

REVIEW ARTICLE: SODIUM STARCH GLYCOLATE AS A SUPERDISINTEGRANT

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Submitted 25th January 2021, Accepted 9th May 2021**ABSTRACT**

Sodium starch glycolate (SSG) is most widely used excipient in the field of pharmaceutical sciences. SSG is extensively used as a superdisintegrant in different drug formulations. This review article aims to discuss chemistry, synthesis, level used as superdisintegrant, different types of SSG's and various physicochemical properties. SSG available as different brands i.e Primojel, Explotab and Vivastar with different properties. Excipient, generally considered as an inert component, are of great importance in drug product development. Interchange between different suppliers can lead to final products with different quality attributes.

Keywords: SSG, Superdisintegrant, Substitution, Swelling, Fast dissolution, Compaction.

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INTRODUCTION

Pharmaceutical tablets are normally manufactured by the quick compression of a multi-component powder section containing a drug and excipients. The tablets must display certain particulars such as quality, friability, disintegration, substance consistency. The prerequisite of a dosage form to adhere to such details has led to the improvement of an extensive variety of excipients which can impart specific tablet properties, for example, microcrystalline cellulose as a binder can be utilized to enhance quality [1]. The disintegration profiles of pharmaceutical tablets can be adjusted by the addition of a "super-disintegrant." These polymeric-based materials, for example, (SSG), croscarmellose sodium, and crospovidone experience volume expansion when in contact with water, bringing about quick deterioration of the tablet matrix [2].

Disintegrants are substances or mixture of substances added to the drug formulations, which facilitate dispersion or breakup of tablets and contents of capsules into smaller particles for quick dissolution. Superdisintegrants, are those substances, which facilitate the faster disintegration with smaller quantity in contrast to disintegrants [3].

Starch is a complex, naturally occurring material which can be utilized in tablet and capsule formulations as a binder, diluent, and disintegrant. The compaction and disintegration properties of starches have been accounted for to be reliant on source. Starch, and modified starches, can be considered as somewhat crystalline materials;

however, the properties of starches are further convoluted by the nearness of other minor parts, for example, lipids.

Starch granules commonly comprise of two polymers, amylose, which is shapeless, and amylopectin, which is semicrystalline. This has evident ramifications for the structure of SSGs, since amylose and amylopectin can be carboxymethylated during the manufacturing process.

SSG is a cross-linked substituted potato starch, which is utilized as a disintegrant as a part of pharmaceutical tablets and capsules. In chemical terms, SSG is described as the sodium salt of a carboxymethylether of starch [4].

Two chemical modification processes carried out to derive SSG from starch: substitution to increase hydrophilicity and cross-linking to reduce gel formation and solubility upon contact with water [5]. The material is accessible from a few manufacturers under trade names, for example, Primojel, Explotab and Vivastar. In the instances of Primojel and Explotab, the materials are prepared by the response of potato starch with Na chloroacetate. Be that as it may, it is not clear whether the potato starch is cross-linked before or after substitution. On account of Vivastar P, the material is cross-linked by means of the Na carboxylate groups and starch alcohol group after substitution [6].

Sodium starch glycolate is the sodium salt of carboxymethyl ether. Starch glycolates are of rice, potato, wheat or corn inception. Sodium starch

glycolate is a white to off-white, bland, odorless, moderately free streaming powder. Sodium starch glycolate is utilized as a pharmaceutical review dissolution excipient for tablets and capsules. Sodium starch glycolate absorbs water quickly, bringing about swelling which prompts fast breaking down of tablets and granules. It is utilized as a disintegrant, a suspending agent and as a gelling agent [7]. Without a disintegrant, tablets may not dissolve suitably and may impact the amount of active ingredient absorbed. The material is available from various manufacturers under several different trade names, such as Explotab, Primojel, and Vivastar.

STRUCTURE

Sodium starch glycolate (SSG) is synthesized from polymers of glucose, namely starch. Glucose may take the α - or the β - form depending on the orientation of the hydroxyl group at position 1.

Starch contains two polymers of α -glucose, in particular amylose (a linear polymer of α -glucose connected at carbon molecules 1 and 4, having a normal level of polymerization of 4,000 in potato starch) and amylopectin (short straight chains connected between carbon particles 1 and 4, branched with extra connections between carbon

molecules 1 and 6, and having a normal degree of polymerization of 2,000,000 [8].

Potato starch contains roughly 21% amylose and 79% amylopectin. An area of an amylopectin atom demonstrating the 1,4- and the 1,6-links.

SYNTHESIS OF SSG

Selection of Starch Source

It's miles possible to synthesize sodium starch glycolate from a wide variety of native starches, however in practice potato starch is used as it offers the product with the great disintegrating properties.

Sodium potato starch glycolate had via a long way the best water uptake rate and gave the quickest disintegration whilst utilized in lactose placebo tablets. In contrast, the disintegration of dicalcium phosphate placebos containing experimental SSG's become no longer significantly affected by starch source, the disintegration of tablets crafted from this insoluble material being more associated with disintegrant swelling and force improvement in preference to water penetration.

Different grades of SSG are available according to particle size distribution, sodium chloride content and pH.

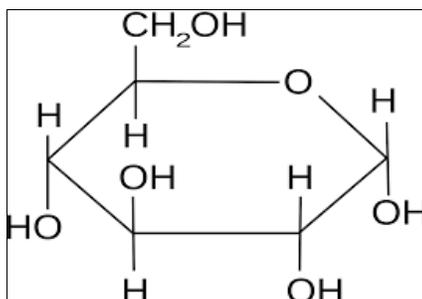


Figure 1: Chemical structure of glucose.

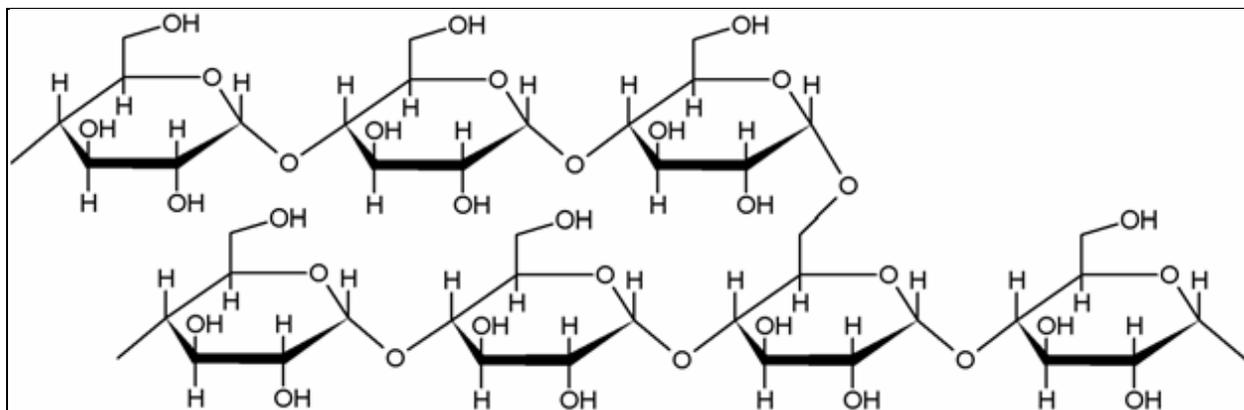
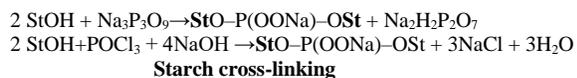


Figure 2: Chemical structure of a section of amylopectin.

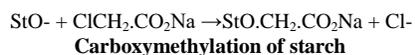
Cross-linking

After choice of the proper starch source the second one step in the synthesis of Ph. Eur. types A and B is cross-linking of the potato starch. An FDA authorised starch esterifying agent such as sodium trimetaphosphate or phosphorus oxychloride in alkaline suspension is used to achieve cross-linking. Both of these agents form cross-linked starch phosphate according to the reactions [9].



Substitution

According to Williamson's ether synthesis, chloroacetic acid or sodium monchloroacetate in an alkaline alcoholic suspension is used to substitute the cross linked potato starch. according to Williamson's ether synthesis. The deprotonated starch nucleophile substitutes chlorine in the sodium chloroacetate [10].



The reaction mixture is neutralized and the sodium starch glycolate is isolated and dried on completion of substitution. The degree of substitution in sodium starch glycolate is within the variety 0.23 to 0.32, as compared to a most feasible value of 3 (i.e. all three hydroxy groups in the anhydroglucose units would be substituted). For this reason, approximately 1 anhydroglucose unit in every 4 is carboxymethylated.

MECHANISM OF ACTION

Rapid and extensive swelling with minimal gelling. SSG'S are low substituted carboxy methyl starches in granular structures. The mechanism includes quick retention of water prompting to a widespread increment in extent of granules result quick and uniform disintegration (**Fig. 3**) [11]. Effective Concentration: 4-6%. Over 8%, disintegration times may really enhance because of gelling and its consequent viscosity delivering impacts [12]. Gels on prolonged exposure to water. High concentration causes gelling and loss of disintegration. The functional mechanism of SSG was revealed by High-Resolution Real-Time Magnetic Resonance Imaging (MRI) revealed the functional mechanism of SSG through investigation of the direction to which the tablet expands when disintegration occurs. SSG acts through swelling as an omni-directional extension was seen with various grades of SSG [13].

PHYSICO-CHEMICAL PROPERTIES

Level

In drug formulation, the range of SSG is between 2% and 8% w/w. Increased SSG levels (2% and 4% w/w) in paracetamol results in short disintegration time (within one minute), while Low SSG levels (0.25%, 0.5% and 1% w/w) brought about long and shifted disintegration times (60 min, 40 min, 2–15 min, separately) [14]. SSG in more elevated amounts (>8% of tablet weight) causes an expansion in disintegration time due to the development of a thick layer which hinders water infiltration in the formulation, independent of the API solubility.

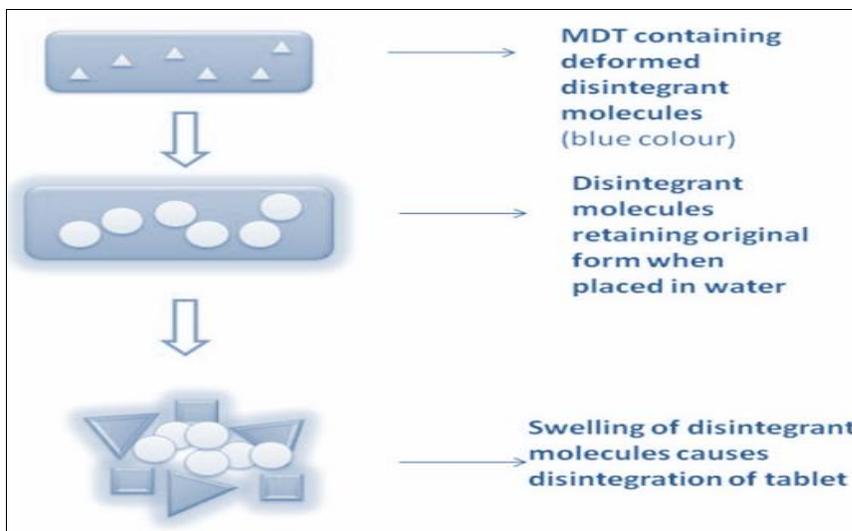


Figure 3: Mechanism of action of mouth dissolving tablet having SSG as a superdisintegrant.

Particle Properties

The size of particles influences disintegrant functionality of SSG, with larger particles being more efficient. Decrease in disintegration time is seen by increasing threefold particle size of SSG [15]. Due to increased interaction with water in small particle size of polymers, a thicker layer is formed that leads to delayed dissolution and creates a barrier for drug diffusion.

Biopharmaceutical Properties

The pH of the medium effects SSG functionality. SSG hydrates as the anionic carboxyl group communicates with water. A neutral form of polymer is gained at low pH, and a less developed association with water is expected [16]. As compared to intestinal media (phosphate support, pH = 6.8) an increased swelling of SSG is observed in simulated gastric media (0.1 N HCl, pH = 1) (Fig. 4).

Molecular Properties

The level of substitution, because of the part of the carboxymethyl assemble on functionality, must be characterized. As indicated by USP, the measure of sodium in SSG is set somewhere around 2.8 and 4.2%, while the level of substitution is not determined. Values for the level of substitution somewhere around 0.23 and 0.32 have been reported. Fast tablet disintegration results from hydration and swelling of SSG, identify with level of substitution. When the substitution increases from 0.20 to 0.29 an increase in swelling and water uptake is observed and the inverse impacts at higher substitution.

An ideal level of substitution value around 0.28 and 0.29 for faster and higher dissolution of aspirin tablets was reported. Drug-excipient interaction can be increased by higher level of substitution as weakly basic drugs can be adsorbed onto the polymer [17-20]. Phosphate group used in Crosslinking provide high spacing between SSG chains that reduce gel formation and increase swelling.

As contrasted with other swelling disintegrants, an increase in swelling of SSG is due to this kind of crosslinking (e.g. croscarmellose is crosslinked through esterification which does not permit this high spacing between the polymer chains). An expansion of 25–35% of crosslinking leads to expanded swelling and water up take, but further increase in crosslinking cause lower swelling and water up take. An ideal value at medium levels of crosslinking (33–35%) for disintegration of aspirin tablets has been reported.

Sodium starch glycolate is a cross-linked substituted potato starch. The material is accessible from different manufacturer under different trade names, for example, Explotab, Primojel, and Vivastar. The commercial evaluations of Explotab and Primojel have been accounted for to show inconspicuous contrasts in their chemical composition and physical characteristics. Bulk Density 0.756 g/cc and Viscosity 200 cP for 4% w/v aqueous dispersion. SSG does not melt, but chars at approximately 200 °C.

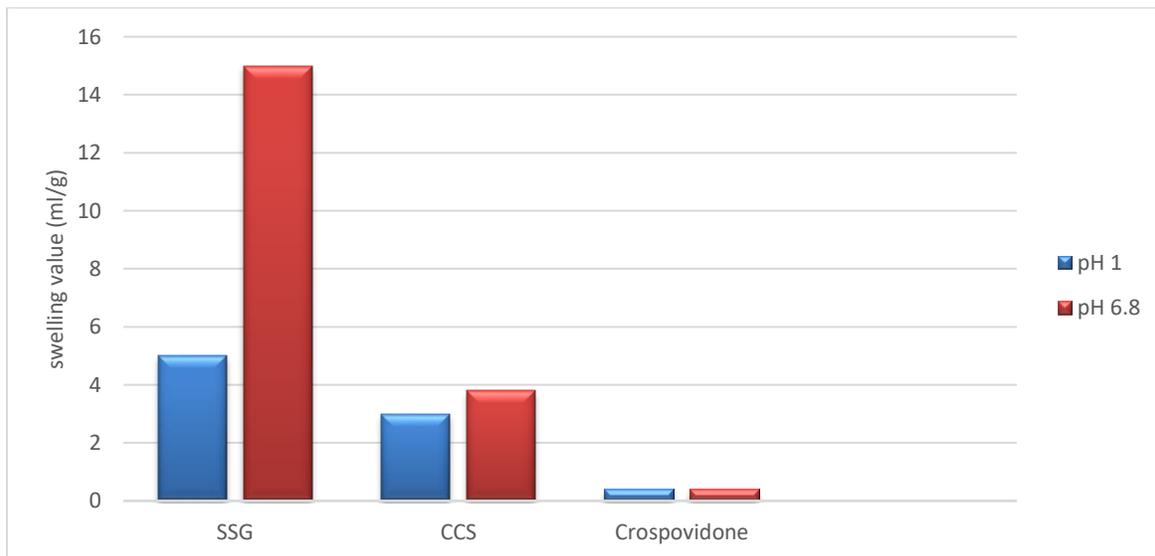


Figure 4: Swelling values of SSG, CCS and crospovidone.

Table 1: Pharmacopeial specifications of different brands of sodium starch glycolate.

Tests	Type A	Type B	Type C
Definition	Sodium salt of cross-linked partly O-carboxymethylated potato starch	Sodium salt of cross-linked partly O-carboxymethylated potato starch	sodium salt of a cross-linked by physical dehydration, partly O-carboxymethylated starch
Na	2.8-4.2%	2.0-3.4%	2.8-5.0%
pH	5.5-7.5	3.0-5.0	5.5-7.5
LOD	≤10.0%	≤10.0%	≤7.0%
Sodium chloride	7.0%	7.0%	1.0%
Sodium glycolate	2.0%	2.0%	2.0%
Assay (of Na)	2.8-4.2%	2.0-3.4%	2.8-5.0%
Size	30-100µm	30-100µm	30-100µm
Identification	The IR absorption spectrum as per reference spectrum	Iodine- blue color	1)K-antimonate-White ppt 2)Mg-Uranyl acetate- yellow ppt

Dynamic Vapor Sorption Properties

Dynamic vapor sorption (DVS) utilized to decide the moisture sorption properties of sodium starch glycolates. The outcomes contrasted with data obtained from potato starch, pregelatinized starch, microcrystalline cellulose (MCC), and crystalline lactose. Sodium starch glycolates show a vast mass gain at 90% relative humidity (RH), contrasted with the other anhydroglucose-based excipients.

However, the sorption limits of potato starch and the modified starches between 10%–70% RH are comparative. It creates the impression that the sorption limit between 10%–70% RH is not drastically influenced by the kind of cross-linking and sodium carboxymethylation (in sodium starch glycolates) and gelatinization (in pregelatinized starch) and that the superdisintegrant properties of the sodium starch glycolates are an outcome of some water-structure collaboration that is well beyond the accessible number of hydration sites [21-24].

Powder Compaction Properties

Primojel and Explotab have low levels of cross-linking with degrees of substitution of 0.23-0.30. However, Na carboxylate and starch primary alcohol groups are reported for the crosslinking of Vivastar rather than simply via starch alcohol groups, which probably occurs in Primojel and Explotab, making direct comparisons difficult. Explotab, Primojel, and Vivastar P, are explored at pressure rates of 0.17 and 30 mm/sec. The outcomes propose that the three "as provided" materials show distinctive pressure and compaction conduct.

Explotab and Primojel show comparative compatibility, though Vivastar P displays the poorest compatibility. This conduct was not reflected in the compressibility of the powders, where Vivastar P and Explotab displayed comparable performance. The materials were studied using x-ray diffraction,

scanning electron microscopy, Carr's compressibility index, and swelling volume.

In terms of material characteristics, all the items displayed comparable swelling in water. Characterization studies recommended that Vivastar P is an inconspicuously unique material to Primojel and Explotab as far as moisture content, crystallographic order, and particle topography [25, 26].

Solubility Enhancement Property

SSG is insoluble in water whereas it is sparingly soluble in ethanol 95%. Most of drugs are poorly water soluble and they require an excipient to increase solubility. Studies by Rane Y. et al suggested that certain hydrophilic swellable polymers such as sodium carboxymethyl cellulose (Na-CMC), sodium starch glycolate (SSG), and pregelatinized starch (PGS) used in solid dispersion, improve the dissolution properties of poorly soluble drugs.

Interaction of SSG on Stability of Dosage Form

In solid dosage forms, chemical instability is result of interaction between drug and excipients. Solid dosage forms are less stable as compared to API. Chemical reaction occurs when excipient act as a catalyst and reacts directly with the drug molecule. It causes the modification in the pH of the microenvironment such that the rate of chemical reaction is enhanced [27-29]. The most common reaction that causes the chemical instability of solid dosage form are: Hydrolysis, Dehydration, Isomerization, Elimination, Cyclization, Oxidation, Photodegradation. Potentially reactive impurities of sodium starch glycolate are Monochloro acetate, nitrites, and nitrates. The example of incompatibility is adsorption of weakly basic drugs and their salts due to electrostatic interactions. In addition, the residual monochloro acetate may undergo SN2 nucleophilic reactions [30].

Table 2: Top medications with this excipient.

Drug	Dosage form
Loratadine	Fast dissolving tablets
Ramipril	fast mouth dissolving tablet
Ondansetron	Fast disintegrating tablets
Ibuprofen	Crystal engineering to improve pharmaceutical performance
Salbutamol sulphate, Cetirizine hydrochloride in combination	Fast disintegrating tablets
Almotriptan malate	Mouth dissolving film
Nortriptyline hydrochloride	Fast disintegrating tablet
Flutamide	Orodispersible tablet.
Losartan potassium	Fast disintegrating tablets
Valacyclovir hydrochloride	Sustained release tablet
Sildenafil citrate nanocrystals	Fast dissolving tablet
Valsartan	Bilayer tablets
Simvastatin	Fast dissolving tablets
Salbutamol sulphate	Fast disintegrating tablets
Cefixime trihydrate	Fast dissolving tablets
Amlodipine besylate and Atorvastatin calcium	Fast dissolving tablet
Venlafaxine hydrochloride	Fast dissolving tablet
Cefdinir solid dispersion	Fast disintegrating tablets
Telmisartan	fast dissolving tablets
Isradipine	Fast dissolving tablets
Telmisartan	Immediate release tablet
Tizanidine hydrochloride	Fast dissolving tablets
Doxylamine succinate	Orodispersible tablet
Amlodipine besylate	Mouth dispersible tablet
Metoclopramide hydrochloride	Sustained release matrix tablets
Nifedipine	Sublingual tablets
Aloe vera gel	Fast dissolving tablets [31-36]

CONCLUSION

Most widely used excipient among all the excipients is sodium starch glycolate. It is used as a superdisintegrant in pharmaceutical formulations. The physical properties of sodium starch glycolate, and hence its effectiveness as a disintegrant, are affected by the degree of crosslinkage, extent of carboxymethylation, and purity. Disintegration time

is affected by level of SSG used in formulation and also by the size of polymer particle. The uses of superdisintegrants are extended in the applications of oral disintegration tablets, fast dispersible tablets, capsules, mouth-dissolving films, etc. TOF-SIMS and SEM/EDX are used to investigate the composition of SSGs particles.

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