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Chemical characterisation of sodium starch glycolate particles

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Abstract

The internal and surface chemical compositions of three sodium starch glycolate (SSG) products, Explotab, Primojel and Vivastar P were studied using scanning electron microscopy (SEM), energy dispersive X-ray analysis (EDX), time of flight secondary ion mass spectrometry (TOF-SIMS) and ^{23}Na nuclear magnetic resonance spectroscopy (NMR). The surfaces of Explotab and Primojel contained very distinct features containing Na and Cl, however, Primojel also contained features which contained Na which may reflect the presence of Na glycolate and/or Na citrates. Vivastar P contained relatively few surface Cl containing features. Analysis of cross-sections of the particles showed that Na appeared to be uniformly distributed throughout the particles of all the products. Additionally, there was a significant concentration of Cl in the periphery of Explotab and Primojel. In the case of Vivastar P, significant levels of Na and Cl were detected in the internal regions of the particles which, together with ^{23}Na NMR, suggests that NaCl is uniformly distributed within Vivastar P. ^{23}Na NMR also suggested that the ratio of organic Na to NaCl was considerably lower in Vivastar P than Primojel and Explotab. Overall, even though all these three products satisfy the pharmacopeial descriptions of SSG, these studies suggest that Primojel and Explotab exhibit different chemical compositions to Vivastar P. Since the three products studied are reported to be prepared from potato starch, the apparent differences in chemical composition probably reflect the different manufacturing processes used, however, batch to batch variations may account for some of the subtle differences. © 2002 Elsevier Science B.V. All rights reserved.

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1. Introduction

The understanding of structure–property relationships of excipients and mixtures of excipients and drugs is crucial for the successful develop-

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ment of new excipients and the understanding of the tableting process. In terms of materials science and chemistry, the characterisation of excipients based on simple inorganic salts, such as dicalcium phosphate, and simple, discrete, low molecular weight organic materials, such as lactose, is relatively straightforward. These low molecular weight materials can be characterised using an array of analytical techniques. The characterisation of higher molecular weight excipients, such as those based on polysaccharides, is more difficult due to their more complex polymer composition. Furthermore, even though these types of materials can be adequately characterised in terms of chemical structure, functional consistency between batches and suppliers cannot be guaranteed.

In addition to chemical composition, polymers are characterised in terms of their molecular weight, molecular weight distribution, crystallinity and solvent content. If the source of the polymer is based on a natural product then characteristics such as impurities and seasonal variations may become important. The situation is further complicated when polymer based excipients are co-processed to produce a new material. One such complex polymer based excipient is sodium starch glycolate (SSG). SSG is a cross-linked substituted potato starch, which is used as a disintegrant in pharmaceutical tablets and capsules. In chemical terms, SSG is described as the sodium salt of a carboxymethylether of starch (Kibbe, 2000). The material is available from several manufacturers under trade names such as Primojel, Explotab and Vivastar. In the cases of Primojel and Explotab, the materials are prepared by the reaction of potato starch with Na chloroacetate (Kibbe, 2000). However, it is not clear whether the potato starch is cross-linked before or after substitution. In the case of Vivastar P, the material is cross-linked via the Na carboxylate groups and starch alcohol groups after substitution (Wroloß, 2000). One surprising fact about SSGs is the range of permitted impurities. Product impurity levels are shown in Table 1 and are typically 5% loss on drying, 5% w/w NaCl and 0.5% w/w Na glycolate. The pharmacopeial specifications of SSG allows for up to 2% w/w Na glycolate, up to 10% w/w NaCl and upto 10% loss on drying (Kibbe, 2000). These pharmacopeial limits imply that a SSG product can be supplied with only 78% SSG polymer in the product and still meet the required specifications. This potential range of impurities makes a direct comparison between SSGs difficult due to the potential inter-batch and inter-brand variations.

Since SSGs may contain significant levels of other materials it can be considered to be a ‘composite excipient’. The disintegration properties of SSG may be a consequence of the substituted starch polymers but other important powder properties such as flow and compactibility will, in part, be due to surface topography and chemistry. SSG can also be described as a co-processed excipient since modified potato starch is (unintentionally) combined with materials such as Na glycolate, Na citrates and NaCl during manufacturing. This further complicates the understanding of the relationship between the source and functionality of SSG.

In order to try to understand the functionality of SSGs and identify any differences between suppliers, the surfaces and cross-sections of particles of three SSGs were studied using scanning electron microscopy (SEM) and energy dispersive X-ray analysis (EDX) and time-of-flight secondary ion mass spectrometry (TOF-SIMS). ^{23}Na Nuclear magnetic resonance spectroscopy (NMR) was also used to investigate the Na environments within the samples.

2. Materials and methods

2.1. Materials

Three fresh ‘as supplied’ commercially available SSGs, Explotab (Penwest, NY, USA. Batch number: E8114), Primojel (Avebe, Holland. Batch number: 99281–5254) and Vivastar P (Retten-

Table 1
Assays of SSGs from data analysis sheets

Assay	Explotab	Primojel	Vivastar P
NaCl	4.0	4.16	6.07
Na glycolate	0.5	0.53	<2.0
Na as SSG	4.2	3.14	2.84

maier, Germany. Batch number: 0005/141–142/73) and potato starch (Roquette Frères, France. Batch number: 682631) were used as supplied.

2.2. Cross-sections

Starch particles were placed in glass vials and epoxy resin suitable for electron microscopy was added (TAAB Premix epoxy resin, TAAB laboratories Equipment Ltd., Aldermaston, UK). The particle/resin mixtures were stirred on a rotator for 2 h then transferred to plastic Beem capsules (Agar Scientific Ltd., Stansted, UK) and the resin polymerised in an oven at 60 °C for 72 h. The samples, now in the form of resin blocks, were cooled and removed from the moulds. Transverse sectioning of particles was achieved by initial trimming of the resin block with a razor blade to reveal particle cross-sections. Freshly broken glass knives were subsequently used in a Reichert OMU3 Ultramicrotome (Leica, Milton Keynes, UK) in order to achieve a smooth block face containing a variety of particle cross-sections. Every effort was taken to reduce the time the materials were exposed to atmospheric moisture.

2.3. Scanning electron microscopy

The resin blocks were mounted vertically on SEM holders, with the smooth block face uppermost, and coated with a thin layer of carbon. SEM was performed using a JEOL JSM6310 scanning electron microscope (JEOL, Tokyo, Japan) equipped with an Oxford Instruments AN1000 X-Ray Analyser (Gatan, Oxford, UK).

2.4. Time-of-flight secondary ion mass spectrometry

Time of flight secondary ion mass spectrometry (TOF-SIMS) data was acquired using a TRIFT II instrument (Physical Electronics, Eden Prairie MN, USA) (Schueler, 1992). A 15 keV Ga^+ ion source was used for high mass resolution spectroscopy. The 600 pA DC primary ion beam was pulsed at 11 kHz frequency with a pulse width of 12 ns. During high spatial resolution imaging, the instrument employed the Ga^+ source at 25 keV with 20 ns pulses. A low energy electron beam was used for charge compensation. The surfaces of the particles were analysed by mounting the particles on sticky tape. The particles were also analysed in cross-section. The cross-sections were prepared as described above.

2.5. ^{23}Na Nuclear magnetic resonance spectroscopy

Solid state ^{23}Na direct-polarisation magic angle spinning (DPMAS) spectra were recorded using a Varian UNITY plus spectrometer (Varian, Palo Alto, USA) with a 5 mm (rotor outside diameter) probe. A 0.2 s recycle delay with a 20° pulse angle (determined using a 1 M solution of NaCl) was used. The sample spin rate was ~ 8.9 kHz and the spectra were recorded at ambient temperature. Spectral referencing is with respect to 1 M NaCl.

3. Results

As previously stated, SSG can be considered to be a composite material which contains starch, modified starch, NaCl, Na glycolate and possibly Na citrates. A simplified structure of SSG is shown in Fig. 1. The assays for SSG, NaCl and Na glycolate from the respective product analysis data sheets are shown in Table 1. Previous studies have reported that even though SSGs exhibit subtle differences in their physical and chemical characteristics the products are, in terms of disintegration and compactibility, pharmaceutically equivalent (Bolhuis et al., 1986; Ferrari et al., 2000).

SSG is a starch derivative. Starch is a complex naturally occurring material which primarily consists of two polymers, amylose, which is linear

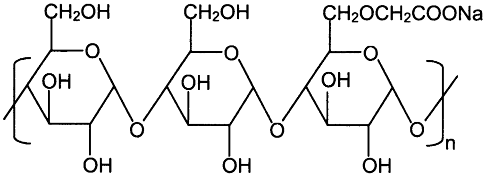

Fig. 1. A simplified molecular structure of SSG.

and amorphous, and amylopectin, which is branched and semi-crystalline (Buléon et al., 1988). Additionally, other impurities such as lipids may be present. When considering the manufacturing process for SSG it is unclear where substitution of the primary starch alcohol groups occurs. Substitution may occur randomly throughout the amylose and amylopectin polymer chains or occur preferentially in one of the polymers. Since the starch polymers are only partly substituted, the modified glucose moieties may be present randomly or as blocks within the amylose and/or amylopectin polymer chains. Substitution may also occur to a greater extent in the periphery of the granules which would have a profound effect on the mechanical properties of the powder.

In order to try to identify any differences between SSGs from various sources, particles and cross-sectioned particles were studied using SEM and EDX and TOF-SIMS. These studies are divided into particle surface composition and particle cross-sectioned composition. Obviously, it would be difficult to evaluate the topography and composition of a particulate material by analysing a relatively small number of samples, however, these techniques may afford some information concerning the chemical composition of any particle surface features.

3.1. Particle surface composition

Samples of Explotab, Vivastar P and Primojel were studied using SEM to investigate the surface morphology. EDX and TOF-SIMS were employed to try to investigate surface chemical compositions.

3.1.1. SEM surface analysis

Typical low magnification SEM images of Explotab, Primojel and Vivastar P have, as expected, suggested that the surfaces of Explotab, Vivastar P and Primojel contained particles of similar macroscopic geometries which reflects the particle sizes of the parent potato starches of the range of 10–100 μm (Kibbe and Rowley, 2000). Additionally, examination at higher magnification suggested that the surfaces of the particles contained small, micron sized, features: the apparent coverage being similar for Primojel and Explotab whereas Vivastar P particles contained relatively few such features.

3.1.2. EDX surface analysis

Low magnification EDX analysis of particles of Explotab, Vivastar P and Primojel suggested the three products contained, as expected, Na and Cl. The EDX count for Cl was greater than that for Na. Many particles were examined in each product to give an indication of the typical surface structures present. As typical examples, areas of the particles shown in Fig. 2 were analysed at high magnification using EDX spot analysis. The results from the analysis are shown in Table 2.

In the case of Explotab, the small platelet structures contained significantly greater levels of Na and Cl than the 'global' counts; the Cl count being greater than that for Na. These platelet structures are probably NaCl, since NaCl is de-

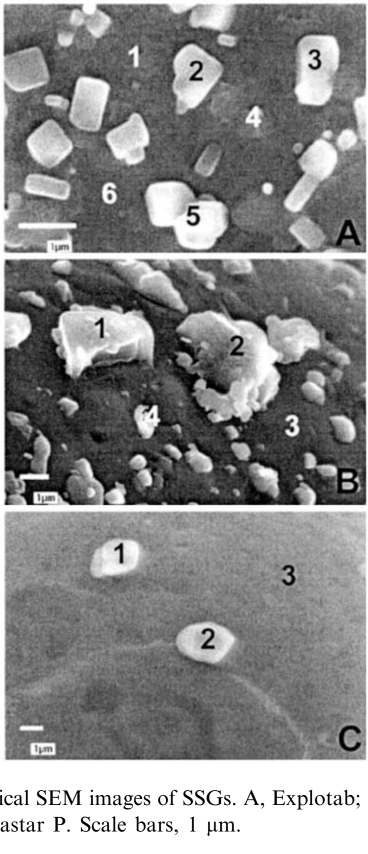

Fig. 2. Typical SEM images of SSGs. A, Explotab; B, Primojel and C, Vivastar P. Scale bars, 1 μm.

Table 2
EDX spot count analysis of SSGs of areas in Fig. 2

Area	Explotab		Primojel		Vivastar P	
	Cl	Na	Cl	Na	Cl	Na
1	41	41	66	116	479	4
2	245	75	33	114	565	6
3	520	115	49	35	16	2
4	33	22	483	121		
5	278	96				
6	61	45				

10 KeV, count time, 100 s.

scribed as being present in the SSGs in the product descriptions and has been identified in Explotab and Primojel but not in Vivastar P using X-ray diffraction (XRD) (Edge et al., 2001). In the case of Primojel, the elemental differences between the platelets and less regular structures were less pronounced. Regions of the surfaces of Primojel were found which contained higher levels of Na than Cl. Similar areas were identified in the surfaces of Explotab particles, however, these features were fewer in number than those found in Primojel. Additionally, features were also found in the surface of Primojel particles which contained higher levels of Cl which is similar to data obtained for Explotab. The surfaces of Vivastar P contained few features. The EDX analysis of the micron sized features on the surfaces of Vivastar P particles showed high Cl content, which again is similar to Explotab. This observation is important since the NaCl in Vivastar P is reported as being present in a comparable concentration to Explotab and Primojel (Table 1).

The identity of the material in some of the surfaces of SSGs is unclear although these products do contain by-products other than NaCl (Table 1). These Na rich features probably represent Na glycolate, which is described in the product literatures, and/or disodium citrate, which has been reported to be present at concentrations of 0.8 and 3.3% w/w for Primojel and Explotab respectively (Bolhuis, 1986). Potato starch particles (not shown) were, as expected (Kibbe and Rowley, 2000), significantly smoother in appearance compared with SSGs suggesting that the topographical features in SSGs are a consequence of the manufacturing processes.

3.1.3. TOF-SIMS surface analysis

Analysis of the SSG particles using TOF-SIMS analysis allows the chemical composition of the surfaces (1–2 nm deep) of the particles to be evaluated. The positive TOF-SIMS spectrum of Explotab is shown in Fig. 3. The low mass range shows fragments for hydrocarbon species (C_xH_y), as would be expected for a starch type sample (Vickerman et al., 1999). Significant peaks are also observed for Na containing species (Na, Na_2, Na_2OH, and Na_2Cl). The mass range *m*/*z* 100–

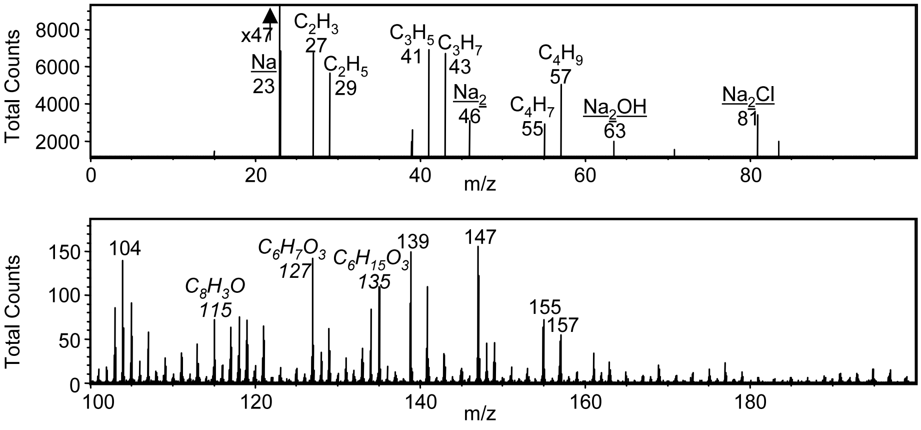

Fig. 3. (+)TOF-SIMS spectrum of the surface of Explotab particles. Characteristic masses for starch are labelled with chemical formulas $C_xH_yO_z$. Characteristic masses for NaCl are underlined.

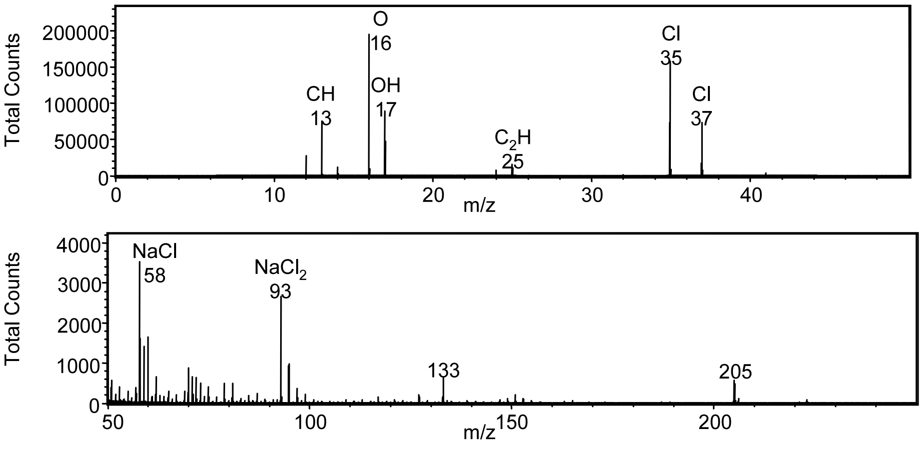

Fig. 4. (−)TOF-SIMS spectrum of the surface of Explotab particles.

200 shows peaks characteristic of starch (*m*/*z* 115 (C_8H_3O), 127 ($C_6H_7O_3$), 135 ($C_6H_{15}O_3$) or cellulose (Belu et al., 2001) as well as significant peaks at *m*/*z* 139 and 147. No other peaks were detected in the high mass range.

The positive and negative ion TOF-SIMS spectra of the SSGs contained signals similar to those obtained for the pure starch control. The spectra of the Explotab particles, however, contain additional signals for Na and Cl containing species, which suggests the presence of NaCl. The negative ion TOF-SIMS spectrum of Explotab is shown in Fig. 4 and is dominated by peaks for Cl, NaCl and $NaCl_2$.

The spectra of Vivastar P and Primojel were similar to those of Explotab. However, the relative intensities of the peaks representing Na and Cl containing species were much smaller. Consequently, the negative spectra of Vivastar P and Primojel were dominated mainly by organic starch-like species: O (*m*/*z* 16), C_2H_5O (*m*/*z* 45), $C_3H_3O_2$ (*m*/*z* 59) and $C_3H_3O_2$ (*m*/*z* 71).

The data in Table 3 shows the relative concentrations of Na and Cl on the surfaces of the SSGs as determined by TOF-SIMS. The amount of Na on the surface of Explotab particles is approximately ten times higher than that for the surfaces of Vivastar P and Primojel. The amount of Cl is also approximately ten times higher for Explotab compared with Vivastar P and Primojel. The comparisons assume that the SSG particles are basically of the same composition, and the secondary ion yields of the species of interest (Na_2, ^{37}Cl) are the same for each sample. The data suggests that NaCl dominates the surface chemisty of Explotab compared with Primojel and Vivastar P. Furthermore, the results show that the peak ratio for Cl is almost ten times higher than the peak ratio for Na in Explotab. This does not reflect absolute concentration of Na and Cl in the sample because the values have not been adjusted for differences in secondary ion yields. However, the results for Explotab can be compared with those obtained for Vivastar P and Primojel, where again the peak ratio for Cl are approximately ten times higher than those of Na. This suggests that the relative amount of Na to Cl in all of the samples is similar. The data is in general agreement with the EDX results, where the apparent NaCl coverage is Explotab > Primojel > > Vivastar P, and previous XRD studies (Edge et al., 2001) which suggested the NaCl content in the surface is Explotab ≈ Primojel with no NaCl being detected in the surface of Vivastar P. It is clear from the TOF-SIMS, EDX and previous XRD studies that NaCl, as micron sized crystals, is not present in the surface of Vivastar P at the same levels as Explotab and Primojel. This observation contradicts the bulk analysis data in Table 1 which suggests a comparable concentration of NaCl in the three SSGs.

Table 3
Relative concentrations of Na and Cl on the surfaces of SSGs determined by TOF-SIMS

Element	Mass values	Assignment	Peak ratio		
			Explotab	Vivastar P	Primojel
Sodium	$46^+/27^+$	Na_2/C_2H_3	0.49	0.05	0.06
Chlorine	$37^-/25^-$	$^{37}Cl/C_2H$	3.78	0.48	0.39

Note, the values do not reflect the absolute concentration of Na or Cl, since they have not been adjusted by sensitivity factors.

The elemental distribution of Na and Cl in the surfaces of SSGs is exemplified by using TOF-SIMS imaging. The Cl images for Explotab and Vivastar P are shown in Fig. 5. The distribution of Cl almost completely covers the Explotab particles. Whereas for the Vivastar P, the Cl is concentrated in small micron sized locations across the surfaces of the SSG particles. Overall, the analysis of the surfaces of SSG particles using EDX and TOF-SIMS suggests that Na and Cl species are in the surfaces of these products. However, the three products appear to contain different levels of surface NaCl. The location of NaCl in particles will be an important factor for determining particle characteristics. In order to determine the distribution of NaCl and the chemical composition of the SSGs cross-sections of particles were studied using EDX and TOF-SIMS.

3.2. Particle bulk composition

The bulk chemical composition of particles will be important in determining the moisture sorption and compressibility of the SSGs. The reaction of potato starch with Na chloroacetate is performed in the solid state since the starch granules would not be expected to dissolve during the process. Since a chemical assay gives only an average sample content it is unclear as to whether the whole starch granule is modified. The chemical analysis of cross-sectioned granules may afford information concerning the degree of substitution of the starch polymers during the process and whether there is any selective substitution in the starch granules.

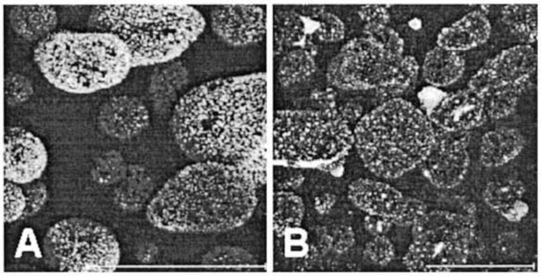

Fig. 5. TOF-SIMS images of Cl for A, Explotab and B, Vivastar P particles.Scale bars, 100 μm.

Samples of the SSGs were mounted in a special resin and cross-sectioned. Samples were studied using SEM/EDX and TOF-SIMS.

3.2.1. SEM/EDX analysis of cross-sections

A typical SEM micrograph of cross-sectioned Explotab particles is shown in Fig. 6. It can be seen from Fig. 6 that the starch granules are clearly visible in the resin matrix. Typical SEM/EDX images of cross-sectioned Explotab, Primojel and Vivastar P are shown in Fig. 7. The images in Fig. 7 suggest that Na is present throughout the SSGs. The presence of Na can only be due to NaCl, Na carboxymethylether substituted starch, Na glycolate or Na citrates. There is no assay for disodium citrate or Na chloroacetate supplied with the product analysis sheets for Explotab, Primojel and Vivastar P. In the cases of Explotab and Primojel, since there is little contrast in the Cl counts between the resin, which contains no Cl, and particles it is reasonable to assume that the Na in the internal regions indicates the presence of substances other than NaCl. It is possible that Na glycolate or Na citrates may be responsible for the internal Na implying that these by-products have not been completely washed out from the samples, as exemplified by the product analysis sheets. This is not true for Vivastar P where Na and a significant amount of Cl is present in the

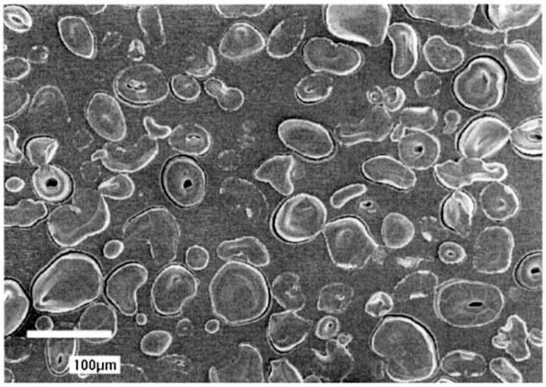

Fig. 6. Typical low magnification SEM micrograph of cross-sectioned Explotab particles in resin. Scale bar, 100 μm.

internal regions of the particles. This observation is an explanation as to the location of NaCl in Vivastar P and must reflect the different manufacturing process used (Wroloß, 2000).

If the internal Na is mainly due to Na carboxymethylated starch the SEM/EDX study suggests that the substitution reaction occurs throughout the starch granules implying that the degree of substitution represents an average for all the polymer chains and not the granule. Additionally, Na glycolate can only be present as a consequence of the migration of Na chloroacetate into the particles again suggesting that substitution occurs throughout the granule. This is an important observation since variations of glucose substitution across the granule would be expected to affect the moisture sorption (disintegration) properties, the compressibility and compactibility.

The data in Fig. 7 also suggest the presence of Cl in the periphery of Explotab and Primojel. This, again, could be further evidence for the presence of NaCl in the surfaces of these materials as observed using EDX, surface TOF-SIMS and previous XRD studies. In order to further characterise the internal composition of the SSGs and try to identify the chemical species responsible for the internal Na, the samples were mounted in resin and cross-sectioned and analysed using TOF-SIMS.

3.2.2. TOF-SIMS analysis of cross-sections

The TOF-SIMS images of the cross-section of Explotab are shown in Fig. 8 and give some insight into the high concentration of Na and Cl found at the surface. The OH image in Fig. 8 highlights the regions of the particles examined in the (−)TOF-SIMS experiments, and, as expected, shows a homogeneous distribution of OH groups across the particles. The Cl image, in comparison, shows a high concentration of Cl around the periphery of the Explotab particles, in micron sized clusters. A more detailed analysis of the Explotab Cl TOF-SIMS image suggested that there is also a relatively low concentration of Cl across the sample. This may be due to a low concentration of NaCl or possibly Na chloroacetate. The (+)TOF-SIMS Na image was acquired in a separate experiment and the area of analysis is shifted by approximately 100 μm in the *x* direction. The Na image also shows micron sized clusters of Na at the periphery of the SSG particles, but it maintains a relatively higher concen-

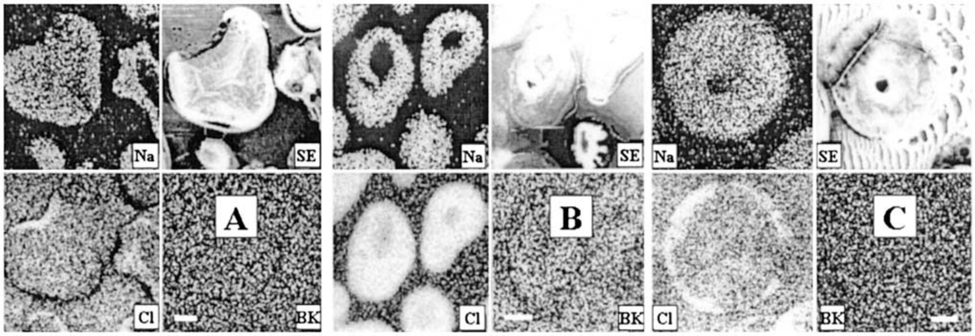

Fig. 7. EDX elemental maps of cross-sectioned SSG particles. A, Explotab; B, Vivastar P and C, Primojel. Scale bars, 10 μm.

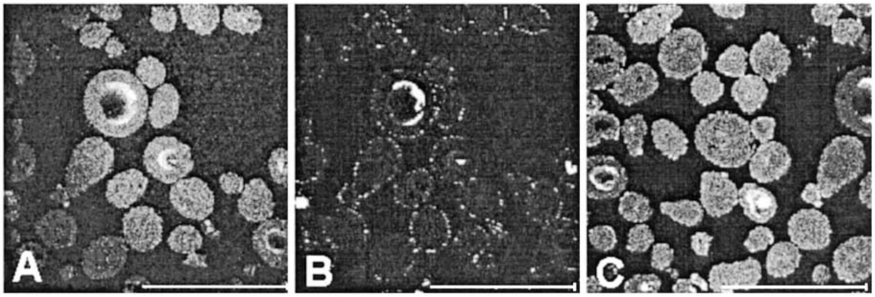

Fig. 8. TOF-SIMS images of cross-sectioned Explotab particles. A, OH; B, Cl and C, Na. Scale bars, 100 μm.

tration of Na across the core of the SSG particles. This suggests that NaCl clusters are located on the outer surface of the Explotab SSG particles and that other Na containing substances are found in the core of the SSG particles which is in agreement with the EDX study.

The cross-sections of particles of Primojel were examined using TOF-SIMS. Again, as expected, a fairly homogeneous distribution of OH was observed across the particles. The distribution of Na, Cl and m/z 351 are shown in Fig. 9 and can be compared with images of the Explotab particles in Fig. 8. For the Primojel particles, however, the Cl image shows Cl to have its highest concentration in the core of the particles. The Cl image suggests that the Primojel particles do not have the high concentration of NaCl particles at the surface which was observed from the Explotab images. The Cl TOF-SIMS images of Primojel also suggests a relatively high concentration of Cl in the centre of the particles. Chlorine was present in the internal regions of Explotab, however, peripheral Cl was present in a greater relative concentration. The source of the Cl in the core of the Primojel particles is not known. The Na image further suggests the absence of NaCl particles at the surface and shows a fairly homogeneous distribution of Na across the entire particle.

The most striking feature of Fig. 9 is the image of species at m/z 351. This species is located mainly in the outer 10 microns of the particles. Spectra can be obtained from regions of interest, to allow further evaluation of the chemical composition of specific regions. The (+)TOF-SIMS spectrum from the outer 10 μm of the Primojel particles is shown in Fig. 10. This spectrum was very different from that of Explotab (not shown) and the peaks in the high mass range at 307, 339, and 351 suggest the presence of a sodium containing molecule. If the parent ion is m/z 351 then the peaks at 339 and 307 represent losses of Na atoms: the mass difference of m/z 22 suggests the loss of Na (−23) and the addition of H (+1). A possible chemical formula for m/z 351 is $C(CH_2CO_2Na)_3(CH_2CH_2COO_2Na)$, which is similar to a Na citrate type species. These signals are less significant in the spectrum of the inner core of the particles. This suggests that this Na containing species is present in higher concentrations in the outer edge of the Primojel particles. Unfortunately, Vivastar P did not produce flat cross-sections and was not studied.

3.2.3. ^{23}Na NMR spectroscopy

In order to gain an insight into the various Na containing species the SSGs were subjected to ^{23}Na NMR spectroscopy. The ^{23}Na DPMAS spectra of Explotab, Primojel and Vivastar P are shown in Fig. 11. The signal at 6.7 ppm is from NaCl and was confirmed by the analysis of pure, solid NaCl. This signal confirms the presence of NaCl in Vivastar P. The second, broad signal between 0 and −40 ppm is more difficult to assign. It may be attributable to the presence of Na carboxymethylether starch. Variations in the local environments within high molecular weight polymers tend to give rise to broad signals such as this. However, Na citrates or Na glycolates could also contribute to the signal. The total, absolute intensity in the spectra shows that there is a similar amount of Na in each sample which is in agreement with the data in Table 1. The proportion of Na in an NaCl environment can be estimated from the relative signals within the spectra. This suggests the order Vivastar P > Explotab ~ Primojel which again is in agreement with the data in Table 1.

4. Conclusions

This study suggests that TOF-SIMS and SEM/EDX are valuable tools for investigating the composition of SSGs. The surface and bulk EDX and TOF-SIMS analysis and ^{23}Na NMR spectra of the particles suggested that Vivastar P is subtly different in terms of surface and bulk Na and Cl distribution compared with Explotab and Primojel. The EDX analysis identified distinct areas of Primojel and Explotab which contained relatively high levels of Na and Cl and features which contained high levels of Cl in the surface of Vivastar P. The surface coverage of these Na and/or Cl containing features, as determined by EDX, was significantly lower for Vivastar P compared with Explotab and Primojel. The micron sized Na distribution of all the product surfaces suggest Explotab ≈ Primojel > > Vivastar P. The use of TOF-SIMS confirmed the observations of EDX in that the relative number of the larger micron sized Na and Cl containing features was considerably lower for Vivastar P. However, TOF-SIMS also suggested that Vivastar P and Primojel exhibited similar overall relative surface Cl and Na contents which were considerably lower than those detected in Explotab. This probably reflects the sampling depths of the techniques. The EDX technique analyses approximately 1 μm into the surface whereas TOF-SIMS has a sampling depth of approximately 1–2 nm.

These results, together with the previous XRD analysis (Edge et al., 2001) give an insight into the surface composition of SSGs. XRD, which analyses to a depth approximately of 1 μm for crystalline materials of particle size > 0.1 μm, showed NaCl to be present in Explotab and Primojel and absent in the surface of Vivastar P. This is supported by the identification of micron sized Na and/or Cl containing features in the surfaces of these two products by EDX and TOF-SIMS. A relatively small number of micron sized features, possibly NaCl, were found in the surface of Vivastar P which were presumably too insufficient to be detected by XRD. These data suggest that the majority of the NaCl in Explotab is present in the surface of the particles. For Primojel, again most of the NaCl is present in the surface of the particles, however, significant amount of organic species are present in the surface which results in lower than expected Na and Cl levels by TOF-SIMS. In the case of Vivastar P, XRD suggested that NaCl was absent in the surface of this product. However, TOF-SIMS suggested that the relative levels of surface Na and Cl are comparable to Primojel. This suggests that NaCl may be present in the surface of Vivastar P as small crystals which are not detected by XRD. However, there is the possibility of some of the surface features being removed during the mixing of the particles in the resin.

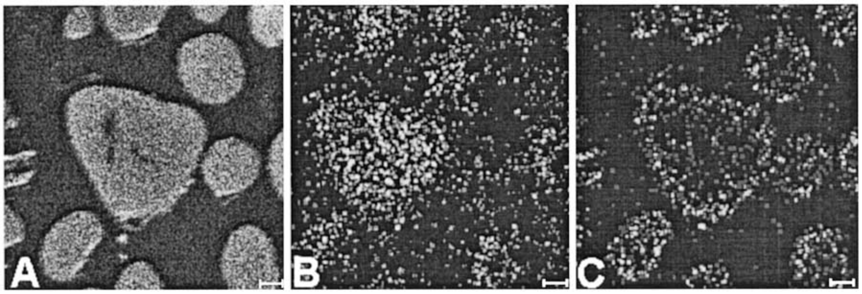

Fig. 9. TOF-SIMS images of cross-sectioned Primojel particles. A, Na; B, Cl and C, m/z 351. Scale bars, 10 μm.

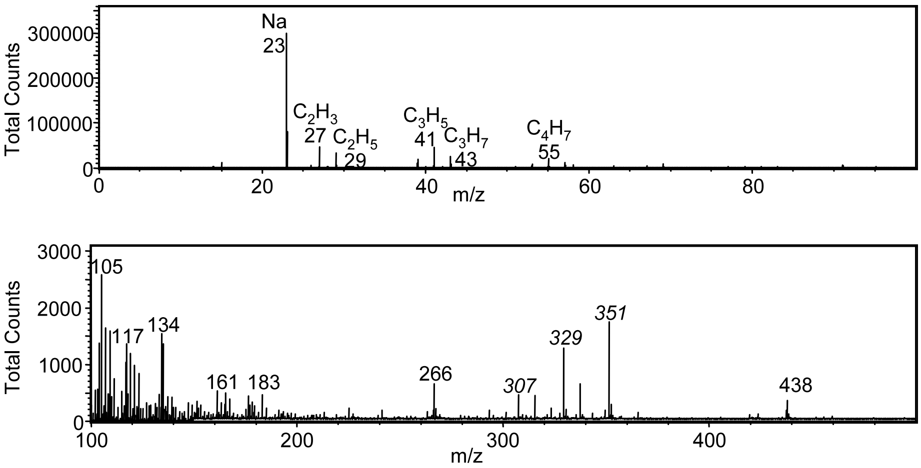

Fig. 10. (+)TOF-SIMS spectrum of outer region of cross-sectioned Primojel particles. $m/z = 117$, 161, 183 are observed throughout the particle and are most likely due to aromatic species of $C_xH_yO_z$.

Analysis of cross-sections of the particles using these techniques gives an indication of the chemical species throughout the samples. The results suggested that Na was uniformly distributed throughout the particles of all the products. However, areas containing Cl were found in the periphery of Explotab and Primojel using EDX. Additionally, TOF-SIMS suggested that Cl was present in relatively minor concentrations in the inner regions of Explotab and Primojel which may reflect the presence of processing by-products. Interestingly, EDX showed a significant level of Cl across Vivastar P particles suggesting that the NaCl by-product in Vivastar P is present within the granules as opposed to Explotab and Primojel where the salt is apparently primarily located at the particle surfaces. The presence of NaCl in the Vivastar P particles was confirmed using ^{23}Na NMR which also suggested a lower ratio of organic Na to NaCl in Vivastar P compared with Primojel and Explotab.

These materials are manufactured by different companies and satisfy the pharmacopeial descriptions of SSG. The particles of each product all appear to exhibit uniform Na concentrations across the granules. However, there are subtle differences in the surface compositions of the products which may be important when flow and compactibility are considered. However, since SSGs are typically used at 1–4% w/w levels in formulations, these apparent differences in composition may not have any significant affect on the properties of a formulation. However, if SSGs are used at higher levels, the surface and internal topography and structure may influence properties such as flow and compactibility. The distribution of molecular species across the cross-section of an SSG particles was demonstrated in the

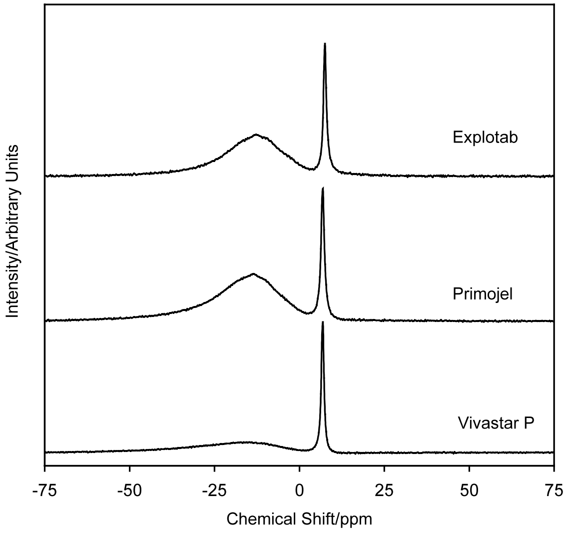

Fig. 11. ^{23}Na DPMAS spectra of Explotab, Primojel and Vivastar P.

analysis of Primojel where the particle was shown to contain distinct differences in chemical composition in the outer 10 μm region. However, batch to batch variations and differences in the structure of the parent potato starches may account for some of the subtle differences in the internal and surface structures of the particles.

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