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Effect of microcrystalline cellulose and cross-linked sodium carboxymethylcellulose on the properties of tablets with methylcellulose as a binder

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

Department of Pharmacy, National University of Singapore, Singapore (Singapore)

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Summary

The action of microcrystalline cellulose and cross-linked sodium carboxymethylcellulose on the water penetration, disintegration and dissolution of tablets containing methylcellulose of varying viscosity as a binder was studied. Microcrystalline cellulose was found to have a limited capability to act as a disintegrant in the presence of methylcellulose. The disintegration time was long, the dissolution was slow and the water uptake was low for these tablets, whereas cross-linked sodium carboxymethylcellulose improved these tablet properties by its marked capacity to absorb water, swell and thereby overcome the binding and adhesive effect of and blocking of tablet pores by methylcellulose. These tablets, with higher viscosity grades of methylcellulose disintegrated into large fragments. As a result, they had a lower disintegration time and a higher water uptake.

Introduction

Methylcellulose is used as a binder in tablet formulations and when in contact with water it absorbs water, hydrates and swells. Microcrystalline cellulose (MCC) and cross-linked sodium carboxymethyl cellulose are widely used as tablet excipients. The binding property of MCC (Nakai et al., 1977; Imaizumi et al., 1983) as well as the cohesive characteristic (Lee et al., 1965; Reier and Shangraw, 1966) have been studied. Tablets formulated with MCC have been found to disintegrate rapidly (Esnard et al., 1973); others have shown that there was no effect on disintegration time (Wan and Choong, 1986a). Cross-linked sodium carboxymethylcellulose has been demonstrated to improve disintegration and dissolution rate (Miller et al., 1980; Gissenger and Stamm, 1980; Caramella et al., 1984). Although much research has been directed on these disintegrants there has been little investigation on their action in tablets with methyl cellulose as a binder. This binder is likely to take up water readily and thereby control the action of the disintegrant.

The aim of this study is to examine the effect of methylcellulose of varying viscosity and MCC or cross-linked sodium carboxymethylcellulose on

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

each other and the resultant action on water penetration, disintegration and dissolution of tablets.

Materials and Methods

Materials

Sulphanilamide, in fine powder and of B.P. grade was chosen as a model drug. The disintegrants were MCC (Avicel PH101, FMC Corp., U.S.A.) and cross-linked sodium carboxymethylcellulose (Ac-Di-Sol, FMC Corp., U.S.A.). The binder was methylcellulose (Tokyo Kasei) with the following viscosity grades: 20–30, 80–120, 350–550, 800–1200, 4000 and 7000–10000 cp.

Preparation of tablets

The drug, disintegrant and methylcellulose were mixed thoroughly using a pestle and mortar for 15 min (as the amount involved was small, not more than 50 g) and granulated through a 1-mm sieve. The granules were dried at 60 °C for 4 h and then regranulated through the same sieve. Those retained by a 0.375-μm sieve were taken as granules and those which passed through this sieve were taken as fines. To the granules, 10% fines were added, mixed thoroughly and then compressed into tablets to an apparent density of 1.266 g cm^{-3}. A weighed amount of the granule mixture containing the equivalent of 250 mg of sulphanilamide was fed manually into the die of a single-punch tablet machine (Manesty, model 2E, England) fitted with flat-surface punches of diameter 9.525 mm.

Liquid penetration measurement

The method adopted was that described previously (Wan and Choong, 1986b). Essentially it consists of a sintered glass filter connected to a horizontal graduated capillary containing distilled water. The uptake of water into the tablet placed centrally on the sintered glass filter is measured by the change in volume of water in the capillary with time. The mean and S.D. of 5 replicates were calculated for each formulation.

Disintegration

The disintegration of individual tablets at 37 ± 0.5 °C was determined using a B.P. disintegration test apparatus (Van-Kel, Model 71, USA) without the disc. The mean and S.D. of 5 determinations were calculated.

Dissolution

The dissolution of tablets at 37 ± 0.5 °C was measured using the rotary basket method (Hanson, Easi-Lift, Model QC72R, USA) and a speed of 100 rpm. Filtered samples were withdrawn periodically and assayed spectrophotometrically (Perkin Elmer, Model 550, USA) at 260 μm. For each formulation 5 dissolution runs were carried out and the mean and S.D. calculated.

Results and Discussion

Microcrystalline cellulose

MCC was incorporated in sulphanilamide tablets at 3 levels, 2.5, 5 and 10% w/w. It was added during the wet granulation process. Methylcelluloses of varying viscosity were used as binders. Tablets containing sulphanilamide without excipients failed to disintegrate within 30 min. The tablets were observed to undergo slow surface erosion as reported earlier (Wan and Prasad,

TABLE 1

Water uptake into and disintegration of sulphanilamide tablets containing MCC and no methylcellulose

MCC conc. (%)	Volume^2 of water penetrated ($\times 10^{-4}$ cm^6)			Disintegration time (s)
	10 s	20 s	30 s	
0	5.36 ± 0.19	9.38 ± 0.22	10.35 ± 0.29	> 1800
10	13.39 ± 1.33	27.56 ± 1.66	32.35 ± 1.31	415.00 ± 15.91

1986a). The addition of 10% MCC reduced the disintegration time of the tablets to about 415 s. The water penetration data (Table 1) shows that the uptake of water into the tablets was increased by about 3-fold in the presence of MCC and this is accompanied by a shortening of the disintegration time. This is in agreement with the findings reported (Nogami et al, 1969; Marshall and Sixsmith, 1975). Penetration of water into the tablet interior causes the breakage of hydrogen bonds holding particles of MCC and drug together. It has been found that water penetration into tablets containing MCC is rapid (Sixsmith, 1977).

Fig. 1 shows the water penetration profiles of tablets containing 2.5% MCC and 2% methylcellulose of varying viscosity. The amount of water taken up is small. There is no distinct pattern of behaviour except perhaps there is an apparent larger amount of water taken into tablets with methylcellulose of higher viscosity. Similar behaviour was noted for tablets with higher levels of MCC, 5 and 10%. Increasing amounts of MCC does not always result in increasing water penetration for any one viscosity grade of methylcellulose.

A long disintegration time could be the result of low water penetration rates. Portions of the tablet that were penetrated by water were seen to have a swollen appearance. On contact with water, methylcellulose has been found to swell (Wan and Prasad, 1987). A slow water uptake encourages the methylcellulose present to swell fully and thereby block the pores in the tablet. As has been documented, absorption of water by MCC is by capillary action, molecular swelling is not significant and the crystal structure of MCC is retained even after water absorption (Caramella et al., 1984).

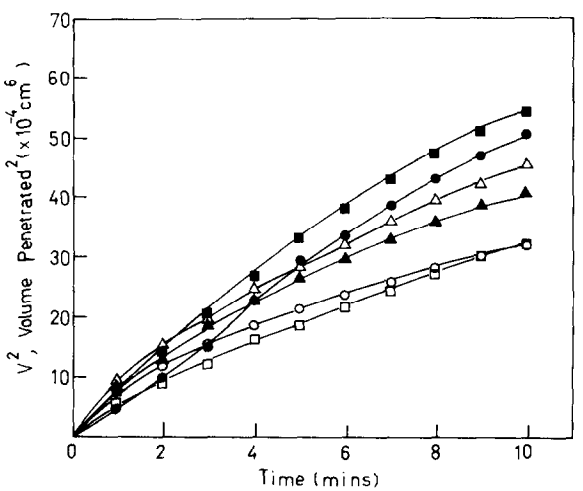

Fig. 1. Water penetration into sulphanilamide tablets containing 2.5% microcrystalline cellulose and 2% MC of varying viscosity: ○, MC_{20-30}; △, MC_{80-120}; □, $MC_{350-550}$; ●, $MC_{800-1200}$; ▲, MC_{4000}; ■, $MC_{7000-10000}$.

Blocking of the pores by the swelling methylcellulose slows down the penetration of water into the tablet pores. These pores could be the interparticular spaces or intra-particular capillaries such as those present in MCC particles. Blocking of these pores regulates the flow of water into the tablet interior and thus prevents MCC from exhibiting its limited 'wicking' action quickly.

It has been shown that water penetration into tablets is the controlling step in the disintegration process when the tablet contains a slightly swelling but hydrophilic disintegrant (Bolhuis et al., 1982). Tablets containing MCC have been found to show a low water uptake and swelling ratio (Imaizumi et al., 1983) as well as a longer disintegration time than those containing starch (Nogami et al., 1969).

Sulphanilamide tablets containing 2.5, 5 and 10% MCC and 2% methylcellulose of varying viscosity did not disintegrate even after 30 min. When removed from the disintegration test assembly, they were observed to be soft to the touch. Although water had penetrated into the tablet interior, the swelling of methylcellulose appears to have retarded the rate of water penetration. In the case of sulphanilamide tablets containing only the drug without excipients, at the end of 30 min of the disintegration test, the tablet interior was found to be not wetted at all. Disintegration was by surface erosion and the water failed to reach the core. MCC has certainly helped in the uptake of water, however slow it may be. Water having penetrated the tablet interior should bring about a breakdown of the tablet matrix and thus cause disintegration. But the 'water-logged' tablets retained their shape even after 30 min of the disintegration test. Disintegration commenced initially

TABLE 2

Dissolution of sulphanilamide tablets with and without MCC

MCC conc. (%)	% Dissolved				
	20 min	40 min	60 min	120 min	180 min
0	31.46 ± 0.77	58.25 ± 1.00	81.90 ± 0.66	98.11 ± 0.11	100
10	29.98 ± 0.41	48.83 ± 1.10	61.98 ± 0.91	85.12 ± 0.30	100

with some flaking off after which surface erosion followed. Flakes could be the loosely bonded crust of the tablet.

The cohesive properties of MCC have been studied and hydrogen bonding has been reported to be responsible for these properties (Reier and Shangraw, 1966). This bonding imparts mechanical strength to the tablet by holding the particles together. The cohesive and adhesive action of MCC leads to difficulty in disintegration when mixtures of starch and MCC are used in various ratios (Nogami et al., 1969). This was particularly so with a high concentration of MCC because this cellulose is more cohesive and adhesive than starch.

The question in this case here is whether the cohesive action of MCC is significant in influencing the disintegration of tablets. Hydrogen bonds which impart cohesiveness are broken by the penetrating water. This is because secondary valence forces are reduced in proportion to the dielectric constant of the fluid appearing across the few Ångstrom distance of separation. When MCC is wetted, bonding energy is reduced to a point where it is not a factor of strength. Under such circumstances, opposition to disintegration would be due to the mechanical interlocking and entanglement between granules and adhesive action of other excipients. Of these, the latter seems to be important. The adhesive characteristic of methylcellulose is well known (Wan and Prasad, 1986b) and it does play a role in the present study. A slow uptake of water into the tablet has assisted methylcellulose in demonstrating this effect.

In the presence of methylcellulose, MCC has limited capability to function as a disintegrant. Although water penetrates into the tablet, the forces of dispersion, reported to be due to the heat of immersion (Matsumaru, 1959) or the swelling of particles (Patel and Hopponen, 1966) are not able to overcome the binding forces caused by the adhesive action of methylcellulose.

The dissolution data on sulphanilamide tablets are given in Table 2. The addition of MCC did not improve the dissolution. On the contrary, tablets with this disintegrant had a lower dissolution rate than tablets containing only sulphanilamide. Both tablet formulations with and without MCC released all the drug within 3 h. Table 3 shows the dissolution data of tablets containing 2% of methylcellulose of various viscosity grades as well as 2.5% MCC. There is practically no differentiation between the tablets. After a period of 4 h, only

TABLE 3

Dissolution of sulphanilamide tablets containing 2.5% MCC and 2% methyl cellulose (MC) of varying viscosity

MC	% Dissolved					
	20 min	40 min	60 min	120 min	180 min	240 min
20–30	13.70 ± 0.64	23.43 ± 1.16	30.49 ± 1.71	50.89 ± 0.82	63.64 ± 1.04	73.19 ± 1.01
80–120	12.40 ± 0.68	19.34 ± 1.01	24.38 ± 1.23	37.43 ± 0.27	50.47 ± 1.61	59.31 ± 0.74
350–550	11.92 ± 0.36	18.21 ± 0.54	22.89 ± 0.45	33.75 ± 0.54	42.41 ± 0.63	49.64 ± 0.36
800–1 200	13.70 ± 0.47	20.29 ± 0.47	25.27 ± 0.54	36.36 ± 1.04	46.14 ± 0.72	53.68 ± 0.72
4000	13.35 ± 0.36	19.99 ± 0.45	24.97 ± 0.44	36.77 ± 0.55	44.31 ± 0.72	50.77 ± 0.62
7000–10000	12.46 ± 0.31	19.10 ± 0.27	24.32 ± 0.37	35.17 ± 0.72	43.42 ± 0.36	50.53 ± 0.36

TABLE 4

Dissolution of sulphanilamide tablets containing 5% MCC and 2% MC of varying viscosity

MC	% Dissolved					
	20 min	40 min	60 min	90 min	120 min	180 min
20–30	13.99 ± 0.27	18.92 ± 0.21	25.15 ± 0.80	32.44 ± 0.63	40.15 ± 1.08	53.62 ± 1.08
80–120	12.52 ± 0.57	19.04 ± 0.71	24.50 ± 0.72	30.60 ± 0.89	35.35 ± 0.98	44.13 ± 0.99
350–550	12.58 ± 0.68	18.98 ± 0.54	24.50 ± 0.37	30.66 ± 0.45	35.53 ± 0.37	44.25 ± 0.27
800–1 200	12.93 ± 0.74	19.51 ± 0.72	24.79 ± 0.54	34.75 ± 2.17	36.53 ± 1.25	46.80 ± 0.99
4 000	12.81 ± 0.64	19.63 ± 0.62	24.68 ± 0.54	30.55 ± 0.72	35.59 ± 0.71	43.59 ± 0.36
7 000–10 000	12.93 ± 0.45	20.11 ± 0.64	24.44 ± 0.67	33.93 ± 0.72	35.41 ± 0.48	44.48 ± 0.36

about 73% and 59% of the drug dissolved from tablets containing MC_{20-30} and MC_{80-120} respectively. All the other tablets showed only about 50% release. The undissolved mass inside the dissolution basket was mucilaginous in appearance. The entire material had been wetted and there were not dry portions even in the interior.

Tablets containing 5% MCC and 2% methylcellulose of different viscosity grades exhibited similar dissolution profiles (Table 4), the only exception being that tablets with MC_{20-30} had a slightly higher dissolution rate. The amount of drug released after 3 h was 54% for tablets with MC_{20-30} and 45% for tablets with all the other grades of methylcellulose studied.

A similar behaviour was observed with tablets containing 10% MCC and 2% methylcellulose of different viscosity grades. A slightly higher dissolution rate was shown by tablets with MC_{20-30} (Table 5). After a dissolution run of 3 h, the amount of drug released by tablets with MC_{20-30} was about 60% and that by the other tablets was 41–45%.

Thus, the results show that tablets containing different amounts of MCC and methylcellulose of varying viscosity exhibit slow dissolution. This is not in agreement with the findings reported (Chalmers and Elworthy, 1976), where MCC when used as a granulated form was found to increase the dissolution even at low concentration. The adhesive nature of methylcellulose can retard dissolution.

Cross-linked sodium carboxymethylcellulose

Cross-linked sodium carboxymethylcellulose (cross-linked Na CMC) was incorporated in sulphanilamide tablets at 3 levels, 1.25, 2.5 and 5% w/w with the same series of methylcellulose as mentioned in the above. Without excipients, tablets of sulphanilamide failed to disintegrate in 30 min but incorporation of cross-linked Na CMC lowered the disintegration time markedly, to a few seconds. The disintegration times for tablets with 1.25 and 2.5% cross-linked Na CMC were 8.4 and 5 s respectively. With 5% of this disintegrant, the disintegration time however, increased to 22 s.

TABLE 5

Dissolution of sulphanilamide tablets containing 10% MCC and 2% MC of varying viscosity

MC	% Dissolved					
	20 min	40 min	60 min	90 min	120 min	180 min
20–30	15.94 ± 0.79	25.27 ± 0.64	32.62 ± 0.80	41.64 ± 0.81	49.35 ± 0.91	60.14 ± 1.07
80–120	12.04 ± 0.27	18.98 ± 0.45	24.20 ± 0.47	30.78 ± 0.36	36.24 ± 0.37	45.61 ± 0.62
350–550	12.22 ± 0.37	18.51 ± 0.62	22.96 ± 0.47	29.12 ± 0.72	34.10 ± 0.45	41.40 ± 0.54
800–1 200	12.39 ± 0.28	18.92 ± 0.54	23.78 ± 0.45	29.72 ± 0.36	34.70 ± 0.36	44.07 ± 0.45
4 000	12.34 ± 0.21	18.98 ± 0.54	23.90 ± 0.63	29.42 ± 0.27	34.64 ± 0.62	43.30 ± 0.45
7 000–10 000	12.51 ± 0.68	18.86 ± 0.64	23.61 ± 0.27	29.42 ± 0.54	33.93 ± 0.37	42.82 ± 0.27

This indicates that there is an optimum quantity of the disintegrant that can be effectively employed to reduce the disintegration time.

Water penetration measurements of tablets containing only sulphanilamide show that water penetration is extremely slow. The volume of water taken up after 3 min was only 0.3690 ml, whilst with 10% cross-linked Na CMC there was a marked increase, 0.1549 ml within 10 s. With smaller amounts of cross-linked Na CMC, 2.5 and 5%, the same volume of water, 0.1549 ml took about 30 s to penetrate into the tablet. This large amount of water taken up could result in the low disintegration times of the tablets.

The rapid disintegration brought about by cross-linked Na CMC has been attributed to the strong relaxation of cellulose fibres, which leave large pores in the tablet matrix, facilitating fast water penetration and breaking of hydrogen bonds. The fibrous nature of this disintegrant allows intraparticulate and extraparticulate 'wicking' of water even at low concentrations. The extent of water penetration is many times higher than that mentioned earlier with tablets containing MCC.

The addition of 2% methylcellulose to sulphanilamide tablets with cross-linked Na CMC increased the disintegration time. For all 3 levels of the disintegrant, the disintegration time was higher than that of tablets without methylcellulose (Table 6). The disintegration time of tablets with 5% cross-linked Na CMC was higher than that with 2.5% of the same disintegrant for all viscosity grades of methylcellulose. In the case of MC_{20-30}, MC_{80-120}, $MC_{350-550}$ and $MC_{800-1200}$ the disintegration time increased with increase in disintegrant concentration. Cross-linked Na CMC has a water soluble content of about 6%. When used at higher levels, the water soluble content which can be expected to exhibit viscous effects associated with sodium carboxymethyl cellulose, could complement the adhesive action of methylcellulose. Only in the case of MC_{4000} and $MC_{7000-10000}$ the disintegration time showed a reduction when the amount of cross-linked Na CMC was increased from 1.25 to 2.5%. A further increase in the amount of this disintegrant to 5% resulted in lengthening of the disintegration time. The low disintegration time in these cases could be because the tablets fragmented into large particles when high viscosity grades of methylcellulose were incorporated in the tablets. Breaking up of the tablet exposes the interior of the tablet to water. The large disintegrated fragments of the tablet remained intact after disintegration test without undergoing further fragmentation.

For a fixed level of cross-linked Na CMC, the disintegration time decreased with increase in viscosity of methylcellulose (Table 6). The tablet disintegrated into large fragments, with larger fragments for those with greater viscosity of the binder. The higher disintegration time of tablets with MC_{4000} and $MC_{7000-10000}$ in the presence of 1.25% cross-linked Na CMC was due to the large fragments not disintegrating fast enough because of the low level of the disintegrant, 1.25%. These tablets however, cracked readily on contact with water.

Fig. 2 shows the water penetration profiles of tablets with 1.25% and 2% of disintegrant and binder respectively. The amount of water penetrated increased with the viscosity grade of methylcellulose. This correlates well with the decreasing disintegration time. Though the disintegration time of tablets with high viscosity grades,

TABLE 6

Disintegration of sulphanilamide tablets containing different amounts of cross-linked Na CMC and 2% MC of varying viscosity

Cross-linked Na CMC (%)	Disintegration time (s)					
	MC_{20-30}	MC_{80-120}	$MC_{350-550}$	$MC_{800-1200}$	MC_{4000}	$MC_{7000-10000}$
1.25	31.20 ± 0.45	30.40 ± 0.55	27.60 ± 0.56	24.40 ± 0.55	29.40 ± 0.55	50.40 ± 0.55
2.5	118 ±4	51.60 ± 1.14	36.40 ± 0.55	32.20 ± 0.84	24.00 ± 0.71	25.80 ± 0.45
5	252.20 ± 7.16	159.20 ± 6.14	108.00 ± 1.58	79.60 ± 1.52	62.00 ± 2.24	47.80 ± 0.45

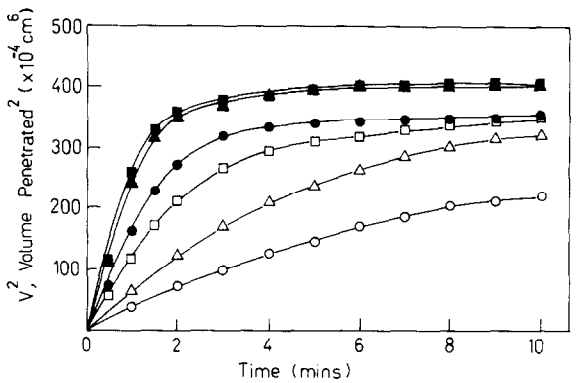

Fig. 2. Penetration of water into sulphanilamide tablets formulated with 1.25% cross-linked Na CMC and 2% MC of varying viscosity; ○, MC_{20-30}; △, MC_{80-120}; □, $MC_{350-550}$; ●, $MC_{800-1200}$; ▲, MC_{4000}; ■, $MC_{7000-10000}$.

MC_{4000} and $MC_{7000-10000}$ was longer, their corresponding water penetration rate was greater relative to the other viscosity grades of methylcellulose. Saturation volumes are higher for tablets with more viscous methylcellulose.

With 2.5% cross-linked Na CMC, a similar trend to that observed with 1.25% was noted (Fig. 3) with respect to water penetration rate as well as

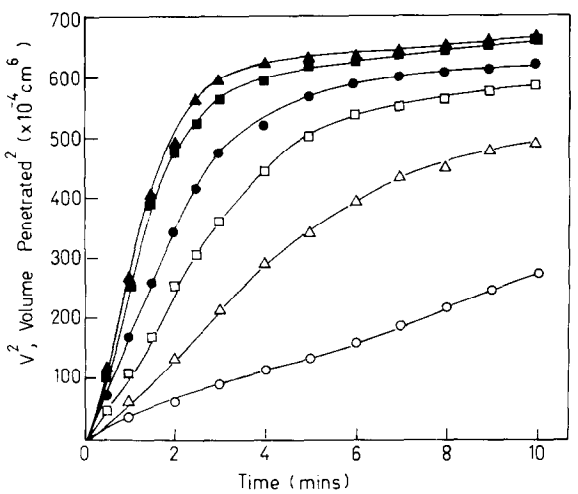

Fig. 3. Water penetration profiles of sulphanilamide tablets with 2.5% cross-linked Na CMC and 2% MC of varying viscosity; ○, MC_{20-30}; △, MC_{80-120}; □, $MC_{350-550}$; ●, $MC_{800-1200}$; ▲, MC_{4000}; ■, $MC_{7000-10000}$.

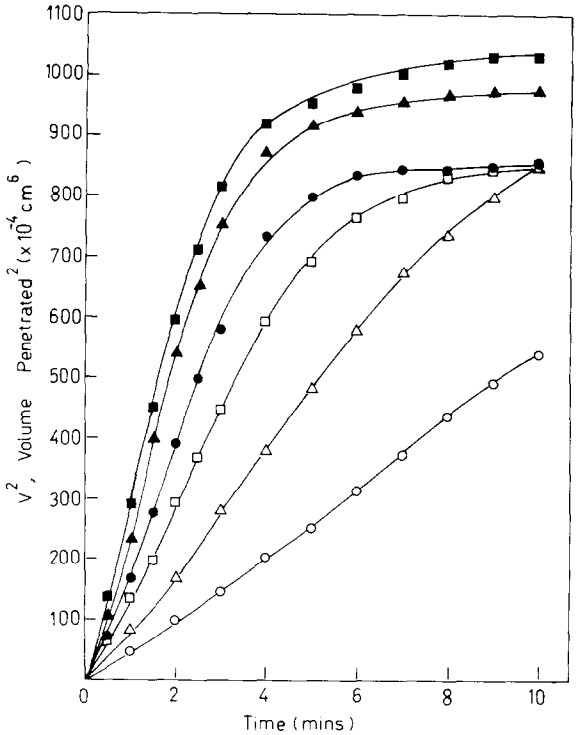

Fig. 4. Uptake of water by sulphanilamide tablets containing 5% cross-linked Na CMC and 2% MC of varying viscosity: ○, MC_{20-30}; △, MC_{80-120}; □, $MC_{350-550}$, ●, $MC_{800-1200}$; ▲, MC_{4000}; ■, $MC_{7000-10000}$.

to saturation volume attained in the tablets. With a further increase of the disintegrant to 5%, the trend did not change (Fig. 4).

A comparison of the saturation volumes of different levels of cross-linked Na CMC (Figs. 2–4) shows that for every viscosity grade of methylcellulose, the saturation volume increased with increase in the amount of cross-linked Na CMC.

Cross-linked Na CMC is most certainly responsible for the high penetration rate and saturation volume but methylcellulose also has a role in this process. Cross-linked Na CMC has a great capacity to take up water. In optimum quantity, it 'propels' the water into the tablets, delivering it to the methylcellulose which then becomes hydrated and exerts its effect on disintegration. Slow uptake of water gives the methylcellulose in the outer layers of the tablet sufficient time to hydrate fully and produce a retarding action on the penetration of water into the tablet by blocking the pores.

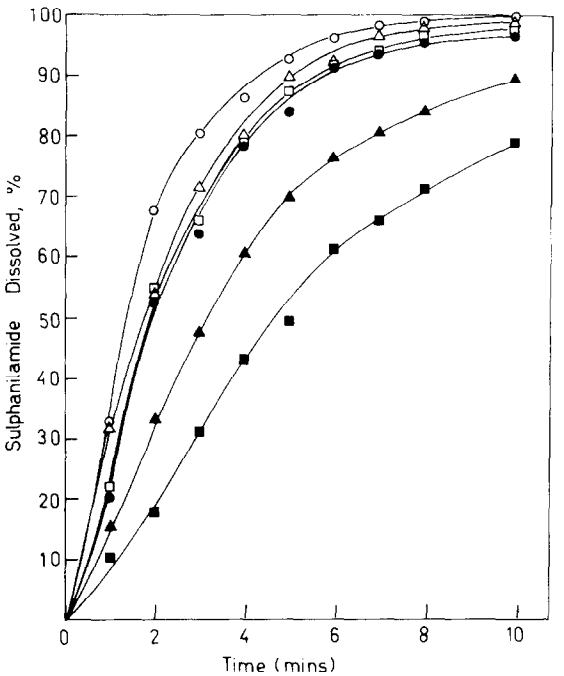

Fig. 5. Dissolution profiles of sulphanilamide tablets containing 1.25% crosslinked Na CMC and 2% MC of varying viscosity: ○, MC_{20-30}; △, MC_{80-120}; □, $MC_{350-550}$; ●, $MC_{800-1200}$; ▲, MC_{4000}; ■, $MC_{7000-10000}$.

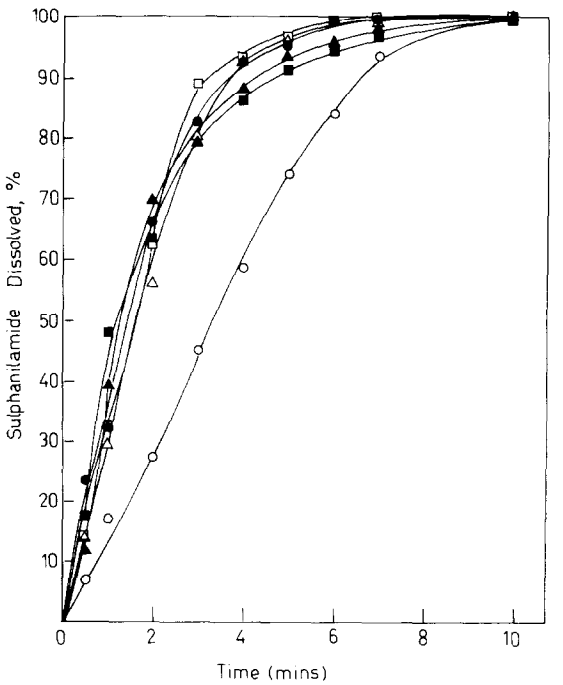

Fig. 6. Dissolution profiles of sulphanilamide tablets containing 2.5% cross-linked Na CMC and 2% MC of varying viscosity: ○, MC_{20-30}; △, MC_{80-120}; □, $MC_{350-550}$; ●, $MC_{800-1200}$; ▲, MC_{4000}, ■, $MC_{7000-10000}$.

Dissolution profiles (Fig. 5) show that dissolution of tablets with 1.25% cross-linked Na CMC is rapid. Those with low viscosity grades were able to release all the drug within 10 min, those with high viscosity grades, MC_{4000} and $MC_{7000-10000}$ released 90% and 80% of the drug respectively at the end of the same period of time. The small amount of disintegrant incorporated in this case apparently is insufficient to counter the adhesive action of methylcellulose. Adhesive action of methylcellulose increases with viscosity and hence reduces dissolution of tablets. In the case of 2.5% cross-linked Na CMC (Fig. 6) there was improvement in the dissolution rate, with practically no differentiation between the dissolution profiles of all the tablets. The exception is the dissolution of tablets with MC_{20-30} in which case the rate of dissolution of tablets was lower. This correlates well with the long disintegration time mentioned for these tablets. All the tablets, however, released the drug completely in 10 min. With 5% cross-linked Na CMC, the drug was released completely within 7 min (Fig. 7). Tablets containing higher viscosity grades of methylcellulose had higher dissolution rates. Cross-linked Na CMC does enhance dissolution of tablets containing methylcellulose as a binder.

Thus, the addition of MCC to sulphanilamide tablets without other excipients does improve the disintegration but this improvement is nullified in the presence of methylcellulose. MCC particles have a limited 'wicking' action. Slow rate of water uptake encourages methylcellulose to hydrate and exhibit its adhesive action, holding the tablet components together thereby retarding disintegration and dissolution. In contrast, cross-linked Na CMC particles have a great capacity to absorb water. High rates of water uptake result in low disintegration times and high dissolution rate. But then, methylcellulose particles do not have sufficient

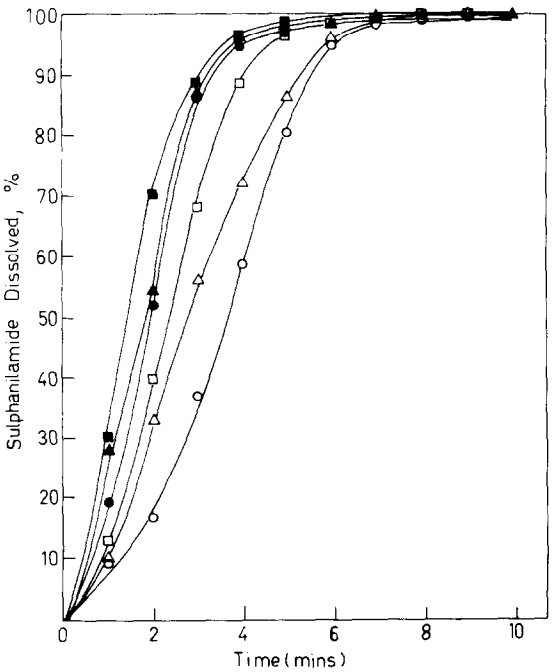

Fig. 7. Dissolution profiles of sulphanilamide tablets containing 5% cross-linked Na CMC and 2% MC of varying viscosity: ○, MC_{20-30}; △, MC_{80-120}; □, $MC_{350-550}$; ●, $MC_{800-1200}$; ▲, MC_{4000}; ■, $MC_{7000-10000}$.

time to hydrate and their adhesive action is not demonstrated.

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