

Superdisintegrants: introduction to chemistry and performance



The pursuit of excipient excellence

Summary

The superdisintegrants Primojel[®] (sodium starch glycolate) and Primellose[®] (croscarmellose sodium) are cross-linked and substituted polymers of glucose. The degree of cross-linking and substitution are important factors in determining the effectiveness of these materials as superdisintegrants. In the case of Primojel[®], the selection of the type of starch is also a key factor, and in the case of Primellose[®], particle size is important. This introduction to the chemistry and performance of superdisintegrants describes how the synthetic processes have been optimised to ensure peak performance of these two materials.

1 Introduction

The two commonest superdisintegrants, sodium starch glycolate (SSG) and croscarmellose sodium (CCS) are both synthesized from polymers of glucose, namely starch in the case of SSG and cellulose in the case of CCS. The chemical modifications in both cases are introduction of carboxymethyl sodium groups and cross-linking of the polymer backbone, although there are differences in the details of these modifications.

The European Pharmacopoeia and USP/NF differentiate sodium starch glycolate Types A, B and C as summarized in Table 1. Primojel[®] complies with the monograph for Type A.

Table 1: Properties of sodium starch glycolate.

| Test | Type A | Type B | Type C |
|----------|-------------|-------------|-------------|
| pH | 5.5-7.5 | 3.0-5.0 | 5.5-7.5 |
| NaCl | Max 7% | Max 7% | Max 1% |
| LOD | Max 10% | Max 10% | Max 7% |
| Assay Na | 2.8% - 4.2% | 2.0% - 3.4% | 2.8% - 5.0% |

Glucose may take the α - or the β - form depending on the orientation of the hydroxyl group at position 1 (see Figure 1 for the numbering scheme).

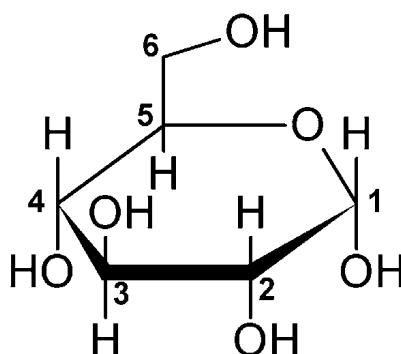


Figure 1: Glucose

Starch contains two polymers of α -glucose, namely amylose (a linear polymer of α -glucose linked at carbon atoms 1 and 4, having an average degree of polymerization of 4,000 in potato starch) and amylopectin (short linear chains linked between carbon atoms 1 and 4, branched with additional links between carbon atoms 1 and 6, and having an average DP of 2,000,000). Potato starch contains approximately 21% amylose and 79% amylopectin. A section of an amylopectin molecule showing the 1,4- and the 1,6- links is shown in Figure 2.

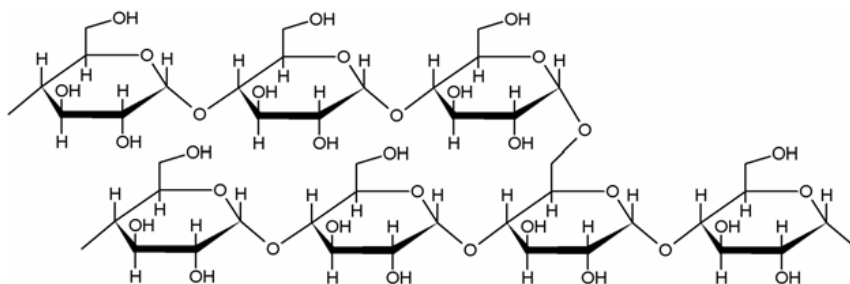


Figure 2: A section of amylopectin.

Cellulose consists of a linear polymer of β -glucose, linked through carbon atoms 1 and 4. A section of the cellulose molecule is shown in Figure 3.

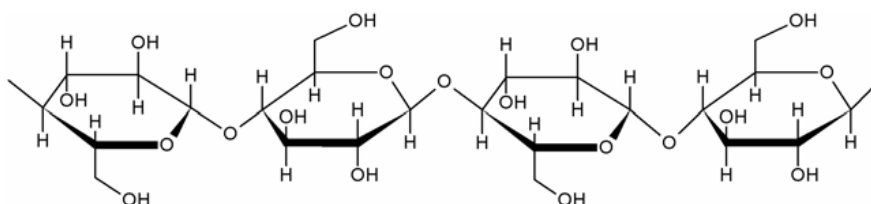


Figure 3: A section of cellulose.

The effect of introduction of the large hydrophilic carboxymethyl groups is to disrupt the hydrogen bonding within the polymer structure. This allows water to penetrate the molecule and the polymer becomes cold water soluble. The effect of the cross-linking is to reduce both the water soluble fraction of the polymer and the viscosity of a dispersion in water. The optimum balance between the degree of substitution and the extent of cross-linking allows for rapid water uptake by the polymer without the formation of a viscous gel that might impede dissolution.

This article discusses the balance of these two modifications for both Primojel[®] and Primellose[®]. It also discusses other factors that can be controlled in synthesis, and that are important for performance.

2 Primojel[®]

2.1 Selection of starch source

It is possible to synthesise sodium starch glycolate from a wide range of native starches, but in practice potato starch is used as it gives the product with the best disintegrating properties⁽¹⁾. The European Pharmacopoeia specifies potato starch as the basis of types A and B. Bolhuis and co-workers synthesised sodium starch glycolate from seven varieties of starch⁽²⁾ and tested the products for water uptake and disintegration performance in placebo tablets. They found that sodium potato starch glycolate had by far the highest water uptake rate and gave the fastest disintegration when used in lactose placebo tablets. In contrast, the disintegration of dicalcium phosphate placebos containing experimental SSG's was not greatly affected by starch source, the disintegration of tablets made from this insoluble material being more related to disintegrant swelling and force development rather than water penetration.

2.2 Cross-linking

After selection of the appropriate starch source the second step in the synthesis of Ph. Eur. types A and B is cross-linking of the potato starch. This is typically carried out using an FDA approved starch esterifying agent⁽³⁾ such as sodium trimetaphosphate or phosphorus oxychloride in alkaline suspension. Both of these agents form cross-linked starch phosphate according to the reactions shown in Figure 4.

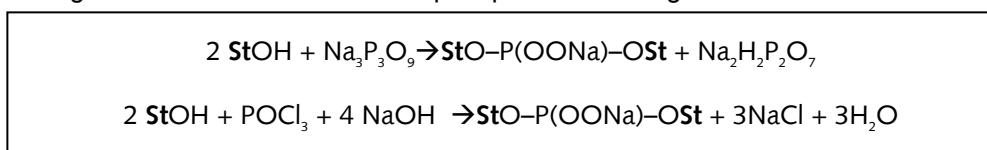


Figure 4: Starch cross-linking (in these equations *St* is starch).

There is no test in the official monographs that relates to the degree of cross-linking, but it is low. The phosphorus content of potato starch is increased by approximately 0.3 mg/g after cross-linking, corresponding to roughly 1 phosphate ester group per 500 anhydroglucose units.

2.3 Substitution

Cross linked potato starch is substituted using chloroacetic acid or sodium monchloroacetate in an alkaline alcoholic suspension according to Williamson's ether synthesis. The deprotonated starch nucleophile substitutes chlorine in the sodium chloroacetate as shown in Figure 5.

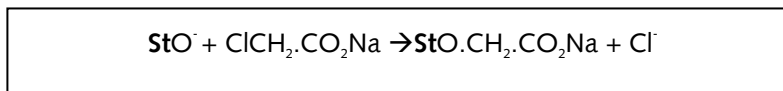


Figure 5: Carboxymethylation of starch

On completion of substitution, the reaction mixture is neutralized and the sodium starch glycolate is isolated and dried. The degree of substitution in sodium starch glycolate is in the range 0.23 to 0.32, compared to a maximum possible value of 3 (ie all three hydroxy groups in the anhydroglucose units would be substituted). Thus approximately 1 anhydroglucose unit in every 4 is carboxymethylated. An example section of Primojel[®] crosslinked with phosphate groups is shown in Figure 6.

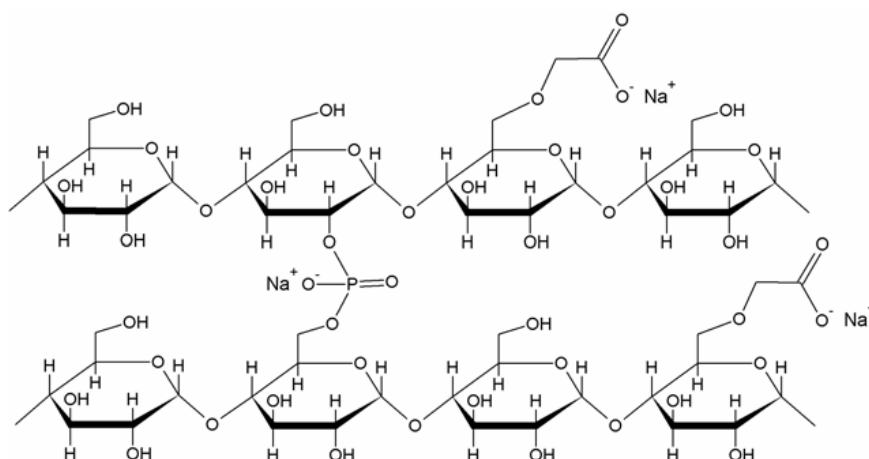


Figure 6: A representative section of Primojel[®]

The degree of substitution is not explicit in the USP/NF or the Ph. Eur. monographs, but it is related to the assay value (ie the sodium content of the dried and alcohol washed substance). Sodium chloride, formed during the synthesis, is removed from the product by washing with 80% ethanol before assay, and remaining "bound" sodium of the carboxymethyl sodium groups is titrated against perchloric acid. The relationship between the assay for sodium and the degree of substitution is shown in Figure 7.

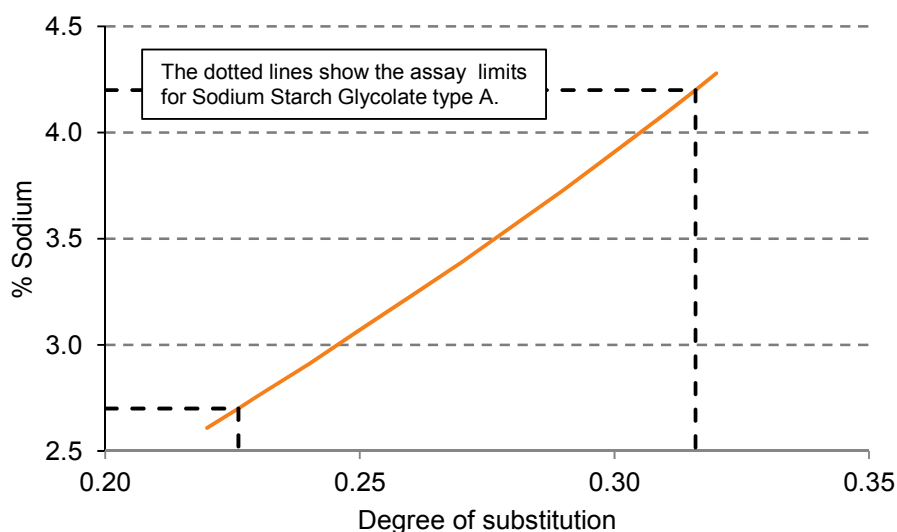


Figure 7: The relationship between assay and degree of substitution of SSG.

The apparently lower assay, and hence degree of substitution, in sodium starch glycolate Type B Ph. Eur. (see Table 1) is an artifact of the test. The lower pH of the product means that not all the carboxymethyl groups are in the form of the sodium salt. By contrast in the USP/NF assay, the sodium starch glycolate suspension is made alkaline to phenolphthalein during the sodium chloride extraction, thus ensuring that all carboxymethyl groups are in the form of the sodium salt.

2.4 Functionality of sodium starch glycolate related to its chemistry

Two papers have examined the relationship between cross-linking, substitution and performance of superdisintegrants.

Rudnic and co-workers⁽⁴⁾ varied the degree of substitution and the degree of cross-linking in a series of experimental grades of sodium starch glycolate. They found that the sedimentation volume of a 1% aqueous dispersion tended to increase both with increasing substitution, and (unexpectedly) with increasing cross-linking.

The experimental superdisintegrants were tested in tablets of aspirin (0.25 – 4% superdisintegrant) and hydrochlorothiazide (1% and 2% superdisintegrant). All formulations contained dibasic calcium phosphate as the direct compression filler. In the aspirin formulations they found very little difference in disintegration when SSG was used at 2% and above, and all tablets disintegrated within 1 minute. At the lowest concentration (0.25%) tablets did not disintegrate within 60minutes. At the intermediate concentrations (0.5% and 1%), disintegration and dissolution data indicated that the optimal degree of cross-linking and substitution are those in the commercial product tested.

A similar trend was noted for the hydrochlorothiazide tablets. With 2% SSG all tablets disintegrated within 1 minute and hydrochlorothiazide dissolved quickly from the tablets. With 1% SSG the tested commercial product again appeared optimal.

Although not explicitly stated in the paper, an estimate can be made of the required level of SSG for effective disintegration. Figure 8 shows the disintegration time ranges obtained with different SSG levels, irrespective of the chemistry. Solid lines show disintegration of the aspirin tablets and the dotted blue line shows disintegration of the hydrochlorothiazide tablets. At least 2% sodium starch glycolate is required for effective disintegration of these tablets containing dicalcium phosphate as the major component.

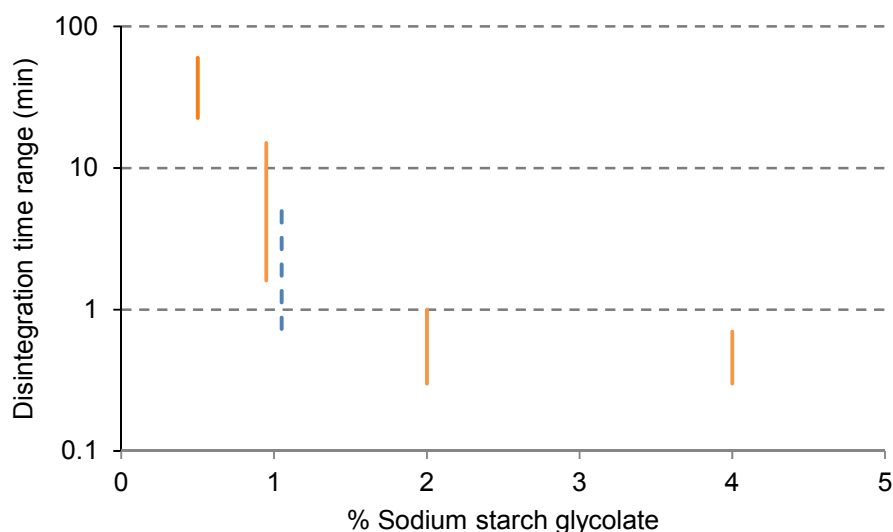


Figure 8: Disintegration data from Rudnic et al ⁽⁴⁾.

Bolhuis and co-workers⁽⁵⁾ studied a series of experimental SSG having a relative degree of cross-linking (DXL) of 0.25 – 4 (where 1 represents the normal degree for Primojel[®]) and a degree of substitution (DS) values of 0.21, 0.27 and 0.32. They also studied uncrosslinked and unsubstituted variants. In contrast to Rudnic et al, they found that the sedimentation volume decreased as the degree of cross-linking increased. The variants were tested in tablets containing 95.5% filler (dicalcium phosphate or lactose), 4% SSG and 0.5% magnesium stearate, and the disintegration time data are summarized in Tables 2 and 3.

Table 2: Disintegration times (seconds) for dicalcium phosphate tablets. Disintegration data from Bolhuis et al ⁽⁵⁾.

| DXL | DS=0 | DS=0.21 | DS=0.27 | DS=0.32 |
|------|-------|-----------|-----------|---------|
| 0 | >1800 | 330 | 1500 | 1800 |
| 0.25 | >1800 | 17 | 18 | 600 |
| 0.5 | >1800 | 12 | 12 | 140 |
| 1 | >1800 | 14 | 13 | 120 |
| 2 | >1800 | 20 | 16 | 40 |
| 3 | >1800 | 40 | 23 | 37 |
| 4 | >1800 | 30 | 30 | 95 |

Table 3: Disintegration times (seconds) for lactose tablets. Disintegration data from Bolhuis et al ⁽⁵⁾.

| DXL | DS=0 | DS=0.21 | DS=0.27 | DS=0.32 |
|------|------|---------|---------|---------|
| 0 | 100 | 130 | 135 | 135 |
| 0.25 | 30 | 26 | 21 | 95 |
| 0.5 | 80 | 23 | 22 | 35 |
| 1 | 90 | 23 | 20 | 35 |
| 2 | 75 | 24 | 22 | 34 |
| 3 | 75 | 25 | 23 | 31 |
| 4 | 30 | 24 | 23 | 32 |

The data in these tables show clearly that both cross-linking and substitution are necessary for effective performance.

For the dicalcium phosphate tablets there is a shallow minimum in the range DS = 0.21 to 0.27 and DXL = 0.5 to 1. For the lactose tablets the best performance is again obtained with DS = 0.21 to 0.27, although there is less detrimental effect when the DXL is increased above 1.

The relative sensitivity of the calcium phosphate formulation to DXL is consistent with reduced swelling on increased cross-linking. As previously noted, the disintegration of lactose tablets relies on water penetration, and swelling is important for disintegration of calcium phosphate tablets.

The data above were generated with SSG containing about 6 – 10% sodium chloride, a product of the substitution reaction. This is partly removed during commercial synthesis such that Primojel[®] contains a level of about 3%. Removal of sodium chloride was found to improve the disintegration by a few seconds in both formulations in the region of the optimized product⁽⁵⁾.

These data suggest that the optimal degree of substitution is in the lower part of the pharmacopoeal range, and support the view that Primojel[®] is optimized for both degree of cross-linking and degree of substitution. Excellent disintegration times are obtained when SSG is used in the range 2% to 4%.

3 Primellose[®]

3.1 General

Croscarmellose sodium is described as a cross-linked polymer of carboxymethyl cellulose. Apart from the differences between the starch and cellulose polymer backbones noted earlier, there are differences between the synthetic processes used to modify the polymer. Most importantly, the DS of croscarmellose sodium is higher than that of sodium starch glycolate, and the mechanism of cross-linking is different.

3.2 Substitution and cross-linking

Again the substitution is performed using Williamson's ether synthesis to give the sodium salt of carboxymethylcellulose. In this case however the degree of substitution is such that approximately 3 anhydroglucose units out of 4 are substituted, in conformance with compendial requirements for a DS of 0.6 to 0.85. A key difference from the chemistry of Primojel[®] is that some of the carboxymethyl groups themselves are used to cross-link the cellulose chains, the process being accomplished by dehydration. Thus the cross-links are carboxyl ester links rather than phosphate ester links as in Primojel[®].

A representative structure of a section of the Primellose[®] molecule as formed by this type of cross-linking is shown in Figure 9.

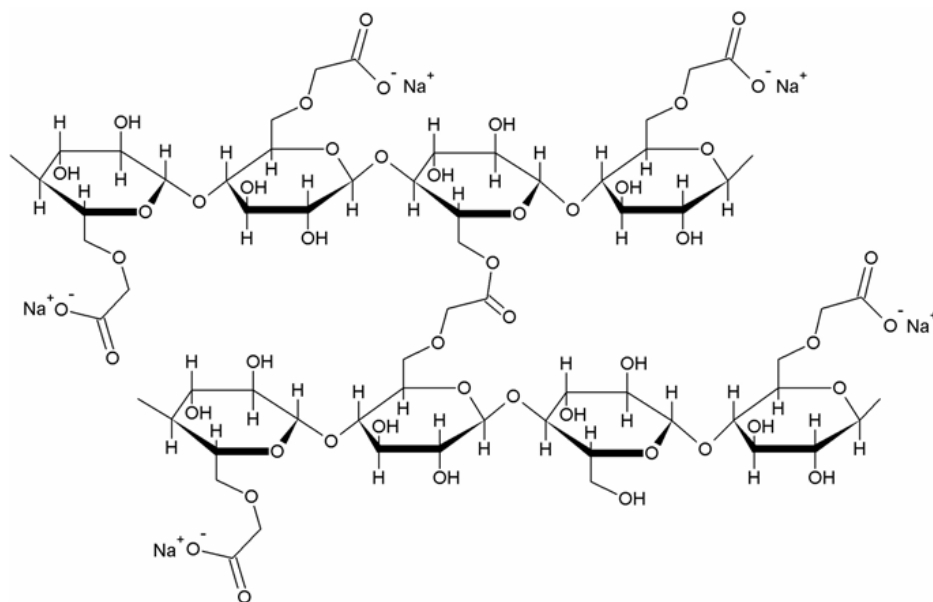


Figure 9: A representative section of Primellose®.

Degree of cross-linking is not explicitly stated in the monographs, but it is related to two of the properties, namely the water soluble material content and the settling volume, both of which reduce as the degree of cross-linking increases.

Unlike sodium starch glycolate, there are no published reports of the influence of structural variations on performance. A publication by Shah et al⁽⁶⁾ examined the effects of viscosity and degree of substitution on the utility of carboxymethyl cellulose as a disintegrant in sulfamethoxazole tablets. They found that high viscosity and low substitution (DS = 0.4) gave the best disintegration. However, the materials were not cross-linked and the DS is outside the range required in compendia, so it is doubtful that these data are relevant to performance of croscarmellose sodium.

3.3 The effect of particle size

It is well known that the particle size of disintegrants can affect their performance, larger particles usually promoting faster disintegration. This phenomenon has, for example, been observed for starch^(7,8) and for crospovidone⁽⁹⁾.

It can also be shown that the selection of particle size is an important performance factor for croscarmellose sodium. Figure 10 shows a plot of croscarmellose sodium particle size (in this case the median particle size as measured by laser light diffraction) against the disintegration time of lactose based placebo tablets containing 4% disintegrant and 0.5% magnesium stearate.

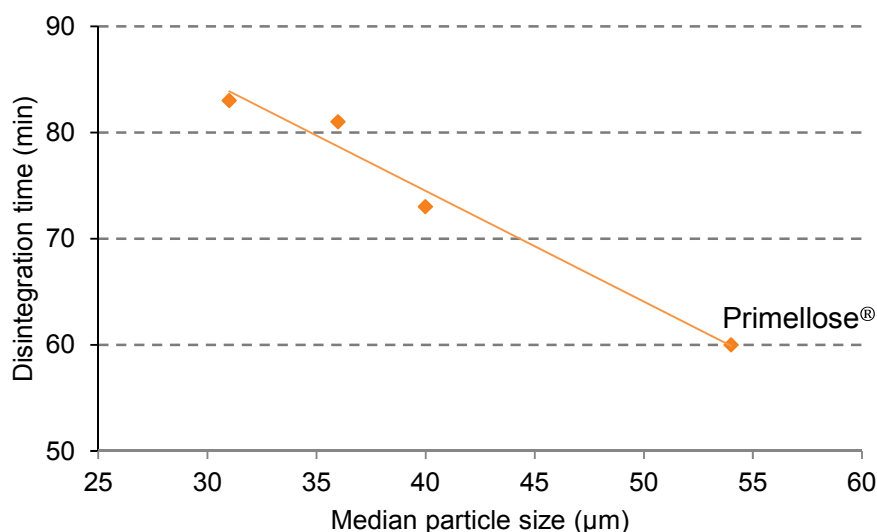


Figure 10: The effect of particle size on the disintegration of lactose placebos containing croscarmellose sodium.

It is clear that the coarser version of croscarmellose sodium promotes the fastest disintegration time. Primellose® (the right hand point of Figure 10) is made with a particle size that promotes rapid tablet disintegration.

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