Carboxymethylcellulose: Effect of Degree of Polymerization and Substitution on Tablet Disintegration and Dissolution

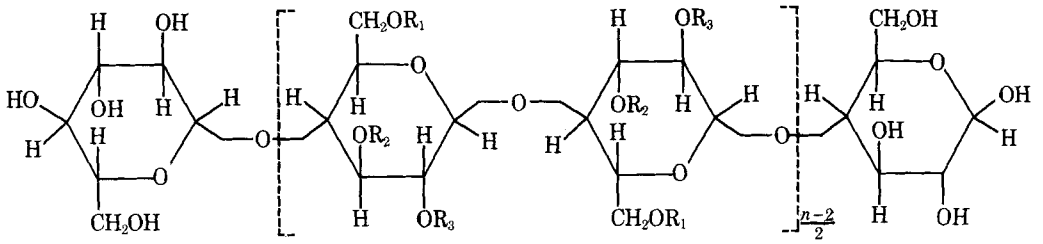
N. H. SHAH *, J. H. LAZARUS *, P. R. SHETH *, and C. I. JAROWSKI ˣ

Received January 21, 1980, from the *Department of Allied Health and Industrial Sciences, College of Pharmacy and Allied Health Professions, St. John's University, Jamaica, NY 11439.* Accepted for publication November 6, 1980. *Present address: Hoffmann-La Roche Inc., Nutley, NJ 07110.

Abstract □ Highly polymerized grades of carboxymethylcellulose sodium serve effectively as disintegrating agents for tablets. The preferred disintegrants have a high degree of polymerization with a small number of carboxymethyl groups. Grades with a low degree of polymerization are poor disintegrating agents irrespective of their degree of substitution. The dissolution rates of sulfamethoxazole tablets correlated with the disintegration times.

Keyphrases □ Carboxymethylcellulose—effect of polymerization and substitution on tablet disintegration and dissolution □ Disintegrants—carboxymethylcellulose, effect of polymerization and substitution on tablet disintegration and dissolution □ Binders—carboxymethylcellulose, effect of polymerization and substitution on tablet disintegration and dissolution □ Disintegration—tablets, effect of carboxymethylcellulose polymerization and substitution □ Dissolution—tablets, effect of carboxymethylcellulose polymerization and substitution

Carboxymethylcellulose sodium is the sodium salt of the polycarboxymethyl ether of cellulose. The cellulose molecule consists of repeating cellobiose units, which are composed of two anhydroglucose units. The structures of the cellulose and carboxymethylcellulose molecules are (1):



cellulose: $R_1 = R_2 = R_3 = H$
carboxymethylcellulose: degree of substitution = 1 when $R_1 = CH_2COOH$, $R_2 = R_3 = H$
degree of substitution = 3 when $R_1 = R_2 = R_3 = CH_2COOH$ (n = number of anhydroglucose units or degree of polymerization)

The degree of substitution refers to the average number of carboxymethyl groups that are substituted per anhydroglucose unit. Thus, carboxymethylcellulose sodium has a degree of substitution of 0.7 when an average of seven carboxymethyl groups have been substituted per 10 anhydroglucose units; it has a degree of substitution of 1.2 when an average of 12 carboxymethyl groups have been substituted per 10 anhydroglucose units.

The average molecular weight of carboxymethylcellulose sodium is determined by the average chain length and the degree of substitution. The viscosity of carboxymethylcellulose sodium dispersions increases as the molecular weight increases and thus is used as a measure of the degree of polymerization.

The USP XX has a specification for sodium content calculated on a dry basis of not less than 6.5% and not more than 9.5% (2). The upper limit represents a degree of substitution of about 0.7. There is no specification for viscosity so the degree of polymerization can vary. As the degree of substitution decreases, the chemical structure of carboxymethylcellulose sodium approaches the chemical structure of natural cellulose.

For many years, carboxymethylcellulose sodium has been used in tablets as a binder and as a viscosity builder in aqueous solutions (1). Carboxymethylcellulose sodium with a low sodium content and a degree of substitution below 0.2 was reported to be a suitable tablet disintegrant (3). Although there are no reports on the effect of different grades of carboxymethylcellulose sodium having varying degrees of polymerization and substitution on tablet characteristics, the physicochemical properties of cellulose are altered significantly with changes in the degree of substitution and polymerization.

The present study evaluated the effect of various grades of carboxymethylcellulose sodium on the disintegration and dissolution rates of a sulfamethoxazole tablet.

EXPERIMENTAL

Materials—Sulfamethoxazole[1], carboxymethylcellulose sodium[2] of various grades, pregelatinized starch[3], and magnesium stearate[4] were used.

Equipment—A single-punch tablet press[5], a friabilator[6], a hardness tester[7], a USP disintegration apparatus[8], a USP dissolution apparatus[9], a viscometer LVT[10], U.S. sieves numbers 14 and 20[11], and a mixer[12] were used.

[1] Research compound, Hoffmann-La Roche, Nutley, N.J.
[2] Hercules Inc., Wilmington, Del.
[3] National Starch, Bridgewater, N.J.
[4] Mallinckrodt Corp., St. Louis, Mo.
[5] Thomas Engineering Co., Hoffmann Estates, Ill.
[6] Hoffmann-La Roche, Nutley, N.J.
[7] Cherry-Burrell Corp., Cedar Rapids, Iowa.
[8] Scientific Glass Co., Bloomfield, N.J.
[9] Van-Kel Industries, Chatham, N.J.
[10] Brookfield Engineering Laboratories, Stoughton, Mass.
[11] U.S. Standard Sieves, Newark Wire Cloth Co., Newark, N.J.
[12] Hobart Manufacturing Co., Troy, N.Y.

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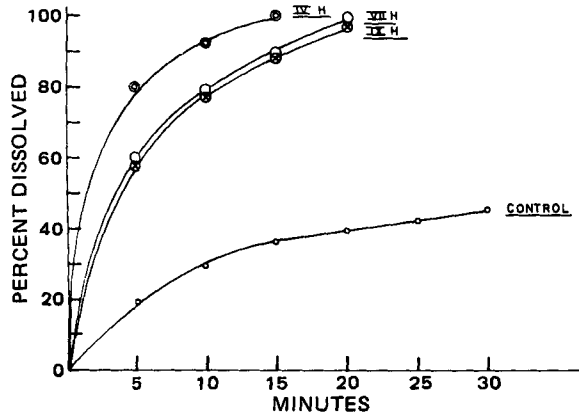

Figure 1—*Effect of the degree of substitution of highly polymerized carboxymethylcellulose sodium on the dissolution rate of sulfamethoxazole tablets.*

Solubility Studies—The solubility of the sulfamethoxazole in various solvents was determined by the method specified in USP XX (2).

Viscosity Studies—The viscosity of various carboxymethylcellulose sodium samples was determined in distilled water at 25° with a viscometer. The percentage concentration, spindle number, and speed recommended by the supplier were used.

Manufacture of Tablets—The raw materials were used as received. The formulations used in the study were as follows:

	control formula, mg	experimental formula 1, mg	experimental formula 2, mg
sulfamethoxazole	500	500	500
pregelatinized starch	25	25	25
carboxymethylcellulose sodium	—	15	25
magnesium stearate	2.5	2.5	2.5

The sulfamethoxazole was mixed with the pregelantinized starch and passed manually through a 20-mesh sieve. The mixture was remixed and granulated with water (240 ml of distilled water for 1000 tablets) and the granulation was placed on trays and dried overnight in an oven set at 54.4°. The dried granulation was screened manually through a 14-mesh screen. Then carboxymethylcellulose sodium was mixed with the dried granulation for 10 min. The granulation was lubricated with magnesium stearate by blending the mixture for 5 min. The tablets were compressed on a single-punch tablet press using 1.3-cm (0.5-in.) diameter flat-faced beveled-edge punches to a hardness of ~15 Strong–Cobb units.

Assay—The UV spectrum of sulfamethoxazole showed a maximum absorption at 265 nm. It obeyed Beer's law in 0.84 *N* HCl.

Disintegration—Tablet disintegration was carried out in simulated gastric and intestinal fluids at 37° using the USP XX disintegration apparatus without disks.

Dissolution Rate—The dissolution rate was measured by the USP XX method using the rotating basket at 100 rpm with 0.84 *N* HCl as the dissolution medium. The percentage of the drug released was determined as a function of time.

Table I—Sulfamethoxazole Solubility in Various Solvents at 25°

Solvent	Solubility, mg/ml
95% Ethanol	30
Methanol	90
0.1 *N* NaOH	16
Water	0.5
0.1 *N* HCl	0.03
0.84 *N* HCl	2.85

Table II—Viscosities of Various Grades of Carboxymethylcellulose Sodium in Water at 25°

Degree of Substitution	Grade[a]	Concentration, %	Viscosity Range[b], cps	Actual Viscosity, cps
0.4	IVH	1	400–1000	1080
0.4	IVM	2	300–600	350
0.4	IVL	2	24 maximum	16
0.7	VIIH	1	1500–2500	1580
0.7	VIIM	2	300–600	320
0.7	VIIL	2	25–50	30
0.9	IXH	1	2500–4500	3200
0.9	IXM	2	400–800	360
1.2	XIIM	2	800–3100	850

[a] The first number represents the degree of substitution. Thus, IV, V, VII, IX, or XII represents the degree of substitution of 0.4, 0.5, 0.7, 0.9, or 1.2, respectively. The L, M, or H signifies low, medium, or high viscosity. [b] According to supplier.

RESULTS AND DISCUSSION

Sulfamethoxazole was poorly soluble in distilled water as well as in 0.1 *N* HCl (Table I). Its solubility was markedly improved in 0.84 *N* HCl. As a consequence, the latter solvent was used in the dissolution studies.

The viscosities of the various grades of carboxymethylcellulose sodium are shown in Table II. In addition, the nomenclature for the various grades is explained.

All tablets manufactured met USP specifications for weight variation, content uniformity, and friability. They had a hardness range of 13–16 Strong–Cobb units. The data on the disintegration and dissolution rates of the various tablets are given in Table III and in Figs. 1–3. The results clearly show that the highly polymerized grades of carboxymethylcellulose sodium are good disintegrating agents. The disintegration properties were significantly influenced by the degree of substitution. The gums with a low degree of substitution together with a high degree of polymerization were excellent disintegrating agents. The disintegration properties of carboxymethylcellulose sodium decreased as the degree of substitution increased and the degree of polymerization decreased. Thus, carboxymethylcellulose sodium with a degree of substitution of 0.4 and a high degree of polymerization would be an excellent disintegrant. However,

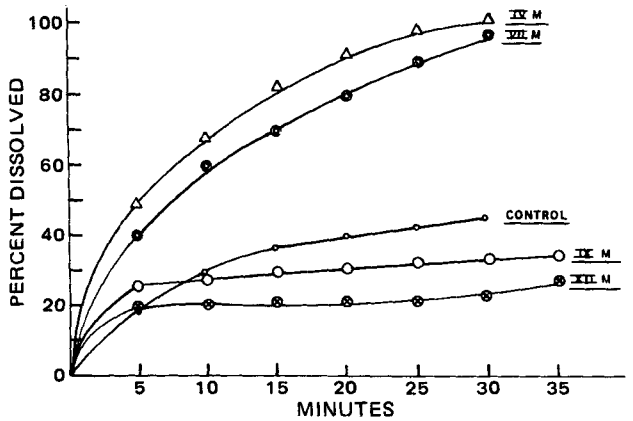

Figure 2—*Effect of the degree of substitution of carboxymethylcellulose sodium on the dissolution rate of sulfamethoxazole tablets.*

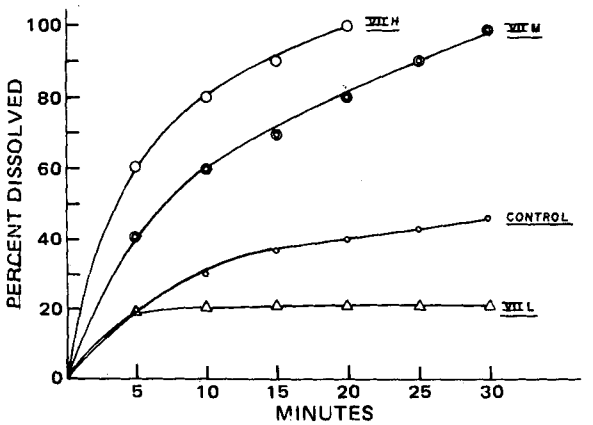

Figure 3—*Effect of the degree of polymerization of carboxymethylcellulose sodium on the dissolution rate of sulfamethoxazole tablets.*

Table III—Disintegration Rates of Sulfamethoxazole Tablets Containing 3% of Various Grades of Carboxymethylcellulose Sodium

Grade	Degree of Substitution	Degree of Polymerization	Disintegration Time, sec: Simulated Gastric Fluid	Disintegration Time, sec: Simulated Intestinal Fluid
—	Control	—	>1800	>1800
IVH	0.4	High	30	30
IVM	0.4	Medium	90	300
IVL	0.4	Low	>1800	>1800
VIIH	0.7	High	90	600
VIIM	0.7	Medium	100	900
VIIL	0.7	Low	>1800	>1800
IXH	0.9	High	100	900
IXM	0.9	Medium	>1800	>1800
XIIM	1.2	Medium	>1800	>1800

carboxymethylcellulose sodium with a degree of substitution of 1.2 and a low degree of polymerization would be a poor disintegrating agent. The results are summarized as follows:

1. The highly polymerized grades of carboxymethylcellulose sodium are good disintegrating agents. The preferred disintegrant has a high degree of polymerization together with a low degree of substitution. Type IVH is preferred over VIIH, which is preferred over IXH (Fig. 1).

2. The medium-polymerized carboxymethylcellulose sodium with a degree of substitution of 0.7 or less has moderate disintegrant properties; but as substitution increases from 0.7 to 1.2, the medium-polymerized grades of carboxymethylcellulose sodium are not as effective as tablet disintegrants. Thus, medium-viscosity carboxymethylcellulose sodium with a degree of substitution of 0.4 or 0.7 has moderate disintegrant properties. Those with a higher degree of substitution, such as 0.9 or 1.2, are poor disintegrants (Fig. 2). Highly substituted carboxymethylcellulose sodium can only be used as a disintegrant when the degree of polymerization is high.

3. With the same degree of substitution, the higher the degree of polymerization, the better are the disintegrant properties. The disintegrant efficacy improves directly with an increase in polymerization. Thus, VIIH is a better disintegrant than VIIM, which is better than VIIL (Fig. 3).

4. Carboxymethylcellulose sodium with a low degree of polymerization is a poor disintegrant irrespective of the degree of substitution. Thus, low-viscosity carboxymethylcelluloses with degree of substitution values of 0.4, 0.7, 0.9, and 1.2 are poor disintegrating agents.

5. The dissolution rate of the sulfamethoxazole tablets correlated with the disintegration times of the tablets.

6. There was no significant difference in disintegration time and in dissolution rate between the two experimental formulas.

Table IV—Minimum Viscosities for Good Disintegration Properties

Degree of Substitution	Minimum Viscosity of 2% Aqueous Dispersion at 25° Using Propeller-Type Mixer, cps
0.4	>150
0.7	>200
0.9	>1500
1.2	>3000

The minimum viscosity required for effective disintegration properties for the various grades of carboxymethylcellulose sodium is shown in Table IV. Aqueous dispersions of carboxymethylcellulose sodium with a degree of substitution of 0.4 should have a viscosity above 150 cps to have good disintegration properties. Similarly, the higher substituted carboxymethylcellulose sodium should meet the requirements for minimum viscosities to be considered a good disintegrant. Whenever a high degree of polymerization is mentioned, the viscosity will be much greater than the minimum stated in Table IV. Carboxymethylcellulose sodium with a low degree of polymerization will exhibit viscosities less than the minimum value in Table IV.

Further studies are in progress to evaluate the effect of carboxymethylcellulose sodium in solid dosage forms for: (*a*) disintegrants in tablets containing weak acids, weak bases, or neutral drugs; (*b*) comparisons with other presently available disintegrants; and (*c*) alteration of drug delivery systems through the utilization of the appropriate grade.

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Rotary Press Utilizing a Flexible Die Wall

GREGORY E. AMIDON, DONALD P. SMITH, and EVERETT N. HIESTAND ˣ

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Abstract □ A die with a flexible wall was constructed and evaluated on a specially modified instrumented rotary tablet press. The design permits an inward deflection of the die wall by a side punch, which rolls past a side compression roll during compression–decompression. The side compression roll is instrumented to monitor the applied side compression roll forces. On decompression, return of the die wall to its original position permits release of residual die wall pressure. The decreased residual die wall pressure can decrease fracture and capping of tablets for problem formulations. The performance was tested on three experimental formulations. For these formulations, tablets made in a conventional die exhibited severe capping problems. However, most tablets compressed in the special die were superior. With proper adjustment of punch and die wall compression forces, excellent tablets could be manufactured. The merits of the special die and modified tablet machine are substantiated, although this initial design did not provide adequate die wall pressure for all formulations. Further engineering efforts could result in practical production equipment.

Keyphrases □ Tableting machine—tablets produced from modified tableting machine with flexible die wall compared with those compressed conventionally □ Tablets—compressed with modified tableting machine compared with those conventionally compressed □ Compressed tablets—produced from modified tableting machine with flexible die wall, compared with tablets produced conventionally

It is generally accepted that bonding in a compressed tablet is the result of establishing and maintaining sufficient true areas of contact between particles. Lamination or capping of tablets, therefore, may seem unexplained since significant portions of a laminated or capped tablet remain densely packed after compression–decompression.

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