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Action of Methylcellulose on Disintegration and Dissolution Properties of Tablets

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The action of methylcellulose (MC) of different viscosity on the properties of tablets was studied. The penetration of water into the tablets was retarded by the presence of MC. The disintegration time of tablets was reduced with increasing viscosity of MC and a high level of starch. This correlates with the water penetration data. Dissolution of tablets is governed to a lesser extent by water uptake into the tablets. It is more influenced by the gel formed by MC and the diffusion of drug through this layer. With higher concentration of methylcellulose the adhesiveness of MC becomes more significant in decreasing dissolution of the tablets. MC in contact with water hydrates, swells, gels and becomes adhesive. These actions are affected by starch, MC concentration and viscosity.

Keywords——methylcellulose; tablets; water penetration; hydration; disintegration; dissolution; gel formation; adhesiveness

Binders can influence the dissolution of drugs.[1-8] Cellulose derivatives have found wide applications as binders and disintegrants.[9] Methylcellulose (MC) has been used in tablet formulation studies[10-12] and it was shown that it has binding and adhesive properties due to gelation[13] and that it improves the strength of tablets.[14,15] MC has a unique property that distinguishes it from other commercial hydrocolloids. Most gums will decrease in viscosity when the temperature of their solution is increased. MC is soluble in cold water and heating reduces its viscosity up to a point.[16] However, at certain elevated temperatures, the viscosity will increase sharply within the range of a few degrees[17,18] and the solution will gel. MC has been used successfully as a tablet disintegrant.[10,11]

The present investigation is an attempt to determine the mechanism by which MC acts in a tablet formulation. For this purpose, sulphanilamide was chosen as a model drug and starch as a disintegrant.

Experimental

Materials——Sulphanilamide, in fine powder and of B.P. grade was used as supplied. The disintegrant was maize starch (Corn Brand, Holland). MC (Tokyo Kasei) of the following viscosity grades: 20—30, 80—120, 350—550, 800—1200, 4000 and 7000—10000 cP were employed.

Preparation of Tablets——Each tablet is made from pre-weighed granules containing the equivalent of 250 mg of sulphanilamide. The amount of starch or MC incorporated is expressed as a percentage of the drug. The drug (25 g) and starch when used were mixed thoroughly for a standardised time. MC was added dry and mixed thoroughly. The amount of water used to moisten the powder mixture was fixed at 16% (w/w) of the drug. The moistened mass was granulated through a sieve of 1.0 mm, dried in an oven at 60 °C for 4 h, the dried granules were regranulated through the same sieve and then sieved through sieve of 0.375 mm. Those retained on this sieve were considered as granules and those that passed through it were termed as fines. To the granules were added 10% fines, mixed and the mixture compressed into tablets using a single punch tablet machine (Manesty, model E2) with flat surface punches of diameter 9.525 mm to an apparent tablet density of 1.266 g cm^{-3}. The granules for each tablet were weighed before compression.

Measurement of Liquid Penetration——The method adopted was that described previously.[19] Essentially it consists of a sintered glass filter connected to a horizontal graduated capillary containing distilled water. The tablet is located centrally on the sintered glass filter and the volume of water taken up was measured by the change in capillary reading and a knowledge of the cross-sectional area of the capillary. The mean and S.D. of five replicates of each formulation was taken.

Disintegration of Tablets——The disintegration of individual tablets at 37±0.5 °C using a B.P. disintegration apparatus (Van-Kel, model 71) without the disc was measured. The mean of five determinations was taken as the disintegration time.

Dissolution of Tablets——The dissolution of tablets in distilled water at 37±0.5 °C was studied using the rotating basket apparatus (Hanson, Easi-Lift model QC 72R) with a basket speed of 100 rpm. Filtered samples were withdrawn periodically and assayed spectrophotometrically (Perkin-Elmer, model 550) at 260 nm. The dissolution of five tablets was determined for each formulation and the mean and S.D. calculated.

Results and Discussion

Water Penetration Profiles

Water penetration into sulphanilamide tablets without starch or MC was determined (Fig. 1). The results showed that the volume (V) of water penetrated increased rapidly in the first few seconds. According to the modified Washburn equation, the square of the penetrated length of the capillary varies with time. The penetration of water into tablets containing starch but no MC increased gradually initially and then markedly (Fig. 2). On

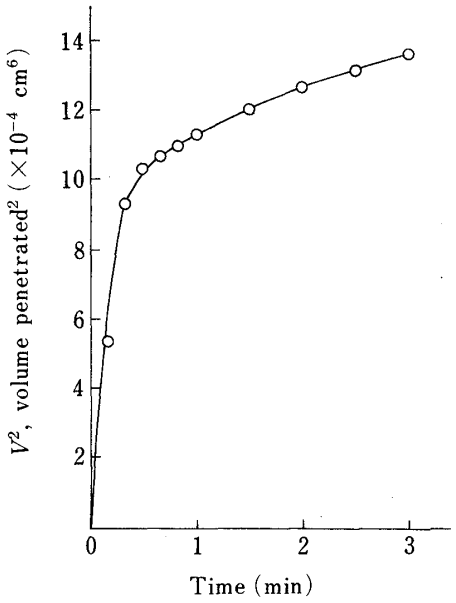

Fig. 1. Penetration of Water into Tablets Containing Only Sulphanilamide without Excipients at 37 °C

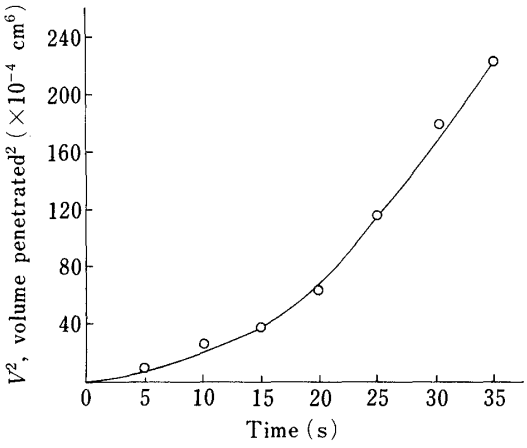

Fig. 2. Penetration of Water into Tablets Containing Sulphanilamide and 10% Starch at 37 °C

TABLE I. Water Uptake into and Disintegration of Sulphanilamide Tablets Containing Starch and No MC at 37 °C

Starch conc. (%)	V^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± 0.24	>1800
10	28.02±4.29	63.37±8.71	181.73±16.53	18.60±1.14

comparison, it is seen that the value of V^2 is about 5 times more in the presence of starch after 10 s, 7 times more after 20 s and 18 times more after 30 s (Table I). The slower increase initially is due to the wetting of the starch particles, which once wetted and hydrated seemed to accelerate the passage of water into the tablet. Sulphanilamide being fairly water-soluble (1.12% at 37 °C)[20] dissolves when in contact with water. The walls of the capillary spaces within the tablet could have collapsed. The low water uptake of sulphanilamide tablets without excipients is probably due to the limits on hydration imposed by the drug molecules, the high water uptake of those with starch is due to the starch itself. Starch has been reported to absorb up to 20% its weight of water.[21]

MC compacts containing MC 350—550 or MC 4000 showed practically no difference

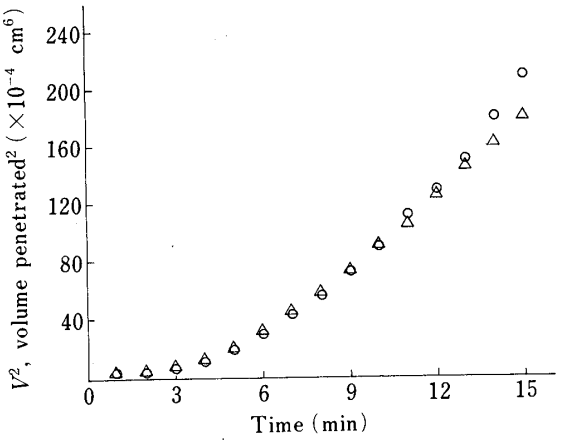

Fig. 3. Penetration of Water into Methylcellulose (MC) Compacts (100 mg) at 37 °C

○, MC 350—550: △, MC 4000.

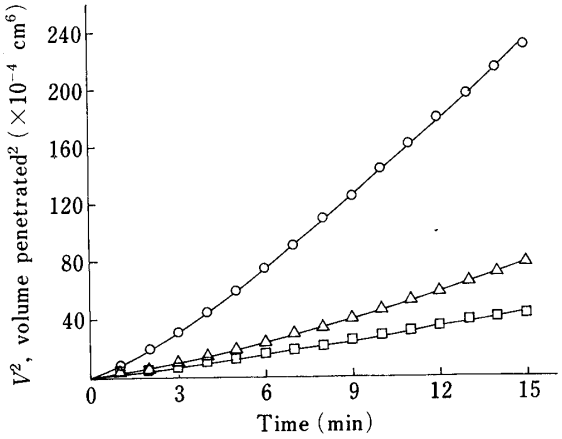

Fig. 4. Uptake of Water into Sulphanilamide Tablets Containing 10% Starch and Varying Concentrations of MC 20—30 at 37 °C

MC 20—30 concentration: 2% (○) 3% (△) 4% (□).

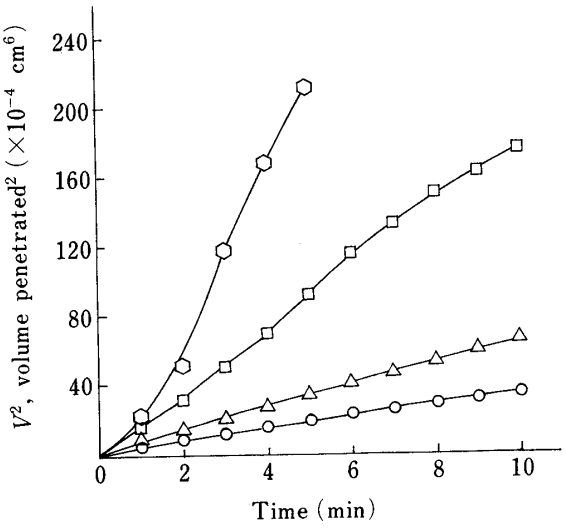

Fig. 5. Uptake of Water into Sulphanilamide Tablets Containing 2% MC 350—550 and Varying Concentrations of Starch at 37 °C

Starch concentration: 0% (○) 2.5% (△) 5% (□) 10% (○).

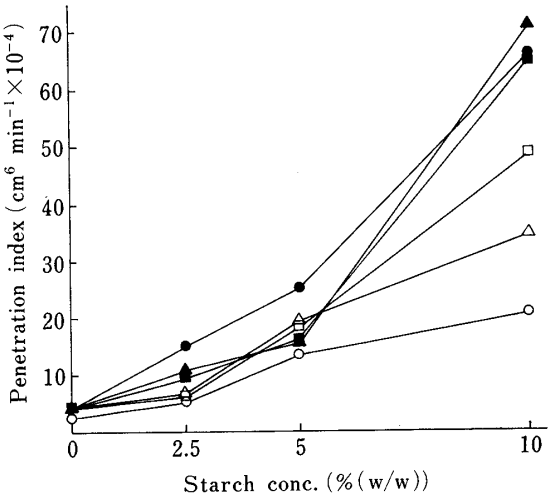

Fig. 6. The Effect of Starch Concentration on Liquid Penetration Index of Sulphanilamide Tablets Containing 2% of Various Viscosity Grades of MC at 37 °C

MC 20—30 (○) MC 80—120 (△) MC 350—550 (□) MC 800—1200 (●) MC 4000 (▲) MC 7000—10000 (■).

in their water penetration profiles (Fig. 3). The penetration of water into sulphanilamide tablets containing different concentrations of MC 20—30 with 10% starch was retarded by the presence of a larger amount of MC (Fig. 4). This behaviour was also demonstrated in similar tablets containing various concentrations of MC 80—120, MC350—550, MC 800—1200, MC 4000 and MC 7000—10000. The hindered water uptake is because MC hydrates, swells and blocks the pores in the tablet and these actions are enhanced by a greater amount of the polymer. It was observed in the penetration studies that the lower portion of the tablet was excessively hydrated and formed a sticky mass, but the upper portion was very dry. The greater amount of MC hydrates more and forms a 'shield' barricading the entry of water. Hence the inter/intra granular spaces within the upper portion of the tablet are not readily accessible to water.

In the case of tablets containing a fixed concentration of 2% of MC 350—550 but with varying concentrations of starch (Fig. 5), the extent of water penetration increased markedly with increase in starch concentration. Tablets containing 2% MC 20—30, MC 80—120, MC 800—1200, MC 4000 and MC 7000—10000 and varying amounts of starch also exhibited a similar behaviour. Starch has a great affinity for water and draws in water rapidly into the tablets. The water penetration profiles, V^2 *vs.* time for these tablets were found to be linear. The liquid penetration index was determined from the slope of the regression lines as shown in Fig. 6, the rate of water penetration into the tablets increased with increase in concentration of starch for all grades of MC. The difference in the rate of water penetration between various grades of celluloses was particularly distinct when a larger amount of starch was used. The incorporation of 2% of MC of varying viscosity as well as 10% starch into the tablets reduced the penetration of water as the amount of water taken up was less than that by tablets containing only the drug and starch. This concentration of starch results in a rapid flooding of the tablet interior by water. MC hydrates readily when in contact with this water. The lower viscosity grades of MC have the tendency to hydrate fast whilst the higher viscosity grades have a greater capacity to hydrate. It has been reported[22] that penetration of water into matrices containing hydroxypropylmethylcellulose and pilocarpine was rapid but decreased with increase in the M_r and concentration of the cellulose.

Disintegration

The disintegration time of sulphanilamide tablets without MC or starch was greater than 30 min. The disintegration pattern observed in these tablets was surface erosion and dissolution of the drug. The tablets retained their shape, only reducing their size with time. The addition of 10% starch to these tablet formulations reduced the disintegration markedly, to about 19 s. Rapid disintegration correlates well with intake of water into the tablets (Table I).

TABLE II. Disintegration Time of Sulphanilamide Tablets Containing Various Concentrations of Starch and Various Viscosity Grades of MC (2%) at 37 °C

Starch (%)	Disintegration (s)					
	MC 20—30	MC 80—120	MC 350—550	MC 800—1200	MC 4000	MC 7000—10000
0	>1800	>1800	>1800	>1800	>1800	>1800
2.5	612.80 ±70.51	1175.80 ±181.85	>1800	1056.00 ±143.12	>1800	>1800
5.0	201.20 ±5.81	150.00 ±24.24	212.40 ±19.68	218.60 ±23.43	1477.40 ±132.04	>1800
10.0	234.00 ±6.89	171.60 ±3.51	122.20 ±7.09	86.00 ±1.58	97.60 ±7.30	62.20 ±1.48

Table III. Dissolution of Sulphanilamide Tablets Containing 10% Starch and 2% of Different Viscosity Grades of MC at 37 °C

MC grade	Sulphanilamide dissolved, %				
	5 min	10 min	15 min	20 min	30 min
MC 20—30	53.48±1.16	85.87±1.32	94.92±1.25	97.64±1.29	99.05±0.94
MC 80—120	88.71±1.77	97.23±0.76	97.80±0.46	98.44±0.19	99.65±0.25
MC 350—550	35.40±0.86	63.73±2.54	81.75±1.75	89.99±1.78	96.19±0.72
MC 800—1200	74.72±2.32	96.32±0.52	99.12±0.52	99.92±0.18	100

Table IV. Dissolution of Sulphanilamide Tablets Containing 10% Starch and 3% of Different Viscosity Grades of MC at 37 °C

MC grade	Sulphanilamide dissolved, %				
	5 min	10 min	15 min	20 min	30 min
MC 20—30	33.71±1.13	62.73±1.84	90.74±1.61	97.23±1.05	98.65±1.00
MC 80—120	26.48±0.02	48.68±1.81	78.36±3.99	91.39±2.46	98.08±1.29
MC 350—550	15.83±1.33	23.46±1.57	28.56±1.89	33.09±2.01	43.59±2.90
MC 800—1200	13.80±0.61	22.01±0.46	27.11±0.87	33.73±0.92	43.06±1.78

A comparison of the disintegration time of tablets containing 2% MC of different viscosity grades (Table II) shows that as the level of starch is increased, there is a decrease in disintegration time for all grades of MC studied. For the very high viscosity grade, MC 7000—10000, a higher level of starch is required to lower the disintegration time. At the 10% starch level, generally there is a decline in disintegration time with increasing viscosity of the polymer. This correlates well with the water penetration studies stated earlier where it was shown that increasing viscosity of the MC results in greater water penetration. It appears that MC within the tablet needs a certain amount of hydration to effect disintegration. Starch, due to its affinity for water provides the water to the MC by hydrating itself first. The higher viscosity grades require more water to swell fully and this is provided by the excess starch.

Two opposing sets of forces can be viewed to take place in the tablet, forces that promote disintegration of the tablet and those that hold it together-cohesive/adhesive forces. Penetration of water into the tablet may result in the collapse of the tablet matrix due to partial/complete dissolution of the constituents. Some substances hydrate and swell, creating disintegrating forces, others hydrate and become adhesive.[10,13] The forces of adhesion oppose disintegration. Thus, when forces opposing disintegration are greater or of the same order as those promoting disintegration, a longer disintegration time is expected. Adhesiveness of a tablet excipient has been found to adversely affect the disintegration time.[10,13,23,24] Jaminet *et al.*[25] also found that adhesiveness and higher viscosity of gums hindered disintegration time.

Dissolution

The dissolution of sulphanilamide tablets containing 10% starch and varying amounts of different grades of MC was determined. A comparison of the dissolution profiles of tablets with 10% starch and 2% MC of different viscosity grades (Table III) shows that the dissolution rate is not reduced with a higher viscosity grade. Water penetration data obtained showed that tablets containing MC 800—1200 allowed a greater amount of water to penetrate into the tablets, but this did not bring about an increase in the dissolution rate. Thus,

although the uptake of water was found to be greater with a higher viscosity grade of MC, the dissolution rate did not follow the same trend.

The incorporation of 3% MC into the tablets with the amount of starch fixed at 10% (Table IV) resulted in a decrease in dissolution rate with increase in the viscosity of the cellulose. This may be explained as being due to sufficient MC present to form a continuous gel around the tablet core and to a more viscous gel being formed due to a higher viscosity grade of MC as well as a higher MC concentration. This does not occur with the lower MC concentration of 2%. The use of 4% MC produced a further reduction on the dissolution rate. Thus, the order of dissolution is: 2% > 3% > 4% for MC 20—30.

Over 90% of the drug was released within 15 min when 2% or 3% MC 20—30 was used but only 40% was released at this period of time in the case of 4% MC 20—30. Dissolution in this case holds a positive correlation with water penetration profiles. The slower dissolution brought about by a high level of MC is accompanied by a fall in the water uptake also. The dissolution profiles of tablets with 2% or 3% MC 20—30 showed a curvature in the later stage of the dissolution process whilst that for 4% MC 20—30 showed a linear plot, indicating that gelation occurred at this level of the polymer. Similar behaviour was also observed for tablets containing the same amount of starch and 2%, 3% or 4% of MC 80—120, MC 350—550, MC 800—1200 and MC 4000, for MC 7000—10000 the concentrations used were lower, 0.5%, 1.0% and 2.0% due to the highly viscous nature of this polymer. MC in the tablet gels when in contact with water, thereby controlling the release of drug by controlling the penetration of water into the tablet interior. With a greater concentration of MC a more gelatinous layer is formed which is more resistant to water penetration, drug diffusion and erosion and hence drug release is slower. This is in agreement with the findings of Lapidus and Lordi[26] which showed that a lower polymer concentration produced a faster drug release.

Conclusion

Although penetration of water into the tablet influences disintegration to some extent, dissolution is not entirely governed by it. The uptake of water is rapid when a higher viscosity grade of MC is used but this does not result in fast dissolution. Dissolution of tablets containing MC is governed by the formation of a gel layer and the diffusion of drug through this layer. With higher concentrations of MC, the adhesive characteristics of the polymer become more significant. Increasing viscosity grades of MC show slower dissolution due to increasing adhesiveness. Tablets with high viscosity grades of MC were observed to retain their shape even after 2 h of the dissolution test. Physical examination of the undissolved tablet cores showed the presence of a mucilaginous layer on the tablet surface. Drug release occurs essentially from surface erosion. The penetration of water into the tablet is not the rate-limiting step for drug release. The adhesiveness of the excipient in the hydrated state affects dissolution adversely.

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