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An investigation into the release of cefuroxime axetil from taste-masked stearic acid microspheres. II. The effects of buffer composition on drug release

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Abstract

The influence of buffer composition on the release of cefuroxime axetil from stearic acid microspheres has been investigated, with particular emphasis on establishing the relationship between buffer composition and release at a single pH value. Studies of drug dissolution and release from spheres in pH 7.0 citrate phosphate buffer (CPB), boric acid buffer (BAB), phosphate buffer mixed (PBM) and Sorensens modified phosphate buffer (SMPB) indicated marked differences in release profile from the spheres, with an approximate rank order of SMPB > CPB ≈ BAB > PBM. The role of added sodium was then investigated by examining the release profiles in SMPB and PBM to which sodium ions had been added. Increases in the sodium content from ≈0.11 to 0.2 M were found to decrease the release rate for the SMPB, while increases from 0.007 to 1.0 M sodium in PBM resulted in a maximum release being seen for the systems containing 0.05 M sodium. Studies on surface disintegration, using scanning electron microscopy (SEM) and sodium uptake using flame emission spectroscopy, indicated an interrelationship between medium composition, disintegration and release. The data are discussed in terms of the possible mechanisms associated with drug release from these spheres.

Keywords: Cefuroxime axetil; Flame emission spectroscopy; Microsphere; Stearic acid; Taste masking

1. Introduction

Stearic acid microspheres may be used as a means of taste-masking unpalatable drugs, particularly for administration to children. This approach has been used for the formulation of the antibiotic cefuroxime axetil, whereby the drug particles are coated via a spray chilling process to produce stearic acid-coated cefuroxime axetil or

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SACA. This material is subsequently formulated as a suspension (Zinnat™) which has been shown to exhibit favourable taste-masking properties and bioavailability in children (Powell et al., 1991; Gooch et al., 1993; Shalit et al., 1994). However, the mechanisms associated with the drug release process are not yet fully understood.

A recent study (Robson et al., 1999) has indicated that the drug release rate from SACA is highly dependent on both the pH and the composition of the medium. More specifically, drug release in Sorensens modified phosphate buffer (SMPB) pH 5.9 and distilled water (pH 6.8) was shown to follow diffusion kinetics, with comparatively slow release rates seen. In SMPB pH 7.0 and 8.0 buffer, however, considerably more rapid release profiles were observed. This was correlated with SEM studies which indicated that the spheres underwent partial disintegration in the neutral and alkaline buffers. It was therefore suggested that in these cases the drug release process is associated with the stearic acid coating undergoing an interaction with the surrounding media.

Given the possibility of an interaction between the spheres and the buffer, rather than simple diffusion through an inert lipid matrix, it is necessary to consider the reactions undergone by stearic and related fatty acids. These materials have been extensively studied (Chapman, 1965; Markley, 1967; Pattison, 1968; Hanahan and Kuksis, 1978; Ralston, 1978; Swern, 1979; Gunstone et al., 1986; Small, 1986; Garti and Sato, 1988). Amongst several other reactions, this material may form salts with metal ions (soaps). Classically, the fatty acids are reacted with sodium or potassium hydroxides and carbonates, although salts with zinc, lead, manganese, cobalt or tin may be generated at elevated temperatures. Soaps have a range of properties which render their behaviour distinct from the parent acids. For example, these materials may undergo a series of thermotropic transitions between liquid crystalline states before forming an isotropic melt, while their comparatively high aqueous solubility, due to the strong affinity of the carboxylate group with water, renders them surface active, hence their extensive use in the detergent industry.

It is therefore logical to suggest that soap formation may be involved in the drug release process from SACA. It should, however, be emphasised that fatty acids may potentially undergo a range of interactions with an alkaline medium. For example, the possibility of the formation of acid soaps should be considered. These are crystals that contain fatty acid and metal carboxylate (soap) ion pairs. The proportion of the two components is stoichiometrically discrete and can be described by the general formula $M_xH_yA_z$ where x, y and z are integers ($x+y=z$), M is Na^+ or K^+ and A is an alkanoate ion of the form $CH_3(CH_2)_nCOO^-$ where n is between 6 and 20 (Lynch, 1997). These systems not yet been studied in the context of pharmaceutical dosage forms.

In this investigation, the mechanisms associated with drug release are further examined by studying the influence of buffer composition on the release profile and morphological properties of SACA in a range of buffers with identical pH values. In addition, the influence of sodium content has been studied using the same techniques. Finally, the possibility of an interaction between the microspheres and buffer sodium ions is further investigated by the use of flame photometry as a means of measuring sodium content in the spheres following immersion in the buffers. In this way, it is intended that the study will clarify the nature of the interacting species, thereby aiding identification of the reaction involved.

2. Materials and methods

2.1. Materials, release studies and SEM studies

The materials, release protocol and SEM studies were conducted as described in a previous study (Robson et al., 1999). For the present investigation, a range of pH 7.0 buffers were prepared (Sorensens modified phosphate buffer (SMPB)), citrate–phosphate buffer (CPB), boric acid buffer (BAB), phosphate buffer mixed (PBM)) according to the Pharmaceutical Codex (1994). In the case of BAB the pH was adjusted from 7.2 to 7.0 using hydrochloric acid. The ionic composition of the

above buffers and those used in the previous study (Robson et al., 1999) are listed in Table 1. A further set of pH 7.0 SMPB and PBM were prepared such that they contained varying levels of sodium as indicated in the text. Any minor adjustments in pH were made using HCl or NaOH as appropriate. In order to facilitate comparison with earlier studies, SMPB pH 8.0 buffer and distilled water SACA systems were prepared and utilised in the flame emission spectroscopy studies.

2.2. Flame emission spectroscopy

Flame emission spectroscopy was performed using a Perkin-Elmer PE-280 spectrophotometer (Beaconsfield, UK). An air–acetylene flame was used and the instrument aspirated with water or sample solutions. The water used throughout this study was obtained from a UHQ filtration device which provides water of an ultrapure quality of which the sodium content was found to be negligible. Five calibration standards were prepared from a 100 ppm stock solution of sodium. All glassware was thoroughly washed with UHQ water to remove any contaminants which might interfere with the analysis. Appropriate volumes of stock solution were pipetted into 100 ml volumetric flasks and made up to volume using UHQ water to give solutions of 0.2, 0.4, 0.6, 0.8 and 1.0 ppm sodium. Each solution was inverted several times to ensure adequate mixing.

After an appropriate warm up time and adjustment of wavelength, the calibration standards were analysed using the spectrophotometer. The instrument was first zeroed using distilled water. The 1 ppm stock solution was then aspirated and after a few seconds a reading was taken. These steps were repeated until consistent readings were obtained ($\pm 2\%$). After aspirating each solution, the capillary was wiped with a tissue before immersing it in water, so as to prevent contamination of the blank. Once a steady value had been obtained for the 1 ppm solution, triplicate readings were taken for the other calibration standards, zeroing the machine using UHQ water between each one. A mean reading was calculated for each calibration standard and a calibration graph of emission intensity against sodium concentration was then plotted. This graph was then used to convert emission intensity values for the unknown solutions into percentage sodium contents. Preliminary studies allowed selection of the most suitable storage containers for the various solutions.

To establish the sodium content of the material, it was necessary for the sodium to be in a water-soluble form. This was achieved by combustion of the organic material in the presence of air to leave the inorganic residue. Up to 10 mg of the sample were accurately weighed into a crucible which was placed on a metal tripod. Using a low bunsen flame, the crucible was gently heated from below until the material became black and charred. Heating was continued for a further 4–5 min. until the material became colourless. During this time the organic matter was totally combusted leaving sodium carbonate as the residue. One mililitre HCl was added to the crucible to dissolve the residue and to produce sodium chloride. Once the reaction was complete (2 min standard reaction time), the contents of the crucible were trans-

Table 1
Buffer ion composition expressed as molar values

Buffer	Molarity of components					
	Na^+	K^+	H^+	PO_4^{3-}	$B_4O_7^{2-}$	BO_4^{3-}
SMPB pH 8.0	0.1300		0.0698	0.0666		
SMPB pH 7.0	0.1068		0.0938	0.0668		
SMPB pH 5.9	0.0737		0.1272	0.0670		
CPB	0.3295		0.3055	0.1647		
BAB	0.0060		0.5657		0.0030	0.1886
PBM	0.0070	0.0020	0.0080	0.0060		

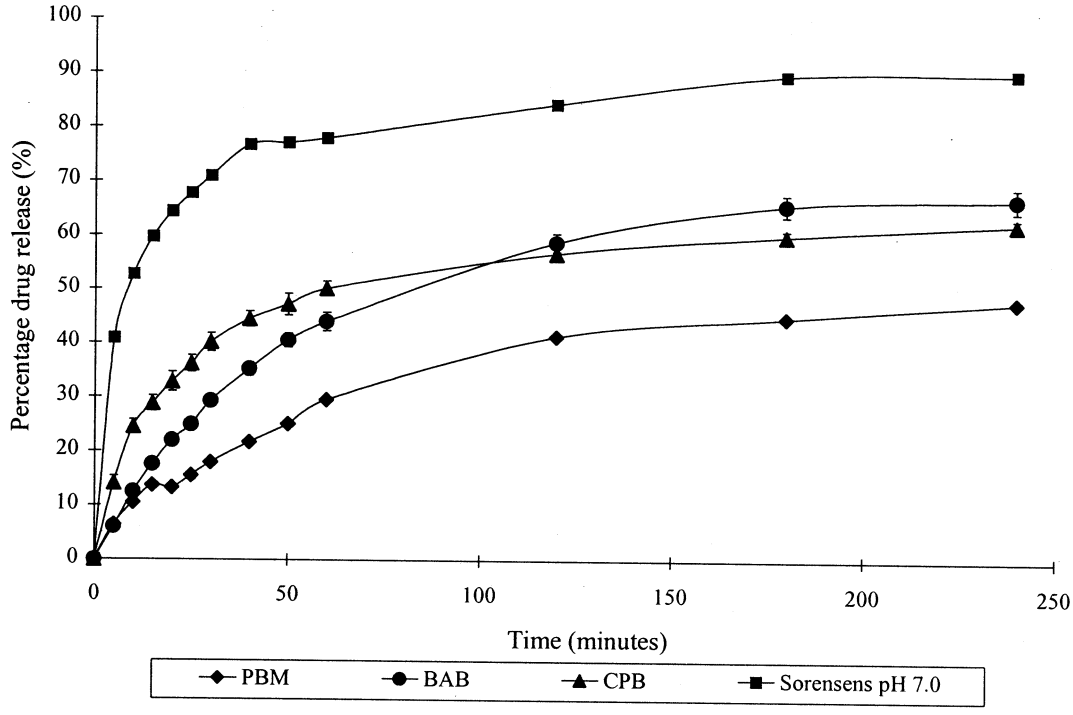

Fig. 1. Release profiles of SACA in citrate–phosphate (CPB), boric acid (BAB), phosphate mixed (PMB) and Sorensens modified phosphate (SMPB) pH 7.0 buffers.

ferred to a 100 ml volumetric flask. The crucible was then thoroughly washed out with distilled water and all washings transferred into the volumetric flask. Finally, the flask was made up to volume with distilled water and inverted several times to ensure adequate mixing of the solution prior to measurement.

3. Results

3.1. Release studies

The release profiles for SACA within the three media and in SMPB pH 7.0 are shown in Fig. 1. Clearly, there are marked differences between the release profiles in the pH 7.0 media, demonstrating the dependence of the release profiles on buffer composition. Of the four pH 7.0 media under study, SMPB yielded a drug release of $70.94 \pm 2.14\%$ in 30 min, while the corresponding figures for the BAB, CPB and PBM were $40.19 \pm 1.16\%$, $29.33 \pm 1.03\%$ and $17.95 \pm 0.23\%$, respectively. It should be noted, however, that while the initial release rate from the CPB systems was greater than that of the BAB, the latter became relatively more rapid as release proceeded. Consequently, one can assign an approximate rank order of SMPB > CPB $\approx$ BAB > PBM.

Examination of Table 1 indicates that H^+ and Na^+ ions are common to all the media, although there was no clear correlation between composition and the rank order of release. Studies on the drug alone showed comparatively small differences in the release rate with the various buffers (SMPB $93.05 \pm 1.88\%$, BAB $90.68 \pm 3.47\%$, CPB $82.22 \pm 3.07\%$, PBM $82.78 \pm 2.71\%$ after 30 min). It is, however, interesting to note that the rank order of the SACA and cefuroxime axetil alone release data in the different buffers is similar, with SMPB showing the fastest release for both systems. It was also noted that after 60 min, when dissolution of the drug alone was effectively complete, the SMPB system showed the highest final

release figure (94.00 ± 1.70%) with BAB, CPB and PBM yielding values of 91.72 ± 3.21%, 79.71 ± 4.20% and 84.43 ± 2.85%, respectively. Previous studies (Robson et al., 1999) have suggested that such incomplete dissolution is a reflection of wetting and sorption effects, hence the differences seen between the release profiles of the SACA samples may be partially associated with such phenomena.

The influence of the sodium content of the media was then investigated. In the first instance, sodium chloride was added to SMPB pH 7.0 to increase the sodium content to 0.2 and 1.0 M. A run was also carried out (total Na^+ content 0.2 M) with the sodium being added in the form of sodium nitrate in order to study the contribution from the anion. The corresponding plots are shown in Fig. 2. It can be seen that the nature of the anion did not appear to influence the release profile of the 0.2 M system, while increasing the sodium molarity of the buffer decreased the overall level of drug release. Percentage drug release values at 30 min were 70.94 ± 2.14% for 0.1068 M (no added sodium), 47.63 ± 1.43% for 0.2 M and 16.30 ± 0.25% for 1.0 M NaCl. The corresponding values for the drug alone, at 60 min (profiles not shown) were 94.00 ± 1.70%, 84.87 ± 4.38%, 83.29 ± 3.19% and 82.96 ± 4.40% for the 0.1068, 0.2(NaCl), 0.2($NaNO_3$) and 1.0 M systems, respectively. Once again, therefore, there does appear to be some correlation between the release behaviour of the SACA and the drug.

As the initial sodium content of SMPB pH 7.0 was relatively high, it was considered of interest to study a system whereby the initial sodium content was lower. A second set of buffers was therefore prepared based on PBM; this was chosen as it contained the lowest amount of sodium (0.007 M) and produced a comparatively low release profile. Fig. 3 shows the percentage released after 30 min for a range of sodium contents. In this case, an initial increase in release rate with sodium content was seen. However, a maximum is seen around 0.05 M Na^+, after which the presence of sodium appeared to have a deleterious effect on drug release. Interestingly, no correlation was seen between the dissolution of the drug alone and the release rate from the SACA for these systems.

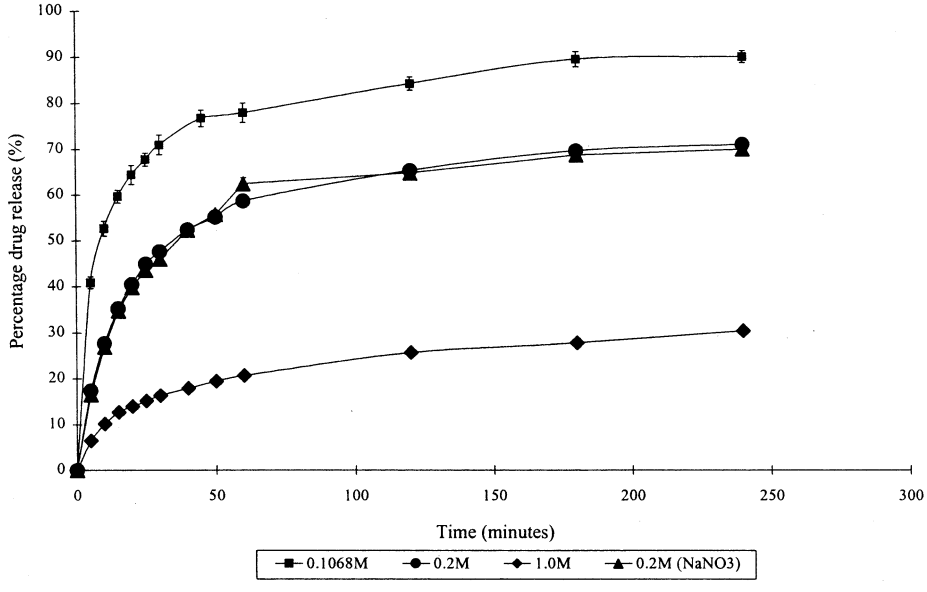

Fig. 2. Release profiles of SACA in SMPB with added NaCl or $NaNO_3$ (total $Na^+ = 0.1068$, 0.2 and 1.0 M).

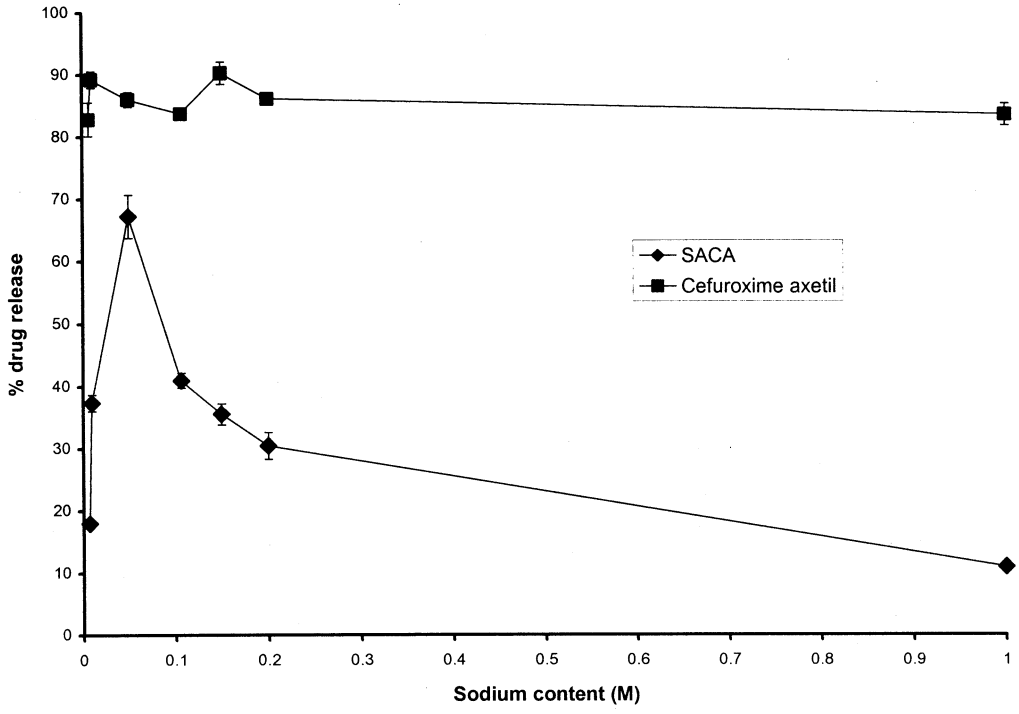

Fig. 3. The effect of added sodium ions on the % cefuroxime axetil released in PBM pH 7.0 after 30 min.

3.2. Scanning electron microscopy

Previous studies (Robson et al., 1999) indicated pH-dependent changes in the integrity of the microsphere surface after immersion in SMPB that correlated well with the drug release behaviour, hence it was of interest to investigate whether a similar correlation with release would be observed using the systems under study here. Fig. 4a to c illustrate particles which had been in contact with CPB, BAB and PBM pH 7.0 buffers for 60 min (the equivalent image for SMPB pH 7.0 has been reported in a previous study (Robson et al., 1999)). CPB produced the greatest surface change out of the three (Fig. 4a), yielding an appearance which was similar to that seen for SMPB pH 7.0. The surface alterations were observed as small striations and a general roughening of the appearance of the spheres. In BAB and PMB, however, the observed changes were comparatively small (Fig. 4b and c). For the systems in PBM pH 7.0, with varying amounts of sodium, surface changes were observed (Fig. 4d). However, given the observation that such alterations were not extensive and varied between particles, it was not possible to draw firm conclusions from the data set regarding the relationship between sodium content and surface disintegration. Overall, therefore, it may be concluded that SMPB and CPB systems showed more marked surface effects, while the BAB and PBM systems demonstrated less obvious changes in surface integrity.

3.3. Flame emission spectrometry

Table 2 records the percentage sodium content of SACA after being removed from a release run in a selection of buffers; this data set includes data from spheres immersed in SMPB pH 8.0 and 5.9 and distilled water in order to allow full comparison with the previous study (Robson et al., 1999). It was noted that the samples in the higher pH SMPB systems showed a greater sodium content than those in the pH 5.9 buffer, with the pH 8.0 system demonstrating a markedly greater uptake than the other systems. It is also interesting to

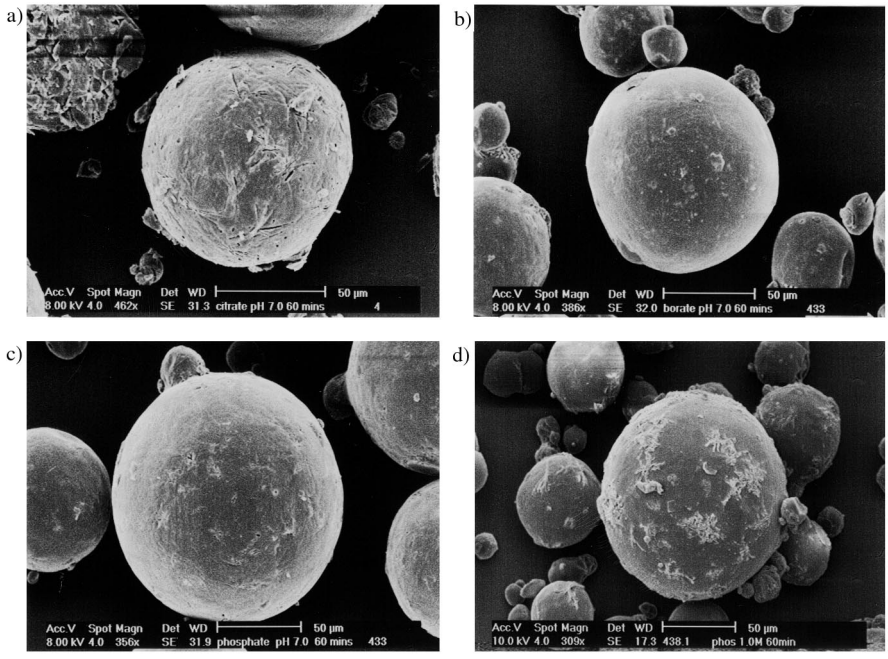

Fig. 4. SEM images of SACA following immersion for 60 min in (a) CPB;(b) BAB;(c) PBM;(d) PBM 1.0 M Na.

note that the pH 5.9 buffer yielded a similar sodium uptake to that seen for the distilled water, the uptake seen in the latter being due to the presence of residual sodium ions. The CPB buffer showed a greater sodium uptake than did the BAB or 0.007 M PBM, hence in these cases the sodium uptake appears to mirror the extent of sphere disintegration and the sodium content of the medium. The data from the systems with added PBM did not show a clear trend with sodium content, other than an initial increase as the Na^+ level was raised. It should be considered when interpreting these results that these spheres have a propensity to exhibit cracks and surface discontinuities, hence the possibility of physical entrapment of sodium within these cracks cannot be fully discounted, despite the rigorous washing steps used. Nevertheless, there does appear to be some correlation between the sodium content of the buffer, the extent of surface disintegration and the sodium uptake in that the SMPB (pH 7.0 and 8.0) and CPB systems have high sodium levels, exhibit disintegration and show high uptake levels. The BAB and PBM systems, however, show a different trend in that the initial sodium levels are lower, less surface disintegration is seen and the uptake is low compared to the CPB and SMPB pH 8.0, although interestingly the figures are comparable to that of the SMPB pH 7.0 systems, hence the correlation between the three parameters is not exact.

Table 2
Percentage sodium content of SACA samples after 10 min immersion in a range of buffers

Buffer	Sodium content (%)
SMPB pH 8.0	1.39 ± 0.23
SMPB pH 7.0	0.17 ± 0.02
SMPB pH 5.9	0.08 ± 0.04
CPB pH 7.0	0.75 ± 0.21
BAB pH 7.0	0.19 ± 0.04
Distilled water	0.07 ± 0.03
0.007 M PBM	0.14 ± 0.01
0.01 M PBM	0.10 ± 0.05
0.05 M PBM	0.24 ± 0.02
0.1 M PBM	0.31 ± 0.03
0.15 M PBM	0.34 ± 0.03
0.2 M PBM	0.35 ± 0.05
1 M PBM	0.25 ± 0.02

4. Discussion

In order to facilitate consideration of the interrelationship between the various parameters under study, it is helpful to summarise the findings of the study. Considering firstly the effect of changing the nature of the buffer, the release studies demonstrated an approximate rank order of SMPB > CPB ≈ BAB > PBM (with CPB showing a faster initial release rate than BAB). The surface disintegration studies showed that the SMPB and CPB systems demonstrated greater surface effects, while the FES investigation also showed greater sodium uptake at least for the CPB system. These two buffers also had the greatest initial sodium content. Overall, therefore, there does appear to be a correlation between release and disintegration, as suggested by Robson et al. (1999), which may also be related to the reaction with sodium ions in the medium. Addition of more sodium, however, has a complex effect. For the SMPB systems, a clear decrease in release rate is seen, while for the PBM systems a maximum is seen with sodium content.

The data therefore supports the hypothesis suggested by Robson et al. (1999) that an interaction is occurring between the microspheres and the buffer which leads to drug release, at least partially as a result of changes to the physical integrity of the spheres. However, the present study has also highlighted the complexity of the nature of that interaction. There is strong evidence for the involvement of sodium ions, although there appears to be an optimal level for maximum release. This may be due to a specific stoichiometry of the interaction, whereby excess sodium causes a change in the equilibrium or kinetics of the reaction so as to decrease release. Alternatively, other factors may be involved. Some evidence has been obtained that drug wetting effects may be of relevance, in that a correlation was seen between the dissolution of the drug alone and the release of the drug from SACA, although the absence of any such correlation for the PMB systems with added sodium would suggest that this factor may be secondary.

5. Conclusion

The study has indicated that the release of cefuroxime axetil from SACA is dependent not only on the pH but also the composition of the media. Evidence has been obtained that the release mechanism is associated with an interaction between the stearic acid and the media that involves the presence of sodium ions. However, the influence of sodium is complex with evidence presented for there being an optimal level for maximum release. It is suggested that this may be due to the interaction having a specific stoichiometry, although it is also suggested that wetting effects may also be involved.

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