DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 12(4), 621-630 (1986)

ON THE SIMILARITY OF SODIUM STARCH GLYCOLATE FROM DIFFERENT SOURCES

G.K. Bolhuis, H.V. van Kamp and C.F. Lerk

Laboratory for Pharmaceutical Technology and Dispensing
State University of Groningen
Ant.Deusinglaan 2, 9713 AW Groningen
The Netherlands

SUMMARY

The physico-pharmaceutical properties of different batches of two brands of sodium starch glycolate have been investigated as disintegrant in direct compression. Differences in disintegration efficiency were found to be related to the purity of the products. The differences, however, were too small to have practical significance. The currently available low-sodium chloride content sodium starch glycolates may consequently be considered as being pharmaceutically equivalent, when used as disintegrant in tablet formulations.

INTRODUCTION

The potential of excipients to affect the workability of pharmaceutical powders and the bioavailability of the dosage form is leading to a more critical investigation of the physico-pharmaceutical properties of these materials. Evaluation of four direct compression tabletting excipients showed (1) that chemically equivalent materials from alternate suppliers do not necessarily possess comparable compression characteristics.

Two brands of commercially available cross-linked sodium carboxy-

0363-9045/86/1204-0621$3.50/0

methyl cellulose, having identical chemical structures and being prepared by the same general reactions, were found (2) to differ in behaviour to such a degree, that this result will certainly have contributed to the incorporation of two sub-monographs in the National Formulary XV for croscarmellose sodium.
For another disintegrating agent, sodium starch glycolate, it was demonstrated (2), that two brands, both meeting the specifications of the National Formulary XV exhibited tremendous differences in their swelling properties.
These, and other results point to the need to study the various commercial products and their comparative functionalities more closely.

A study on the effect of both degree of substitution and cross-linking of one commercial brand of sodium starch glycolate[1] (3, 4) showed that relatively small changes in molecular structure can cause substantial modification of disintegrant properties. Recent work (5) demonstrated the existence of a pronounced relation between both the molecular structure and purity of another brand[2] of sodium starch glycolate and its efficiency as a tablet disintegrant.

The goal of the present study was to compare the chemical and physical properties, and to evaluate the equivalence as pharmaceutical disintegrant of different lots of two currently marketed brands of sodium starch glycolate.

EXPERIMENTAL

Materials

Sodium starch glycolates were obtained from two suppliers. From supplier A[3], sodium starch glycolate[2] with two degrees of purity were used. The product with about 8% sodium chloride (SSG I) was marketed until August 1983 and is now out of commerce. The currently available product (SSG II) contains about 5% sodium chloride. Two lots of both products were investigated. From supplier B[4], two lots of the commercial product[1] were used (SSG III).

The other materials used were: unmilled dicalcium phosphate dihydrate N.F.[5], lactose Ph.Eur., 100 mesh quality[6] and magnesium stearate Ph.Ned. grade[7].

Methods

The viscosity of the sodium starch glycolate samples was measured in 1% and 3% aqueous dispersions, respectively, using a rotation viscosimeter[8] with spindle 2 at 20°C. The rotation speed was 20 rpm.

The sedimentation volume was determined after sedimentation of a 1% aqueous dispersion of the disintegrant at 20°C in a 100 ml graduated cylinder for 24 hrs.

The degree of substitution (DS) of the sodium starch glycolates was determined by acid/base titration of the carboxymethylated starch (purified by dialysis) in which the substituents were transformed into the acid form with hydrochloric acid.
The pH values given are for 3%-dispersions.

The sodium chloride content was determined by a potentiometric titration with silver nitrate in an aqueous acid dispersion.

The disodium citrate and sodium glycolate content were determined as their respective acids by HPLC. Separation was made on a strong cationic exchanger (H^+-form) and diluted surfuric acid as the eluant (6).

The content of water-soluble carbohydrates was determined by means of the anthron reaction (7).

The total cold-water soluble fraction was determined from the dry matter content of the clear upper layer of a 2% aqueous dispersion at 20°C and -if necessary- after centrifugation for 3 min at 5000 rpm. A correction was made for the differences in the electrolyte concentrations in the extra- and intragranular phases.

The water uptake measurements in compacts of pure disintegrants (100 mg, 9 mm in diameter, compressed at 20 kN) were performed as previously reported (8).

Tablets were prepared from mixtures of dicalcium phosphate dihydrate and lactose 100 mesh, respectively, with 4% disintegrant and 0.5% magnesium stearate. Filler and disintegrant were mixed for

15 min in a tumbling mixer[9] at 90 rpm; after the addition of the lubricant, the mixing procedure was continued for 5 min. The tablets were compressed by manually introducing a weighed quantity of 500 mg of the mixture into a 13 mm die of a compression device. The compression force used was 20 kN for the dicalcium phosphate dihydrate tablets and 30 kN for the lactose tablets, respectively. The tableting procedure and the determination of disintegration time and crushing strength were performed as previously reported (9).

BACKGROUND

Sodium starch glycolate is prepared by both crosslinking and substitution by carboxymethylation of potato starch. Crosslinking can be carried out by chemical methods, using reagents like phosphorus oxytrichloride, sodium trimetaphosphate, etc. or by physical methods. Carboxymethylation is carried out as a Williamson ether synthesis i.e. starch is reacted with sodium chloroacetate in an alkaline medium and subsequently neutralized with citric acid or other acids. Sodium starch glycolate can be characterized by the degree of substitution and -because no proper chemical analysis of the usually very low degree of crosslinking is available- by a number of physical properties such as viscosity and sedimentation volume of a dispersion, which were both found to be strongly dependent on the degree of crosslinking (5). The carboxymethylation reaction and the subsequent neutralization with citric acid introduces sodium chloride, sodium glycolate and disodium citrate as by-products in sodium starch glycolate. These salts are currently only washed out partly, so they are commonly present in the commercial products.

RESULTS

Table I lists the degree of substitution, a number of physical properties and the pH of the different kinds of sodium starch

TABLE I

Degree of substitution, viscosity, sedimentation volume and pH of different kinds of sodium starch glycolate

Type and lot nr	degree of substitution	viscosity (mPa.s) of a dispersion containing		sedimentation volume (ml)	pH
		1%	3%		
SSG I, E 201	0.28	10	20	29.5	6.5
SSG I, E 202	0.28	8	20	29	6.35
SSG II, E 443	0.30	12	40	36.5	6.7
SSG II, E 453	0.28	12	48	40	6.8
SSG III, 1838x	0.23	12	24	34	6.5
SSG III, 1960x	0.23	12	30	38	6.9

glycolate investigated. The degree of substitution was found to be lower for SSG III, when compared with the other products, but all the values fall within the limits of the NF XV monograph for sodium starch glycolate.

Both sedimentation volume and viscosity of the aqueous dispersions were lower for the product (SSG I) with the higher sodium chloride content (see Table II) when compared with the data of SSG II and SSG III. The pH-values of all the materials were of the same order of magnitude.

Table II lists the degree of purity of the sodium starch glycolates. SSG I, which has a sodium content of about 8% is now out of commerce, because previous work has shown that a decrease of the sodium chloride content enhanced the disintegration efficiency of sodium starch glycolate (5).

TABLE II

Degree of purity of different kinds of sodium starch glycolate

Type and lot nr	sodium chloride content (%)	disodium citrate content (%)	sodium glycolate content (%)	cold water soluble carbohydrates (%)	total cold water soluble fraction (%)
SSG I, E 201	7.7	0.8	1.1	0.9	10.4
SSG I, E 202	8.2	0.8	1.0	0.7	10.4
SSG II, E 443	4.9	0.8	0.8	1.3	7.4
SSG II, E 453	5.3	0.8	0.7	1.1	7.7
SSG III, 1838x	4.5	3.3	0.7	2.1	12.1
SSG III, 1960x	4.4	3.2	0.6	2.4	11.5

The currently available product, SSG II, contains about 5% sodium chloride, which is comparable to the sodium chloride content of SSG III. The content of disodium citrate was about 0.8% for SSG I and SSG II but about 2.5% higher for SSG III. For the sodium glycolate content no essential differences were found for the products investigated. The content of cold water soluble carboxyhydrates was about 1% higher for the SSG III compared to the products I and II. The total cold water soluble fraction was highest for SSG III, even higher than for the product containing the high sodium chloride content (SSG I).

As water uptake by disintegrants plays an important role in tablet disintegration (10), water uptake profiles were recorded of tablets, compressed from the different sodium starch glycolates only. As seen from figure 1, the highest values for both penetration rate and volumetric water uptake were found for SSG II, whereas there were only minor differences between the water uptake profiles of SSG I and SSG III.

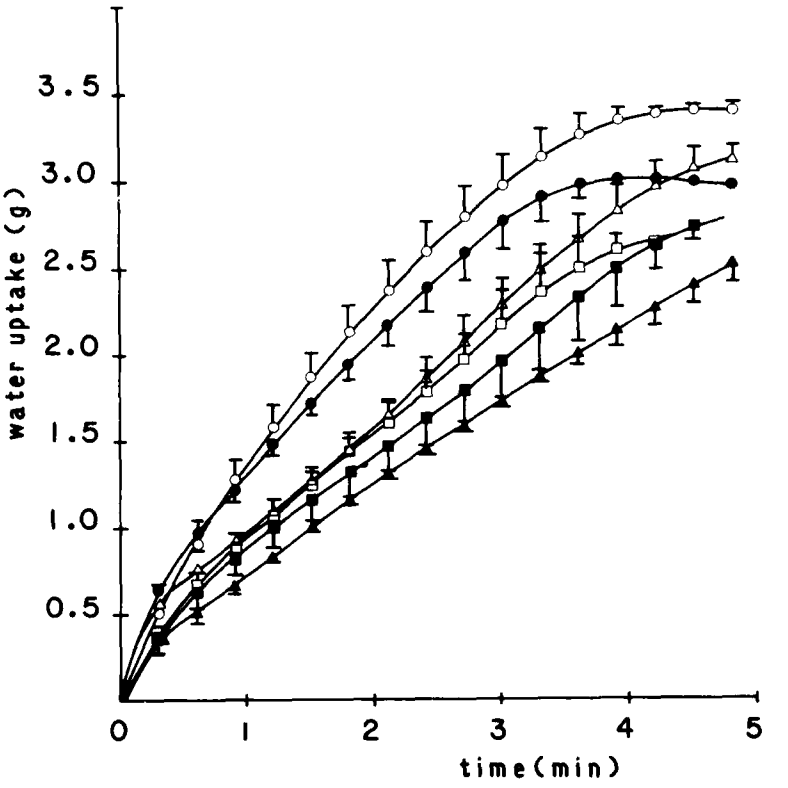

FIGURE 1

Water uptake profiles for tablets compressed from different kinds of sodium starch glycolate: ■ SSG 1, lot E 201; □ SSG I, lot E 202; ● SSG II, lot E 443, O SSG II, lot E 453; ▲ SSG III, lot 1838x; Δ SSG III, lot 1960x.

The efficiency of the sodium starch glycolates as a disintegrant was experienced by incorporation of the different products into an insoluble (dicalcium phosphate dihydrate) and a soluble (lactose) tablet system, respectively. Characterisation data for the tablets are given in table III.

Taking into account the standard deviations, the crushing strength of the tablets appeared to be hardly dependent on the disintegrant used. Although all tablets showed an extremely fast disintegration, small differences were observed in the disintegration efficiency

TABLE III

Effect of different kinds of sodium starch glycolate on the properties of tablets containing 4% disintegrant. (± standard deviation)

Type and lot nr	dicalcium phosphate dihydrate tablets		lactose tablets	
	crushing strength (kg)	disintegration time (s)	crushing strength (kg)	disintegration time (s)
SSG I, E 201	4.8 ± 0.4	12 ± 2	3.1 ± 0.2	22 ± 1
SSG I, E 202	4.3 ± 0.3	11 ± 2	2.9 ± 0.3	22 ± 1
SSG II, E 443	3.8 ± 0.5	8 ± 0	2.9 ± 0.1	20 ± 1
SSG II, E 453	3.8 ± 0.1	8 ± 0	2.7 ± 0.2	19 ± 1
SSG III, 1838x	3.9 ± 0.3	14 ± 4	3.2 ± 0.2	27 ± 1
SSG III, 1960x	3.9 ± 0.3	12 ± 4	3.1 ± 0.2	24 ± 0

of the sodium starch glycolates used. For both systems the disintegration time seems to increase in the sequence SSG II < SSG I < SSG III.

DISCUSSION

The effectiveness of SSG as a disintegrant has been found to be affected by both the molecular structure (3-5) and purity (5) of the product. The molecular structure of SSG is determined by the degree of substitution and by the degree of crosslinking. Previous results(5) showed the disintegration efficiency to be almost independent of the degree of substitution in the range 0.2-0.3 for crosslinked SSG. The small differences in disintegration time observed between the products tested, will consequently not be

caused by the slight differences in degree of substitution. The degree of crosslinking of SSG is characterized by its physical parameters like viscosity and sedimentation volume. These physical properties, however, are also affected by the purity of the material, though to a lower extent. Assuming an identical degree of crosslinking for the SSGs I and II, which were both produced under identical reaction conditions, the lower values found for the viscosity and sedimentation volume of a dispersion and the decreased water uptake of SSG I, compared to SSG II, consequently can only be caused by the presence of a higher amount of sodium chloride in product I. Not knowing the degree of crosslinking of SSG III in relation to that of SSG I and SSG II, the faster and higher water uptake of SSG II, compared to SSG III, may be produced either by a difference in crosslinking or a lower total water soluble fraction, or a combination of both. Noticing that viscosities and sedimentation volumes are of the same order of magnitude for SSG II and SSG III, the differences in water uptake profiles will most probably be caused by the much lower sodium citrate content of SSG II, compared to SSG III.

The tendency of slightly increasing disintegration times as found for both the dicalcium phosphate dihydrate-SSG and lactose-SSG tablets in the sequence SSG II < SSG I < SSG III may consequently be attributed to a difference in purity of the disintegrants tested. The differences in disintegration times observed, however, are too small to have practical significance. In conclusion, the currently marketed brands and lots of SSG with a low sodium chloride content, may, in spite of differences in the degree of purity, be considered as pharmaceutically equivalent, when used as a disintegrant in tablet formulations.

FOOTNOTES

[1] Explotab^{R}

[2] Primojel^{R}

[3] Avebe, Veendam, The Netherlands

[4] Ed.Mendell Co., New York, U.S.A.

[5] Emcompress[R], Ed.Mendell Co., New York, U.S.A.

[6] DMV, Veghel, The Netherlands

[7] Lamers & Indemans, 's-Hertogenbosch, The Netherlands

[8] Brookfield, type HAT

[9] Turbula, model 2P

REFERENCES

(1) M.N. Shah, M.A. Carroll and L.G. Miller, Pharm. Technol. 7 (2), 45 (1983).

(2) R. Shangraw, A. Mitrevej and M. Shah, Ibid. 9 (10), 49 (1980).

(3) E.M. Rudnic, J.L. Kanig and C.T. Rhodes, J. Pharm. Sci. (1984) in press.

(4) E.M. Rudnic, J.L. Kanig and C.T. Rhodes, Drug Dev. Ind.Pharm. 9, 303 (1983).

(5) G.K. Bolhuis, H.V. van Kamp, C.F. Lerk, J.W. Gielen, A.W. Arends and G.J. Stuut, Acta Pharm. Technol. 30, 24 (1984).

(6) V.T. Turkelson and M. Richards, Anal. Chem. 50, 1420 (1978).

(7) R.L. Whistler and M.L. Wolfrom, Eds., Methods in Carbohydrate Chemistry, Vol. I, Academic Press, New York, 1962, p. 490-491.

(8) H.V. van Kamp, G.K. Bolhuis and C.F. Lerk, 3rd Int.Conf. on Pharmaceutical Technology, Paris 1983, Vol. V, p. 35.

(9) G.K. Bolhuis, A.J.Smallenbroek and C.F. Lerk, J. Pharm. Sci. 70, 1328 (1982).

(10) G.K. Bolhuis, H.V. van Kamp, C.F. Lerk and F.G.M. Sessink, Acta Pharm. Technol. 28, 111 (1982).