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Uptake of water into tablets with low-substituted carboxymethyl cellulose sodium as disintegrant

Lucy S.C. Wan and Kanneganti P.P. Prasad

Department of Pharmacy, National University of Singapore (Singapore)

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Summary

Low-substituted carboxymethylcellulose sodium (Nymcel ZSB 10, ZSD 16) which differ in the degree of substitution were used as disintegrants in sulphanilamide tablets formulated with methylcellulose (MC) of varying viscosity as a binder. The disintegration time of tablets with ZSD 16 was much higher than that of tablets containing ZSB 10 due to the higher content of water-soluble substances in the former. Both in the presence and absence of MC, the disintegration time increased with increasing concentration of either ZSB 10 or ZSD 16. Water uptake in tablets with MC and either of the two disintegrants followed the order: 1.25% > 5% > 2.5% Nymcel. The higher uptake at 5% disintegrant level did not, however, result in a lower disintegration time which was also found to decrease with an increase in the viscosity of MC. This was accompanied with increasing water uptake due to the higher hydration capacity of high viscosity MC. Both grades of low-substituted carboxymethylcellulose sodium were most effective when used in low concentrations. When observed microscopically, ZSB 10 particles were found to swell more than those of ZSD 16.

Introduction

The phenomena of disintegration and the mechanism of action of tablet disintegrants have been widely researched. Among other factors, tablet disintegration has been reported to be brought about by the expansion of entrapped air due to the heat of wetting caused by penetrating water (Matsumaru, 1959) and the swelling action of the disintegrant (Billups and Cooper, 1964; Ingram and Lowenthal, 1966; Patel and Hopponen, 1966). Swelling follows water uptake and is recognized as the most commonly observed mechanism of action of disintegrants (Lowenthal, 1973).

In modern times, a range of commercial disintegrants that are often branded as 'super disintegrants' are available. Added in small amounts to tablet formulations, these disintegrants can markedly improve the disintegration and dissolution properties of tablets (Shangraw et al., 1980).

Carboxymethylation of cellulose makes it soluble in water forming a viscous colloidal solution. The degree of substitution (DS) is the average number of carboxymethyl groups per glucose unit and can theoretically vary from 0 to 3. Most of the commercial products have DS between 0.5 and 1.

Correspondence: L.S.C. Wan, Department of Pharmacy, National University of Singapore, 10 Kent Ridge Cresent, Singapore 0511.

Nymcel is a brand of low-substituted carboxymethylcellulose (Nijma B.V., 1986).

Sodium carboxymethylcellulose with a low degree of substitution and a high degree of polymerization (DP) has been reported to be a good disintegrant (Shah et al., 1981). Its disintegrating properties were found to decrease as the degree of substitution increased and the degree of polymerisation decreased.

Drug release from hydrophilic matrices has been found to be influenced by disintegrants (Alderman, 1984). Studies conducted earlier involved the action of methylcellulose of different viscosity on the properties of tablets containing various 'super disintegrants' such as cross-linked sodium carboxymethylcellulose (Wan and Prasad, 1988a), sodium starch glycolate (Wan and Prasad, 1987a) and cross-linked polyvinylpyrrolidone (Wan and Prasad, 1988b).

This investigation together with an earlier presentation (Wan and Prasad, 1988d) examines the action of two different grades of low-substituted carboxymethylcellulose sodium on the water uptake and disintegration of tablets containing methylcellulose of varying viscosity.

Materials and Methods

Materials

Sulphanilamide of B.P. grade was chosen as a model drug. Two grades of low-substituted carboxymethylcellulose sodium (Nymcel ZSB 10, ZSD 16; Nyma B.V., The Netherlands) were used as disintegrants. The degree of substitution for Nymcel ZSB 10 was 0.20–0.26 while that for ZSD 16 was 0.28–0.36. The corresponding content of water-soluble substance was 18% and 70% w/w, respectively. The binder was methylcellulose (Tokyo Kasei, Japan) of the following viscosity grades: 20–30, 80–120, 350–550, 800–1200, 4000 and 7000–10000 cp.

Preparation of tablets

Tablets were prepared according to the procedure described in a previous study (Wan and Prasad, 1988a).

Aqueous penetration measurement

The method that has been adopted to study the penetration of water into the tablets is the same as described earlier (Wan and Prasad, 1986).

Disintegration time

The disintegration time (DT) of individual tablets at $37 \pm 0.5\,^{\circ}C$ was determined using a B.P. disintegration test apparatus (Van-Kel, model 71, U.S.A.) without the disc.

Microscopic examination

The experimental set-up for determining the shape and size of tablet excipients through microscopic examination is described in a previous publication (Prasad and Wan, 1987). It consists of a video camera (Hitachi VK-C500, Japan) linked to a microscope (American Optical, series one-ten Microstar, U.S.A.). The images of the particles when observed on the monitor screen (Sony Trinitron, KX-14 CP1, Japan) had a magnification of $\times 950$. A video recording of the particles was made using a video recorder (JVC VHS professional editing recorder BR-8600 E, Japan). Each second of recording had 25 frames of picture and using an editing control unit (JVC RM-86 U, Japan), a frame-by-frame analysis could be carried out. The procedure adopted for the microscopic study of the hydrated disintegrant particles is described elsewhere (Wan and Prasad, 1988c).

Results and Discussion

Nymcel ZSB 10

Three different levels of Nymcel ZSB 10 – 1.25%, 2.5% and 5% w/w – were added during wet granulation to sulphanilamide tablet formulations containing 250 mg of the active ingredient and 2% MC of varying viscosity. Tablets that contained sulphanilamide alone without any disintegrants did not disintegrate even after 30 min (Wan and Prasad, 1986). The disintegration time was reduced to about 57 s upon the addition of 1.25% ZSB 10 to the formulation (Table 1). However, the use of 2.5% and 5% ZSB 10 resulted in the DT being over 220 s. Water penetration into these tablets is shown in Fig. 1. The square of the

TABLE 1

Disintegration time of tablets containing varying amounts of Nymcel ZSB 10 and ZSD 16 in the absence of methylcellulose

Nymcel (%)	Disintegration time (s)	
	ZSB 10	ZSD 16
0	1800	1800
1.25	57.20 ± 3.70	248.60 ± 1.14
2.50	226.80 ± 2.39	428.80 ± 1.48
5.00	228.40 ± 1.14	676.40 ± 23.71

volume of water that has penetrated into the tablet (V^2) bears a linear relationship to the time (t) in accordance with the Washburn equation (Washburn, 1921).

Penetration of water is influenced by the amount of disintegrant in the tablet. The rate of penetration is much higher at the 1.25% level of the disintegrant than when 2.5% or 5% was used. At the end of 60 s, the value of V^2 (Table 1) increased, by about 12 times in the presence of 1.25% ZSB 10. Consequently, DT of the tablets prepared with 1.25% Nymcel ZSB 10 was also short. However, when larger amounts of the disintegrant were used, there was slight improvement in water penetration and DT as might be expected. This is in contrast to the action of the classical disintegrant, maize starch which was observed to improve water penetration and disintegration in an earlier study (Wan and Prasad, 1986). The use of higher concentrations of this disintegrant resulted in higher water uptake and lower DT.

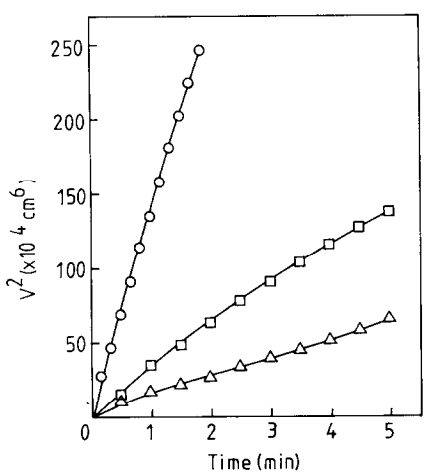

Fig. 1. Water penetration into sulphanilamide tablets containing different amounts of Nymcel ZSB 10 in the absence of methylcellulose: ○, 1.25%; △, 2.5%; □, 5%.

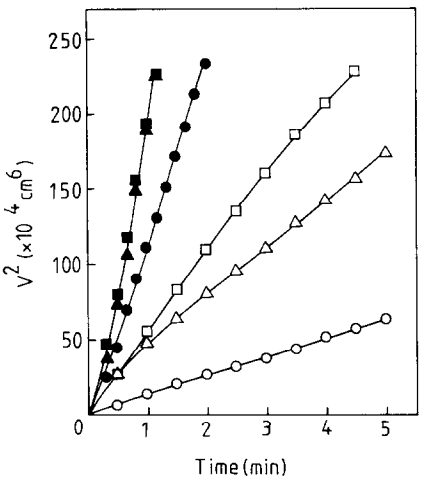

Fig. 2. Penetration of water into sulphanilamide tablets formulated with 1.25% Nymcel ZSB 10 and 2% methylcellulose (MC) of varying viscosity: ○, MC 20–30; △, MC 80–120; □, MC 350–550; ●, MC 800–1200; ▲, MC 4000; ■, MC 7000–10,000.

In comparison to the case when 1.25% ZSB 10 was used, the water uptake was low and DT was long when 2.5% and 5% ZSB 10 were added in the tablet formulation (Fig. 1 and Table 1). Tablets with 5% ZSB 10 have a slightly higher water uptake than those containing 2.5% ZSB 10 but this higher uptake of water did not result in a corresponding decrease in DT. Increased water uptake at a high concentration of this disintegrant is thought to be caused by the slow hydration of the disintegrant present on the tablet surface and outer layers of the compact. Whilst this takes place, the penetration of water into the tablet interior is hindered by the swollen disintegrant.

Tablets containing 1.25% ZSB 10 and 2% MC of varying viscosity also showed a linear relationship between V^2 and t (Fig. 2). Water uptake by these tablets is influenced by the viscosity grade of the MC. Formulations containing MC of a greater viscosity experience higher aqueous uptake. High viscosity grade MC has a high DP and greater capacity to absorb water and swell. Small amounts of Nymcel ZSB 10 improve the water uptake

TABLE 2

Effect of viscosity of methylcellulose on liquid penetration index of sulphanilamide tablets containing 2% methylcellulose and various amounts of Nymcel ZSB 10

MC grade	Liquid penetration index		
	1.25%	2.5%	5%
MC 20–30	0.21	0.22	0.27
MC 80–120	0.54	0.32	0.28
MC 350–550	0.86	0.63	0.42
MC 800–1200	2.08	1.17	0.65
MC 4000	3.59	1.32	1.19
MC 7000–10000	3.60	1.75	0.93

property of the tablet considerably due to the affinity of the disintegrant for water. According to the manufacturer (Nijma B.V., 1986), 1 g of Nymcel absorbs 50 g of water. The disintegrating property of Nymcel is based on its ability to absorb water and swell. Besides, it could also be aiding the hydration of the MC. In earlier studies, disintegrants such as maize starch (Wan and Prasad, 1986), cross-linked sodium carboxymethylcellulose (Wan and Prasad, 1988a) and sodium starch glycolate (Wan and Prasad, 1987a and b) were also found to facilitate the transport of water into the tablet interior and higher viscosity MC attained greater degree of hydration.

Water uptake by tablets formulated with 2.5% and 5.0% ZSB 10 and 2.0% MC also increased with increasing viscosity of the MC. The water penetration profiles, V^2 vs t for these tablets were found to be linear. Liquid penetration index, defined as the slope of the regression lines of plots of V^2 vs t was determined for various formulations (Table 2). Generally the liquid penetration index was higher for a tablet formulation containing a higher viscosity grade MC.

Viscous forces retard the entry of water at higher concentrations of the disintegrant. This is true both in the presence and absence of different viscosity MC. In the absence of MC, the order for water penetration is: 1.25% > 5% > 2.5% (Fig. 1), while in the presence of MC, the order is: 1.25% > 2.5% > 5% (Fig. 2, Table 2).

MC hydrates on contact with water and swells (Wan and Prasad, 1987c) and its adhesive effects are well known. The swelling and viscosity effect of MC could complement that of ZSB 10 and slow down the entry of water. This could be more apparent at higher concentrations of the disintegrant.

Wetting of tablet and penetration of water precede disintegration. Hence disintegration is usually correlated to water penetration. The *DT* of tablets with 2% MC and varying amounts of ZSB 10 decreased with an increase in the viscosity of the MC (Table 3). This is a consequence of the increased uptake of water when higher viscosity MC are used (Table 2). A similar observation was made in an earlier study using cross-linked sodium carboxymethylcellulose as a disintegrant (Wan and Prasad, 1988a). High viscosity MC has a greater capacity to adsorb water as discussed earlier. High viscosity would mean greater adhesive action which would in turn result in an increased DT. But the observations relating to disintegration (Table 3) do not support this hypothesis. It is possible that although high viscosity MC has greater adhesive action, these adhesive forces come into effect only when the MC is fully hydrated. In addition, high viscosity MC takes more time to hydrate fully due to its greater capacity to hydrate. Low viscosity MC, on the other hand, becomes fully hydrated quickly and exhibits its adhesive effect sooner. Thus the *DT* is longer for formulations containing the low viscosity MC.

Nymcel ZSD 16

Nymcel ZSD 16 was used at 3 concentrations – 1.25%, 2.5% and 5% – as a disintegrant in sulphanilamide tablets. In the presence of 1.25%

TABLE 3

Disintegrating time of tablets containing 2% methylcellulose (MC) and varying amounts of Nymcel ZSB 10

MC grade	Disintegration time (s)		
	1.25%	2.50%	5.00%
MC 20–30	90.20 ± 2.39	153.20 ± 2.28	387.80 ± 9.83
MC 80–120	50.00 ± 2.24	41.80 ± 1.48	323.40 ± 2.19
MC 350–550	40.40 ± 2.07	39.00 ± 1.00	268.60 ± 1.67
MC 800–1200	28.80 ± 1.79	32.60 ± 0.89	223.60 ± 1.14
MC 4000	25.40 ± 0.89	22.80 ± 0.84	141.40 ± 1.14
MC 7000–10000	25.00 ± 0.71	20.40 ± 0.55	135.00 ± 1.22

ZSD 16, *DT* was about 250 s (Table 1). *DT*, however, increased upon increasing the amount of ZSD 16 in the tablets to 2.5% and 5%. This effect is similar to the one shown by tablets containing various amounts of Nymcel ZSB 10 (Table 1). The *DT* of lactose tablets containing 10% Nymcel ZSD 16 has been reported to be greater than that of those containing 7.5% (Khan and Rooke, 1974). The *DT* of tablets formulated with ZSD 16 was higher than that of formulations containing ZSB 10 at all levels of the disintegrants (Table 1).

Penetration of water into sulphanilamide tablets containing varying amounts of ZSD 16 is shown in Fig. 3. The order for water penetration rate is: 1.25% > 5% > 2.5%, which is similar to that observed for tablets made using ZSB 10 (Figs. 1, 2). Tablets with 1.25% ZSD 16 have V^2 values (after 60 s) only 3 times higher when compared with those made without disintegrants. Tablets containing 5% ZSD 16 have more water uptake than those containing 2.5% ZSD but this increased water uptake did not result in a lower *DT*. Increased water uptake in the case of tablets with 5% ZSD 16 was thought to be the result of surface saturation, i.e. hydration of disintegrant present on the tablet surface, the tablet interior being relatively inaccessible to the water. A comparison of tablets containing ZSB 10 and ZSD 16 shows that the former have a higher water uptake and

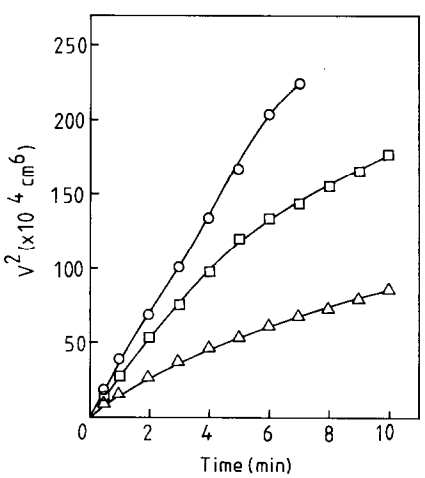

Fig. 3. Uptake of water by sulphanilamide tablets containing different amounts of Nymcel ZSD 16 in the absence of methylcellulose: ○, 1.25%; △, 2.5%; □, 5%.

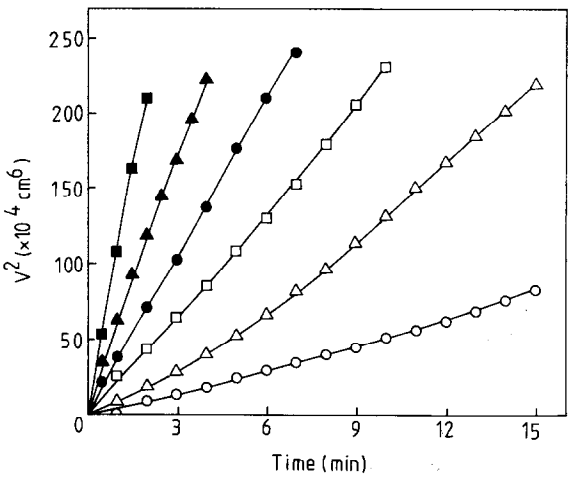

Fig. 4. Water penetration into sulphanilamide tablets formulated with 1.25% Nymcel ZSD 16 and 2% methylcellulose (MC) of varying viscosity: ○, MC 20–30; △, MC 80–120; □, MC 350–550; ●, MC 800–1200; ▲, MC 4000; ■, MC 7000–10,000.

correspondingly lower *DT* probably because of retarded water uptake following swelling of ZSD 16 particles and blockage of the pores within the tablet.

The incorporation of MC in sulphanilamide tablets formulated with Nymcel ZSD 16 as a disintegrant has an effect on the water uptake and *DT* of these tablets. A higher uptake of water was observed in tablets containing high viscosity MC and 1.25% ZSD 16 (Fig. 4). The order of water uptake was similar to that observed in the case of tablets with varying amounts of Nymcel ZSB10. But when 2.5% and 5% ZSD 16 were used, this pattern of behaviour was not followed as indicated by the liquid penetration indices (Table 4). Tablets with low viscosity MC still have lower water uptake rates; however, the tablets containing the high viscosity MC do not exhibit water uptake rates in the order of increasing viscosity. The high viscosity of the MC combined with the viscous forces that arise due to the high solubility of this grade of Nymcel retarded the entry of water into the tablets. In the absence of MC, the order of water uptake was: 1.25% > 5% > 2.5%, and this order held even in the presence of MC, indicating that ZSD 16 has a more dominant action than MC in influencing water penetration into the tablets.

TABLE 5

Disintegration time of tablets containing 2% methylcellulose (MC) and varying amounts of Nymcel ZSD 16

MC grade	Disintegration time (s)		
	1.25%	2.50%	5.00%
MC 20–30	673.20 ± 2.86	791.80 ± 5.31	978.40 ± 6.11
MC 80–120	303.60 ± 7.16	616.60 ± 6.66	937.00 ± 12.71
MC 350–550	129.40 ± 3.36	534.40 ± 7.13	914.00 ± 10.68
MC 800–1200	179.80 ± 4.49	472.20 ± 13.05	728.00 ± 4.69
MC 4000	90.40 ± 2.70	313.20 ± 4.32	709.40 ± 5.68
MC 7000–10000	53.40 ± 2.41	417.80 ± 16.56	661.40 ± 6.62

The disintegration times of tablets containing 2% MC and varying amounts of ZSD 16 decreased with increasing viscosity of the MC (Table 5). This was true at all 3 concentrations of ZSD 16. Erratic water uptake at higher concentrations of the disintegrant as discussed earlier did not seem to influence the *DT*. At all levels of the disintegrants, *DT* in the case of tablets with ZSD 16 was higher than that of tablets with ZSB 10 (Tables 3 and 5). The relatively lower water uptake shown by tablets with ZSD 16 could be an influencing factor.

Swelling of disintegrants

Swelling action that follows absorption of water is widely recognized as being responsible for the disintegrating activity of many disintegrants. Disintegration is the net outcome of the forces that hold the tablet together (adhesive forces) and forces that tear apart the tablet structure (disintegrating forces). These forces are activated when the constituents of the tablet are wetted.

TABLE 4

Effect of viscosity of methylcellulose on liquid penetration index of sulphanilamide tablets containing 2% methylcellulose and various amounts of Nymcel ZSD 16

MC grade	Liquid penetration index		
	1.25%	2.5%	5%
MC 20–30	0.08	0.12	0.16
MC 80–120	0.18	0.19	0.23
MC 350–550	0.35	0.26	0.23
MC 800–1200	0.57	0.20	0.26
MC 4000	0.92	0.35	0.41
MC 7000–10000	1.81	0.29	0.34

The size and shape factors of dry and hydrated Nymcel particles were studied as described in earlier studies (Prasad and Wan, 1987; Wan and Prasad, 1988c). Increases in the projected area diameter and perimeter diameter for hydrated ZSB 10 particles are over 60% and 42%, respectively, while the increases for hydrated ZSD 16 particles are about 52% and 6%, respectively. The lower degree of swelling shown by ZSD 16 particles may be due to its higher solubility. Adhesive forces that follow solubility of the disintegrant also retard swelling. The higher swelling shown by ZSB 10 could account for the lower *DT* observed for tablets containing this disintegrant. Swelling follows absorption of water and hence a higher degree of swelling would require a greater amount of water uptake. Besides, the swelling disintegrant creates cracks and fissures in the tablet into which the water penetrates partly by capillary action.

In conclusion, Nymcel ZSB 10 and ZSD 16 are effective disintegrants at low concentrations. At high concentrations, the disintegration time is high and water uptake is slow which is in contrast to the action of classical disintegrants such as starch. Formulations containing a higher viscosity MC have higher aqueous uptake but the *DT* is still low due to the adhesive action of the MC. Microscopic examination of Nymcel particles shows that ZSB 10 particles swell more than ZSD 16. Nymcel ZSB 10 is a better disintegrant than ZSD 16.

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