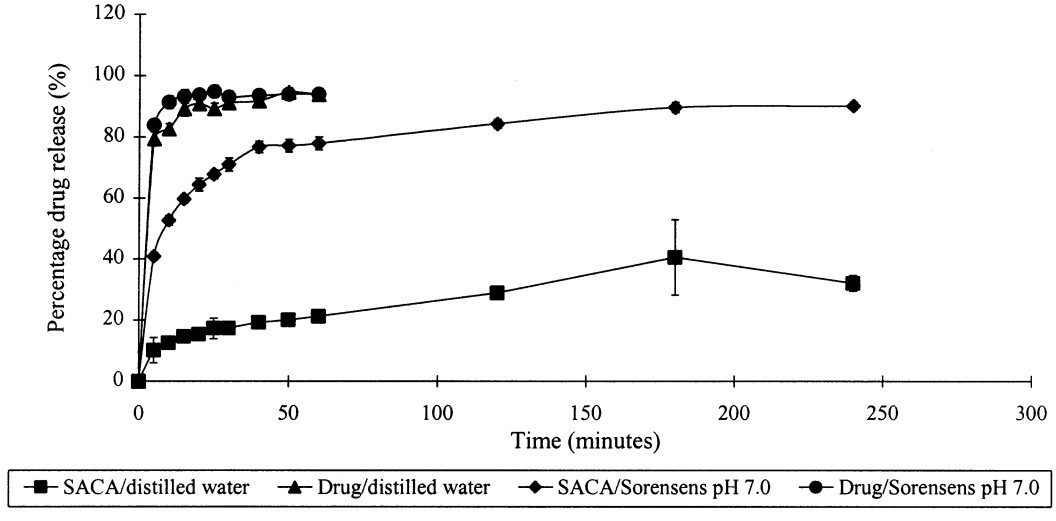

Fig. 1. Dissolution profiles of cefuroxime axetil and SACA in distilled water and pH 7.0 Sorensens modified buffer.

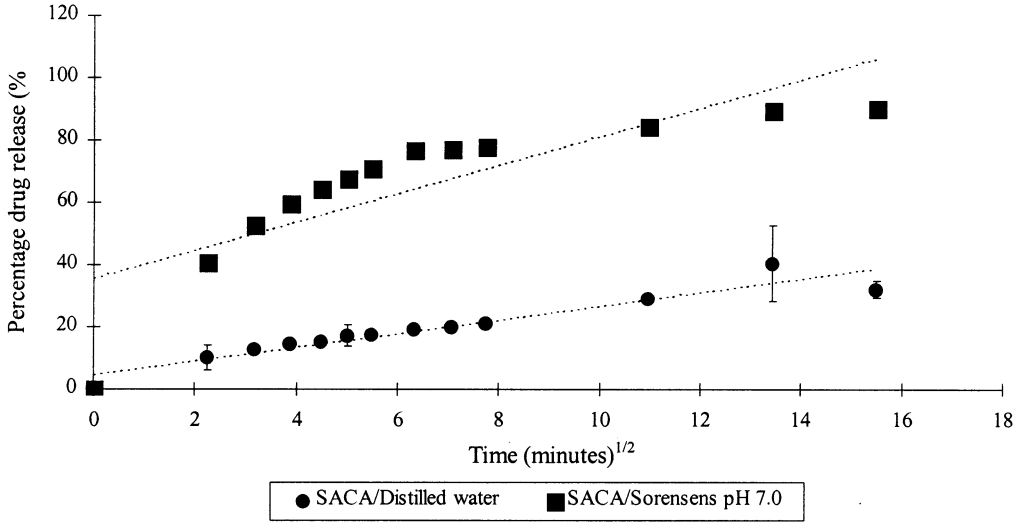

Fig. 2. Drug release against the square root of time for SACA in distilled water and pH 7.0 Sorensens modified buffer.

However, the release rate is itself highly dependent on the dissolution media, either due to differences in pH or, given the similarity in pH values between the two media, ionic content.

The data for the release from the SACA systems was fitted to a standard Higuchi plot, whereby the release is plotted against the square root of time (Fig. 2). While the data using Sorensens pH 7.0 buffer did not yield a satisfactory fit, the data for the release into distilled water showed a linear relationship with $t^{1/2}$ (correlation coefficient 0.9093) indicating a diffusional mechanism of release for this medium. The data for the pH 7.0 systems was found not to fit standard erosion/diffusion equations such as those proposed by Beren and Hopfenberg (1978), and Langer and Peppas (1981) which have been shown to be applicable to other lipid-based controlled release systems (Sutananta et al., 1995a,b). However, the aforementioned expressions refer to steady state release, while clearly the systems under study here were running to drug exhaustion, hence only the initial sections of the curves would be suitable for kinetic study. Given the paucity of data available over this initial period further modelling was not attempted.

In order to expand upon these observations the effect of altering buffer composition with respect to drug release was examined. Two further Sorensens pH buffers were used, hence although the levels of individual components within the media differed, the actual salts used in their preparation remained the same. The dissolution profiles for SACA in Sorensens pH 5.9 and 8.0 are compared to pH 7.0 in Fig. 3. Again, a clear dependence of dissolution rate on the pH of the medium is observed, with the most rapid release seen for the pH 8.0 systems and the slowest observed for the pH 5.9 medium. The release from the pH 5.9 (but not the pH 8.0) medium was again found to follow the Higuchi relationship. The release profile of the drug alone showed considerably less marked differences, although it is noted that the percent dissolved after 60 minutes was lower for the pH 8.0 medium ($81.23 \pm 5.18\%$ as opposed to $90.50 \pm 1.81\%$ and $94.00 \pm 1.70\%$ for pH 5.9 and 7.0, respectively).

3.2. SEM studies

The appearance of the microspheres after exposure to pH 7.0 Sorensens buffer for different time periods is shown in Fig. 4. Fig. 4a shows material which had undergone the drying protocol without being immersed in the dissolution media. The appearance of these spheres was extremely similar to that of untreated samples, hence it was concluded that the drying process was not causing

extensive changes to the external morphology of the spheres. Fig. 4b–d show the appearance of the spheres on immersion in the pH 7.0 buffer for time periods up to 60 min. Fig. 4b shows that after 10 min the surface characteristics of the particles remain essentially unchanged compared with the control. However, after 30 min small striations can clearly be seen on the outer surface of the spheres (Fig. 4c). These alterations were further apparent after 60 min, whereby evidence for fusion with small neighbouring spheres was also observed (Fig. 4d).

SACA was then examined after immersion in Sorensens pHs 8.0 and 5.9. Representative images are shown after 60 min immersion in Fig. 5a and b. Fig. 5a clearly shows that surface changes have also occurred to SACA immersed in the alkali media, these changes being more pronounced than those occurring for the pH 7.0 buffer. The surface of the spheres in the pH 8.0 media had a blistered appearance which became progressively more apparent at time periods up to 60 min. However, the systems in the pH 5.9 media showed little change in surface morphology (Fig. 5b).

In the second stage of this investigation the washing step was removed and SACA remained suspended in the dissolution media during the drying process. Fig. 6a–c clearly indicates that the changes seen after washing and drying the spheres are considerably more marked if the systems are left to dry in the dissolution media. Fig. 6a and b indicate that after 60 min in the pH 7.0 and 8.0 media, the spheres have disintegrated. However, in the pH 5.9 media the spheres remain intact (Fig. 6c), even under these more extreme treatment conditions.

4. Discussion

The data presented here clearly indicate medium dependence of the release characteristics and external appearance of stearic acid microspheres. This raises the questions of the macroscopic and molecular basis of the drug release process. In the forthcoming discussion, the first of these may be largely answered in terms of the data presented here, while a limited range of possibilities may be presented for the molecular mechanisms involved.

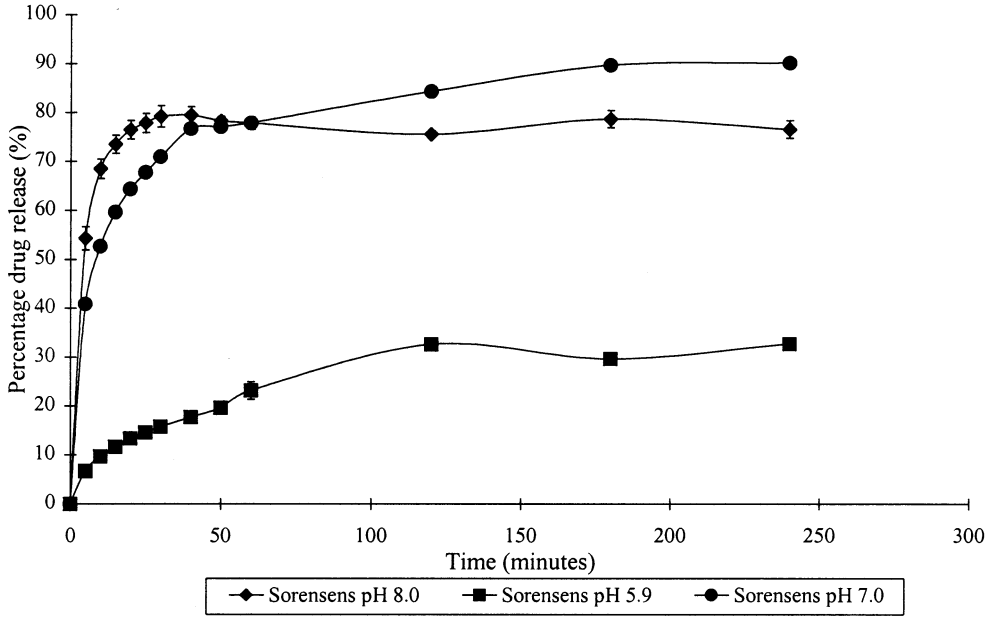

Fig. 3. Dissolution profiles of cefuroxime axetil and SACA in pH 5.9, 7.0 and 8.0 Sorensens modified buffer.

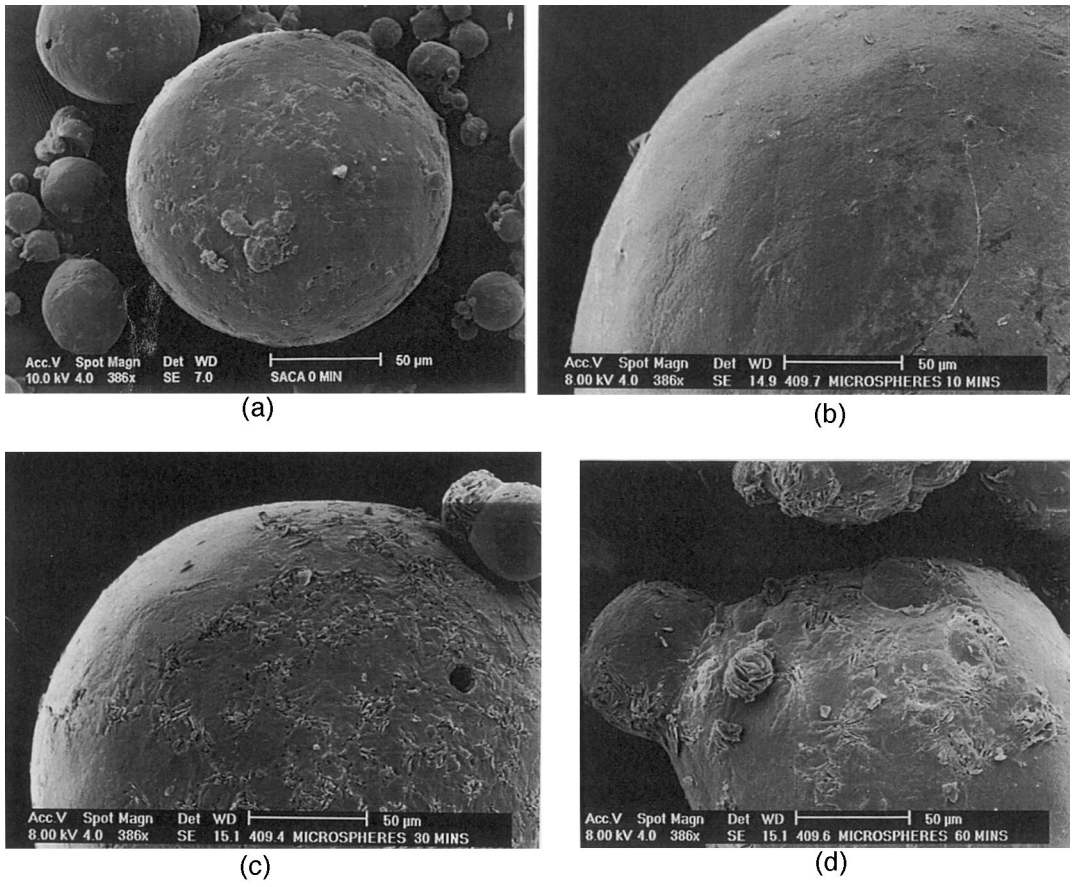

Fig. 4. SEM images of SACA after immersion in pH 7.0 Sorensens modified buffer for (a) 0, (b) 10, (c) 30 and (d) 60 min (washed before drying).

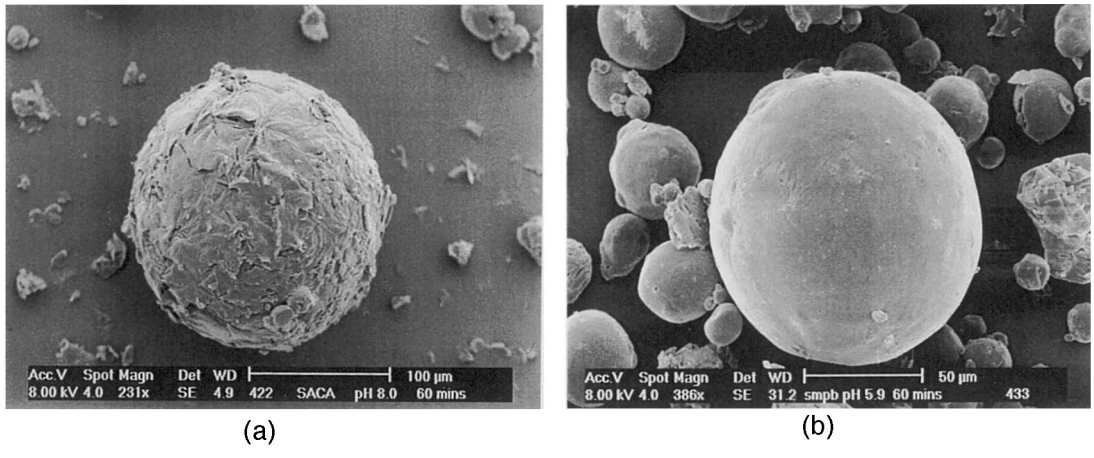

Fig. 5. SEM images of SACA after immersion in (a) pH 8.0 and (b) pH 5.9 Sorensens modified buffer for 60 min (washed before drying).

The SEM studies clearly indicate that the release is at least associated partially with changes in the physical integrity of the spheres, as the systems which show the most marked alterations (pH 7.0 and 8.0) also showed the most rapid release. However, it should also be noted that the pH 5.9 systems, which demonstrated no discernible changes in the appearance of the spheres, showed a considerable level of drug release. Consequently, the 'blistering' of the spheres may be an important contributing process to drug release but may not be the only mechanism involved. The fitting of the data to the Higuchi plots for the distilled water and pH 5.9 media indicates that there is a diffusion process underlying any effects due to disintegration. However, the appearance of the spheres in alkaline media, while clearly showing changes in surface characteristics, do not indicate a change in overall sphere dimensions that corresponds in any discernible manner to the release profile. Consequently, simple erosion of the matrices does not appear to explain the observed release behaviour.

In terms of the molecular mechanisms involved, it is clear that the drug release in pH 7.0 and 8.0 buffers is not simply a function of diffusion through a water insoluble matrix but instead involves a reaction between the stearic acid and the media. Given the similarity in pH values between the distilled water used and the Sorenens pH 7.0 buffer, it is reasonable to suggest that the reaction is dependent on both the pH and the composition of the dissolution fluid. An obvious (but not necessarily correct) explanation is that in alkali conditions the stearic acid is reacting with sodium

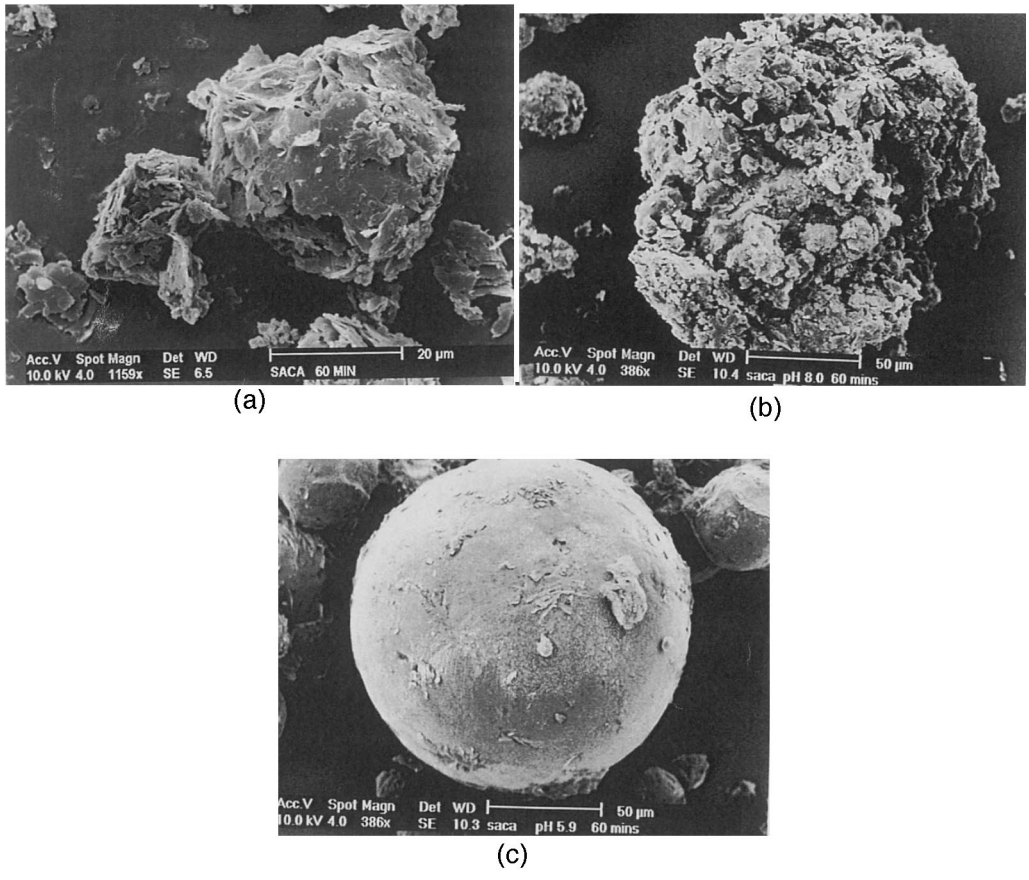

Fig. 6. SEM images of SACA after immersion in (a) pH 7.0, (b) pH 8.0 and (c) pH 5.9 Sorensens modified buffer for 60 min (not washed before drying).

ions in the buffer to form water soluble sodium stearate, leading to the disintegration of the spheres. This hypothesis will be explored in a subsequent communication.

5. Conclusions

The study has indicated that cefuroxime axetil release from SACA is highly dependent on the dissolution media used. In particular, two release mechanisms have been identified. In pH 5.9 Sorensens modified buffer and distilled water (pH 6.8) the release is dominated by a diffusion process, while in pH 7.0 and 8.0 Sorensens modified buffer an additional mechanism is apparent. This involves a reaction between the stearic acid microspheres and the buffer, the molecular mechanism for which this has not yet been identified. Clearly, this knowledge has important implications for understanding not only the behaviour of SACA in liquid formulations but also within the GI tract. More specifically, the data indicate that the rate of drug release will increase markedly when the spheres reach the intestine, hence facilitating the dual requirements of adequate taste masking on ingestion while also allowing release in the lower gastrointestinal tract.

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