International Journal of Pharmaceutics, 11 (1982) 131–148
Elsevier Biomedical Press

Influence of additives on (hydroxyethyl) methylcellulose properties: relation between gelation temperature change, compressed matrix integrity and drug release profile

Elka Touitou and Max Donbrow

Department of Pharmacy, School of Pharmacy, Hebrew University of Jerusalem, P.O.B. 12065, Jerusalem (Israel)

(Received September 25th, 1981)
(Modified January 14th, 1982)
(Accepted January 19th, 1982)

Summary

Tablets comprising a compressed matrix of a methylcellulose (MC) derivative mixed with various drugs and additives show 3 distinct types of behaviour in a disintegration test: rapid disintegration (D), gradual attrition (A) and maintenance of integrity (ND). Kinetic studies showed that ND matrices gave drug release related to square-root of time (i.e. matrix diffusional model) whereas a typical A matrix (salicylic acid-MC) deviated positively but observed the Hixson-Crowell cube-root equation for dissolutional control, as applicable to polyphase mixtures. In line with these models, the matrix-controlled system was unaffected by ar... the dissolution one dependent on stirring conditions.

For clarifying the mechanism of matrix behaviour, gelation temperature and viscosity were studied using dilute aqueous systems. Gelation temperature was raised by ND additives, salts containing large organic ions (including sodium benzoate, octanoate, salicylate, tetracaine-HCl, potassium phenoxypenicillin, chlorpheniramine maleate) thiocyanate and iodide. It was lowered by inorganic and small organic ions, lactose and some free organic acids causing A and D behaviour. The elevation, which has not hitherto been noted, is especially interesting.

Intrinsic viscosity was raised by sodium salicylate and lowered by sodium chloride, the Huggins' constant being lowered by the former and raised by the latter. These gel point and viscosity changes reflect increased hydration and extension of the macromolecule chain in the former system and dehydration in the latter, such changes being associated with increased or decreased polymer cohesion in the compressed matrix.

0378-5173/82/0000–0000/$02.75

Pharmaceutically, it has been shown that the composition of such hydrophilic compressed matrices determines whether they will maintain their integrity in water or not, and what type of drug release will result in the different situations.

Introduction

Although hydrophilic matrix formulation of a variety of polymers and drugs intended for sustained release has been the subject of many works, recently reviewed by Buri and Doelker (1980), few quantitative studies have been made on such preparations. One of the most important remains that of Lapidus and Lordi (1968), who measured drug release mainly from hydroxypropyl cellulose tablets. They found that the Higuchi model for diffusional release from inert matrices (Higuchi, 1962) was applicable to whole tablets only during a relatively short initial stage, after which the tablets disintegrated or underwent attrition, processes which caused deviation from the initial pattern. Neverthless, the diffusional behaviour alone has been noted in citations by other authors (Borodkin and Tucker, 1974; Buri and Doelker, 1980) and the general acceptance that it is the correct model for all hydrophilic matrices is therefore misleading.

Little attention has in fact been paid to the effect of the drug and additives on the properties of such matrices and through this on the drug release profile. These are investigated in the present work using methylcellulose as the hydrophilic matrix, a system of special interest in view of the discovery during preliminary work that the intial diffusional stage could be entirely absent or could constitute the major process controlling drug release, depending on the nature and concentrations of the drugs and excipients used.

Materials and methods

Materials

The polymer Tylose MH [1] (a methylcellulose submitted to a minor ethoxylation process) had a viscosity of 4000 centipoises at 25°C; degree of substitution (DS) 1.5; degree of polymerization (DP) 760; mean mol. wt. 140,000 and methoxyl content 23%.

Ammonium thiocyanate [2], benzoic acid [3], *p*-hydroxybenzoic acid [4], potassium iodide [5], sodium acetate anhydrous [2], sodium benzoate [2], chloride [3], octanoate [4],

[1] Hoechst AG.
[2] BDH.
[3] Mallinckrodt.
[4] Sigma.
[5] Merck.

o-methoxybenzoate[4] and propionate[4] were analytical grade, sodium formate[2] and sulphate[6] were reagent or pure grade, chlorpheniramine maleate[7], potassium penicillin V[8] were BP and dextrose[5], lactose[5], salicylic acid[5], sodium salicylate[5], sorbitol[5], tetracaine-HCL[9] and urea[5] were USP.

Methods

Preparation of the tablets

The tablets were prepared by direct compression as follows: the sifted powders[10] were added to the homogenized mixture and compressed directly in a KBr die[11] at high pressure to form flat tablets 13 mm in diameter. The mean tablet weight was 700 mg.

Preliminary results showed that the method of preparation did not affect tablet disintegration behaviour. Most of the compositions were therefore compressed using the direct method.

Disintegration test

The apparatus used[12] was based on the US pharmacopoeial method with water as the medium and 2 h operation at 37°C. Tests were also conducted on static tablets in water. Agitation rate appeared to be without influence on tablet disintegration behaviour.

Determination of release rates from the tablets

Measurements were made either by a closed circuit method or by removal of samples at regular intervals from the release medium.

The tablets were inserted in a rotating basket (Donbrow and Touitou, 1977) consisting of a perspex disc containing four cylindrical compartments with the exterior covered by 10 mesh perspex netting in the present work. The basket was rotated at constant speed[13] in a covered beaker at 90 rpm, using 1400 ml solvent at 37 ± 0.5°C in standard work, conditions being changed only where specified for testing the influence of special parameters. A flow rate of 16 ml per minute in the closed circuit obtained by means of a peristaltic pump[14], was found optimal for direct lag-free spectrophotometric measurement in a flow cell, with print out at 30 min intervals.

Where it proved impossible to work at a dilution allowing direct reading, 5 ml

---

[6] Frutarom (Israel).
[7] Ikapharm (Israel).
[8] Rafa (Israel).
[9] Siegfried.
[10] Glatt.
[11] Research and Industrial Instruments.
[12] Erweka.
[13] Fisher "Stedi-speed" Adjustable Stirrer.
[14] H.R. Flow Inducer, Watson-Marlow.

samples were removed and replaced by the same volume of water. Molar extinction coefficients were obtained experimentally for each drug tested.

Determination of methylcellulose concentration in aqueous solution

This analysis was based on the colour reaction of antron with carbohydrates (Samsel and Delap, 1951); 1 ml of the solution under test, 4 ml water and 10 ml fresh antron solution (0.5% in concentrated sulphuric acid) were well mixed and stood for 10 min. The carbohydrate concentration was determined at the absorbance maximum (625 nm) using as the blank 5 ml of water mixed with 10 ml antron solution. The methylcellulose calibration curve observed Beer-Lambert's law. Since lactose interfered, the test was only applied in its absence.

Preparation of methylcellulose solutions

The polymer was mixed with hot water (ca. 80°C) using some two-thirds of the final volume and, after some 15 min at room temperature, adjusted to volume or weight with cold water in which the additives, if used, were dissolved. The solution was refrigerated for 48 h to complete hydration (Neely, 1963).

Gelation temperature measurement

Solutions (80 ml) were heated slowly in a wide-mouthed vessel using a thermostat bath [15] the temperature of which was raised by 1°C per min and determined by means of a digital thermometer [16] (±0.05°C) inserted in a control vessel containing a solution of identical composition. The viscosity was measured by means of a rotating viscometer [17], the gelation temperature being estimated graphically as the minimum in the viscosity–temperature curve.

Results and discussion

Integrity of methylcellulose tablets in water and effects of tablet ingredients

Screening of the tablet matrix integrity of a number of drug-excipient methylcellulose compositions was carried out by measurement of disintegration time in water at 37°C using the standard USP XVII test. Three types of behaviour were clearly distinguishable: (1) rapid loss of shape and disintegration into flocks of gellified material (D); (2) swelling without loss of the initial cylindrical form but with gradual attrition of surface gel layer: the gel-coated core remained intact but diminished in size (A); and (3) swelling with maintenance both of shape and matrix integrity during the whole test period of 2 h (ND). Visual observations were confirmed by sectioning and measuring intact tablets of Types A and ND during the tests and by colorimetric analysis of the methylcellulose in the distintegration medium using

[15] Grant, Cambridge, SU2.
[16] Mettler, TM15.
[17] Brookfield Synchro-Lectric Viscometer, LVT.

antron reagent (Samsel and Delap, 1951). Compositions tested and their behaviour are listed in tables 1a and b. In Type D matrices containing the polymer with sodium sulphate, chloride, formate, acetate or propionate at the same concentration level and also in mixtures in which there was 10% of sodium salicylate and 10% of one of these salts, disintegration occurred within 5 min. Lactose or dextrose at higher concentrations in the polymer base also caused disintegration, as did salicylic acid at 35% level or salicylic acid with lactose. This type of behaviour was also shown by matrices which were non-disintegating in water when a pH 5 phosphate buffer (0.1 M $Na_2HPO_4 \cdot 12\ H_2O$/0.05 M $C_6H_8O_7 \cdot H_2O$) replaced the water, this being an example of the effect of an external ion, phosphate being known to reduce hydration of methylcellulose (Savage, 1971).

Coherent matrices which underwent gradual attrition (Type A) were given by methylcellulose alone and by mixtures of the polymer with from 10 to 30% salicylic acid, or 35% sodium salicylate or 20% sorbitol, whereas 20% urea did not cause attrition.

Stable intact matrices (Type ND) were obtained with sodium salicylate from 5 to 30% with the polymer alone and also in various mixtures with lactose in which the polymer fraction was held at 65% while the drug/lactose ratio was varied, provided the drug content remained above 5%, below which Type A behaviour occurred. At a weight fraction of 80% of polymer with 10% of sodium salicylate, various salt additives at 10% level still caused Type D disintegration; on the other hand non-ionic hydrophilic substances gave Type A (sorbitol) or ND (lactose, urea) matrices. Again 5% of sodium chloride at 15% drug content gave Type ND behaviour indicating that the disintegrating effect of the former salt might be neutralized by increase in the amount of the organic ion. No methylcellulose was detectable colorimetrically at the end of the disintegration test on these sodium salicylate polymer matrix compositions. The other large organic ions, viz. tetracaine hydrochloride, potassium phenoxymethyl penicillin and chlorpheniramine maleate behaved similarly to sodium salicylate, complete tablet integrity being maintained from below 10% up to at least 20 or 25% drug content, even in the presence of 10% lactose at 25% drug content, or in some case sodium chloride.

Varying sodium benzoate compositions also showed evidence of alternation between Type A and ND behaviour. However, in pH 2 buffer (0.2 M HCl/KCl) benzoate, sodium salicylate and chlorpheniramine maleate compositions gave Type A behaviour instead of the Type ND observed in water, a result attributable to protonation of the polymer.

Release profiles from whole tablets: varation of release pattern

The compositions which remained intact (Type ND) in the disintegration test were subjected to kinetic studies in a rotating basket apparatus. To test if the diffusional matrix model held, cumulative drug release Q′ was plotted against square-root of time: there was no deviation from linearity during the test period, i.e. up to 60% drug release (Fig. 1). This was true for all compositions maintaining the tablets intact such as shown in Fig. 2. The absence of positive deviations resulting from attrition and the greatly extended period of integrity of the tablets as compared

TABLE 1a

BEHAVIOUR IN USP DISINTEGRATION TEST IN WATER AT 37°C OF METHYLCELLULOSE TABLETS CONTAINING ONE ADDITIVE

Additive	Percent of additive						
	5	10	15	20	25	30	35
Salicylic acid		A	A	A	A	A	D
Sodium salicylate	ND	ND	ND	ND			A
Sodium benzoate		ND					
Sodium chloride				D[a]			
Sodium sulphate				D			
Tetracaine-HCl		ND		ND			
Potassium penicillin V		ND				ND	
Chlorpheniramine maleate		ND		ND			

A = attrition; D = disintegration; ND = no disintegration.

[a] Similar results were obtained with 20% sodium formate, acetate or propionate and 80% MC; with lactose 35% or dextrose 30% in MC and with 10% sodium salicylate together with 10% sodium sulphate, formate, acetate or propionate in MC. Salicylic acid 20% together with 15% lactose also gave Type D.

TABLE 1b

BEHAVIOUR IN USP DISINTEGRATION TEST IN WATER AT 37°C OF METHYLCELLULOSE TABLETS CONTAINING 2 ADDITIVES

Sodium salicylate 5 + Lactose	30	ND
Sodium salicylate 10 + Lactose	25	ND
Sodium salicylate 15 + Lactose	20	ND
Sodium salicylate 20 + Lactose	15	ND
Sodium salicylate 25 + Lactose	10	ND
Sodium salicylate 10 + Sorbitol	10	D
Sodium salicylate 10 + Urea	10	ND
Sodium salicylate 10 + NaCl	10	A
Sodium salicylate 15 + NaCl	5	ND
Sodium benzoate 10 + Lactose	10	A
Potassium penicillin V 25 + Lactose	10	ND

with Lapidus and Lordi's results is noteworthy. On the other hand, when attrition did occur, (Type A), a positive deviation was observed in the $Q' - t^{1/2}$ plot (Fig. 3) for 10% salicylic acid in a methylcellulose matrix and 10% sodium salicylate in a polymer-matrix containing 10% sodium chloride. Whereas in the former the deviation was continuous, the latter appeared to be linear for the first hour of release, approximately.

It is noteworthy that the diffusion model is not applicable to this type of matrix and a suitable kinetic treatment is investigated below. A detailed study of diffusional release from Type ND whole tablets will be presented in a subsequent paper.

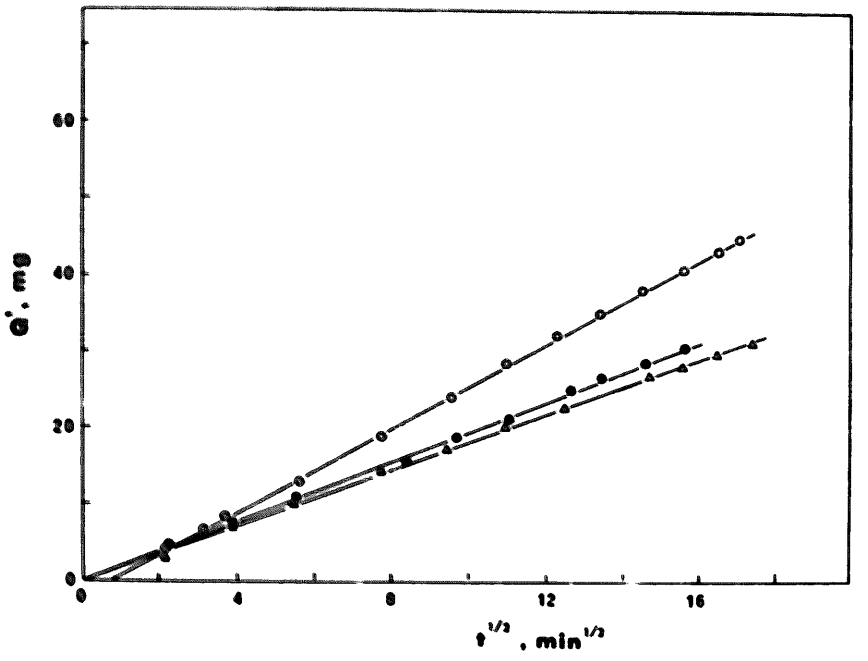

Fig. 1. Release rates from methylcellulose matrix (whole) tablets: sodium benzoate (○); tetracaine hydrochloride (●); chlorpheniramine maleate (△). Abscissa: time$^{1/2}$; ordinate: cumulative amount of drug Q'; matrix drug content 10% w/w.

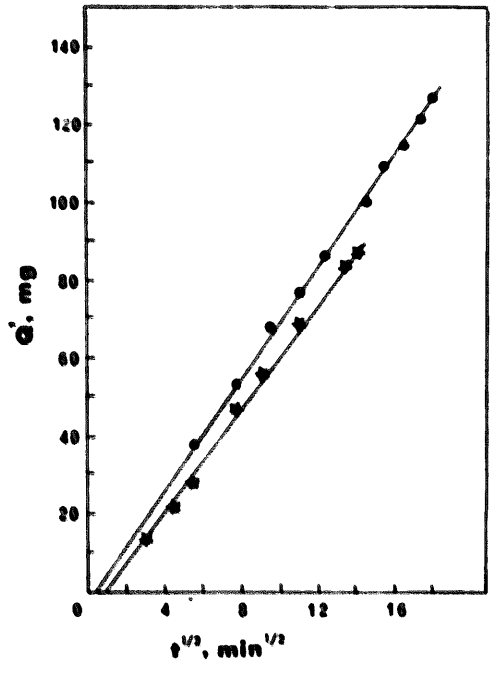

Fig. 2. Release rate profiles for sodium salicylate 25% w/w (★); potassium phenoxymethyl penicillin 30% w/w (●) in methylcellulose matrices.

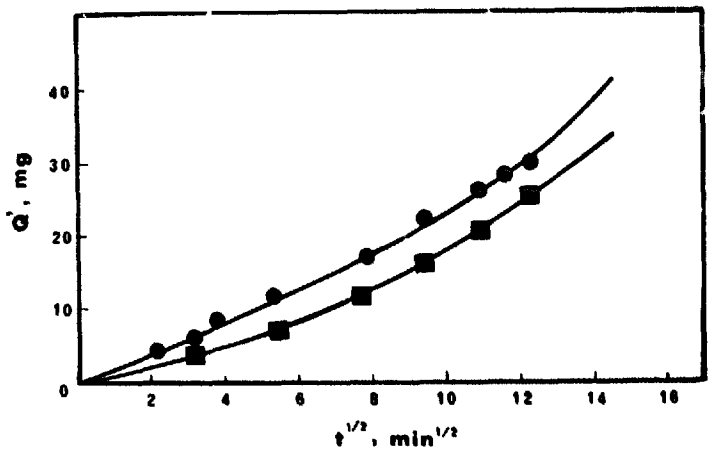

Fig. 3. Release rate profiles for salicylic acid 10% w/w (■) and sodium salicylate 10% w/w with sodium chloride 10% w/w (●) in methylcellulose matrices.

Dissolution model for system undergoing attrition

Release rates were measured for salicylic acid 10–30% in methylcellulose matrices spectrophotometrically and for the methylcellulose, gravimetrically. The latter was determined on tablets sampled at suitable intervals, dried in vacuum at 37°C to constant weight and corrected for salicylic acid release as measured experimentally. Since these Type A tablets maintained their initial shape while undergoing attrition under well-stirred conditions, it seemed that dissolution might control the release rate and that the Hixson-Crowell dissolution equation would then be applicable (Hixson and Crowell, 1931):

$$W_0^{1/3} - W^{1/3} = k \cdot a \cdot t \qquad (1)$$

W_0, W are the quantities of the component measured initially and at time t and $a = \alpha_{SV}/\rho^{2/3}$, in which α_{SV} is the appropiate geometric shape factor of the matrix and ρ its density. The cube-root weight vs time plots were linear throughout all experiments (Fig. 4) and were reproducible to within 3%. The rates of dissolution, 3K, were obtained from the slopes $K \cdot a$ of these lines. For this purpose, α_{SV} was calculated to have the value 7.27 for a cylinder while ρ, obtained directly from the tablet weight and volume was 1.19; the density did not change significantly from tablet to tablet over the compositions studied. The value of a was 6.43 ± 0.05 ($\bar{X} \pm$ S.D.).

The dependence of the initial dissolution rates of the acid and the polymer on tablet composition for polymer fractions 0.7 – 0.9 are given in Table 2. The values for the polymer are relatively constant while those for the acid rise with its weight fraction in the matrix.

This behaviour is best explained by a dissolution model for polyphase mixtures (Higuchi, 1965). For the two-component methylcellulose (MC)-salicylic acid (SA) mixture, considered not to react and form a new chemical species, in which N_{MC},

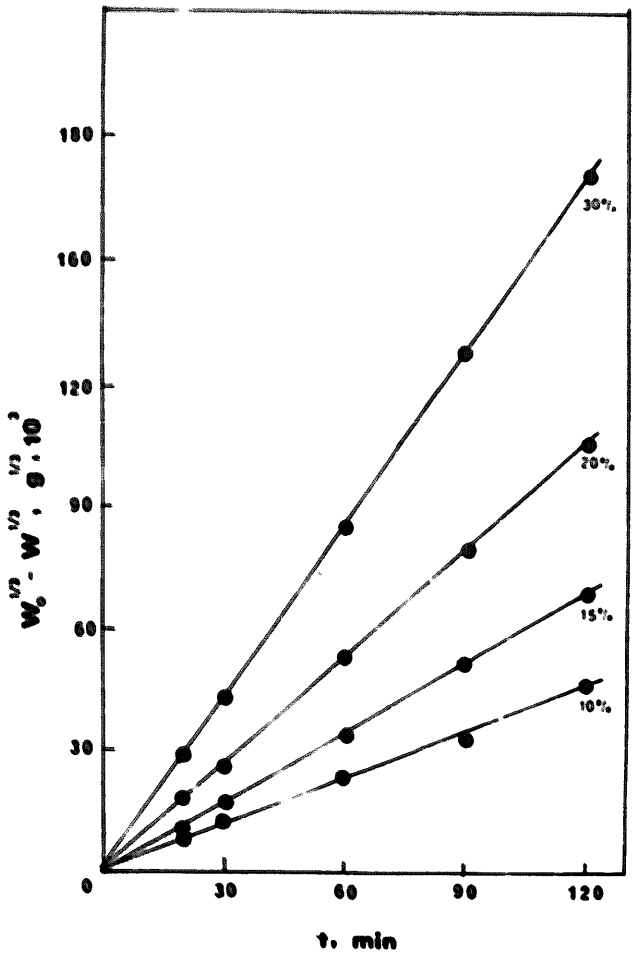

Fig. 4. Release profiles for salicylic acid of content indicated (% w/w) from methylcellulose matrix, plotted using the Hixson-Crowell equation. For key see text.

N_{SA} are the initial quantities, the dissolution rates G_i are proportional to the products of the solubilities and diffusion coefficients of each component in the solvent, i.e. $G_i \alpha D_i {}^sC_i$. If after a short time and because of the different dissolution rates the surface layer is devoid of the solid component which has been reached at the higher rate, this solid is SA, due to the inequality:

$$N_{MC}/N_{SA} > D_{MC}{}^sC_{MC}/D_{SA}{}^sC_{SA} \quad (2)$$

The left hand side ranges from 9 to 2.33 in the 90–70% matrices. The D_{MC}/D_{SA} ratio estimated from the Stokes-Einstein equation for monomer molecules of mol. wt. 140,000 and 140 is under 0.1 and will in fact be considerably less at 37°C for the aggregated methylcellulose gel. The saturation solubilities at 37°C in water are 6.3 $g \cdot l^{-1}$ for the acid and about 4 $g \cdot l^{-1}$ for the polymer near its aggregation concentration.

TABLE 2

EXPERIMENTAL AND CALCULATED DISSOLUTION RATES OF SALICYLIC ACID FROM METHYLCELLULOSE MATRIX TABLETS

N_{SA}/N_{MC}	$3K_{SA}$ [c] ($g \cdot min^{-1} \cdot cm^{-2} \times 10^4$)	G_{SA} [b] ($g \cdot min^{-1} \cdot cm^{-2} \times 10^4$)	$3K_{MC}$ [a] ($g \cdot min^{-1} \cdot cm^{-2} \times 10^4$)
$\frac{72}{648}$	1.81	1.77	15.9
$\frac{100}{600}$	2.68	2.75	16.5
$\frac{140}{560}$	4.10	4.12	16.5
$\frac{210}{490}$	6.70	6.98	16.3

[a] Methylcellulose dissolution rates obtained from Hixson-Crowell plots.
[b] Salicylic acid dissolution rates calculated using Eqn. 4.
[c] Salicylic acid dissolution rates obtained from Hixon-Crowell plots.

Consequently, the polymer dissolution is given by Eqn. 3:

$$G_{MC} = D_{MC}{}^{s}C_{MC}/h \tag{3}$$

It will thus be invariant over the compositions used. The acid dissolution should follow the equation:

$$G_{SA} = G_{MC}N_{SA}/N_{MC} \tag{4}$$

The nearness of the calculated G_{SA} values to the experimental ones (3K) (Table 2) show that the cube-root treatment of the experimental rate data fits closely to the polyphase model of dissolution for whole tablets of methylcellulose-salicylic acid in water.

It may be noted that although the polyphase treatment was also applied successfully to dissolution from a rotating disc of salicylic acid with another hydrophilic polymer, polyvinyl pyrrolidone (Gibaldi and Weintraub, 1968), the different polymers did not show identical behaviour, as expected from variation in the values of the parameters in Eqn. 2; thus while G_{SA} changed with composition in the MC matrix, with G_{MC} invariant, the reverse occurred from the polyvinylpyrrolidone matrix over a similar concentration range.

Other factors being kept constant, dissolution control will also be evidenced by agitation rate effects, in contrast to interfacial control or diffusional matrix control which are independent of stirring rate (Fig. 5). Dissolution rates of the salicylic acid-polymer matrices were measured from 90 to 300 rpm and indeed a strong dependence was found. A log–log plot (Fig. 6) showed that the experimental 3K values observed a linear relation with a slope of 1, which is in accordance with the

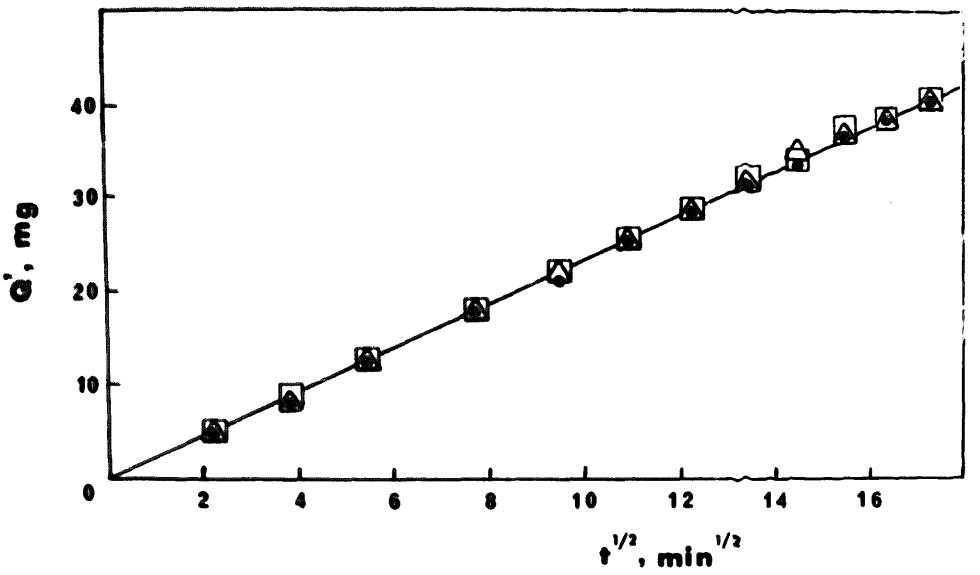

Fig. 5. Effect of agitation rate variation on sodium salicylate (10%) release from methylcellulose matrix, non-disintegrating. ●, 90 rpm; ▲, 200 rpm; □, 300 rpm.

empirical equation $K = a' \cdot (N)^b$ (Wurster and Taylor, 1965) which has been found applicable to transport dissolution, where K is the dissolution rate, N the agitation rate and a' and b are constants.

The release mechanism for the salicylic acid-methylcellulose composition is thus in strong contrast to the Higuchi diffusional one operative for Type ND matrices containing the salts of large organic ions such as sodium salicylate and tetracaine-HCl.

Influence of temperature and components on gelling behaviour and viscosity of methylcellulose in aqueous solutions

On the assumption that the tendency of the matrix to maintain its integrity or undergo attrition or disintegration reflects corresponding cohesive properties of the gel formed on hydration of the compressed polymer, the effects of some drugs and additives on gelation temperature and viscosity were investigated as phenomena parallel to their effects on the compressed matrix.

The gelation temperature at which methylcellulose sol–gel transformation occurs is a function of the concentration, the degree of polymerization and substitution, and the presence of additional compounds in the solution. It is defined as the temperature at which the relative viscosity is at its minimum value on the viscosity–temperature curve; the relative viscosity of the aqueous methylcellulose solution used fell steadily with temperature to a minimum and then rose till the gel separated out (Fig. 7), the gelation temperature being 74°C, which is in agreement with published data (Savage, 1971).

The gelation behaviour may be explained as follows: at low temperature, strong solute–solvent interaction protects the hydrated polymer molecules against aggregation. Removal of the sheath of water molecules favours solute–solute interaction and

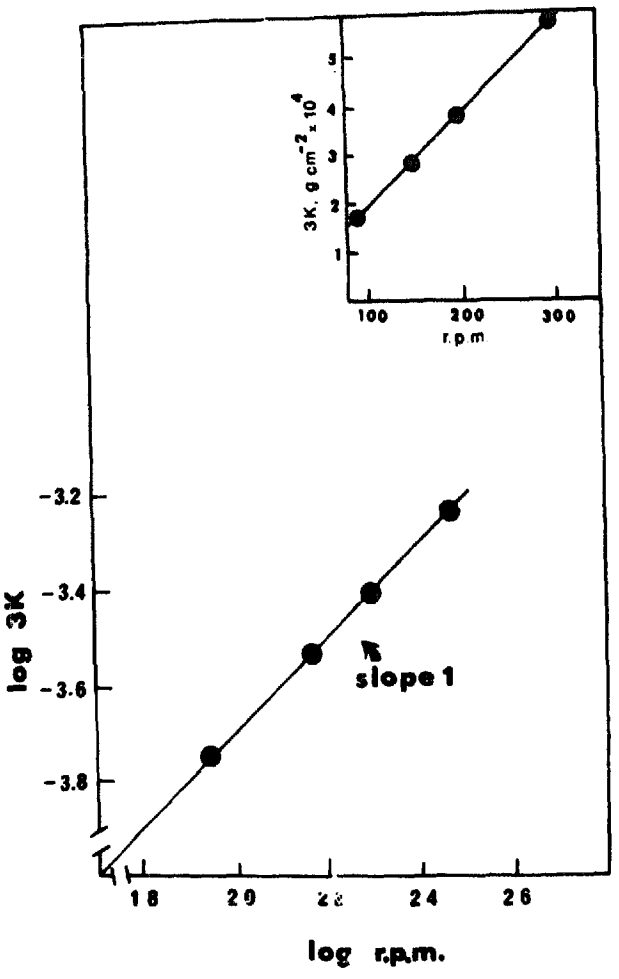

Fig. 6. Effect of agitation rate variation on salicylic acid release from methylcellulose matrix undergoing attrition. For key see text.

hence aggregation. The viscosity–temperature and gelation profile is thought to involve two stages of dehydration (Heyman, 1936) together with polymer structure change (Marriott and John, 1973). The descending curve describes the first dehydration step on raising the temperature, a stage during which the RMS end-to-end length of the macromolecule decreases and the viscosity falls. Further temperature rise causes dehydration, with displacement of immobilized water present between the chains together with the beginning of association. The curve reverses its direction and rises, the increasing viscosity during this stage being explained by Neely (1963) as due to the increasing molecular weight of the polymer as it associates by hydrophobic bonding, a similar association phenomenon occurring at high concentations or in the presence of electrolytes. Similar gelation phenomena on temperature rise are exhibited by other ether-containing hydrophilic polymers, exemplified by polyethylene glycol solutions at high concentrations (Bailey and Kolske, 1976).

The general form of the above relation is maintained in systems containing

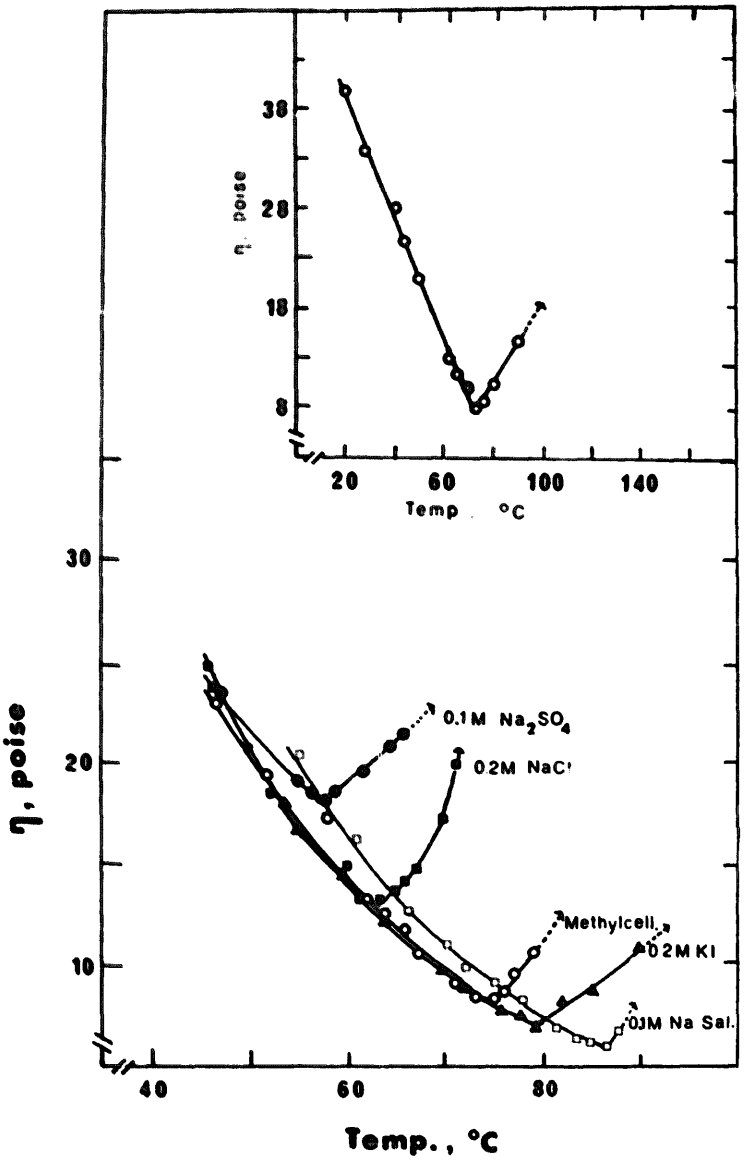

Fig. 7. Viscosity–temperature curves for 2% methylcellulose solutions alone (upper curve) and containing additives.

additives (Fig. 7) but the gelation temperature changes, rising in sodium salicylate or potassium iodide and falling in sodium sulphate or chloride solutions. The effects of the additives studied on the gelation temperature T of 2% methylcellulose solution are shown in Table 3. T is seen to be linearly related (Fig. 8) to the molarity of the additive, M, following the empirical equation:

$$T = aM + b \tag{5}$$

in which a is the negative or positive slope and b the gelation temperature in the

TABLE 3

GELATION TEMPERATURES OF METHYLCELLULOSE 2% [a] IN THE PRESENCE OF ADDITIVES

Additive	(deg·M^{-1}) Slope [b]	Gelation temp. (°C) at concn. (M):			
		5×10^{-1}	2×10^{-1}	10^{-1}	2×10^{-2}
sodium sulphate	−140	-	47	60	73
sodium chloride	−62	43	61	68	73
potassium iodide	+20	85	79	77	75
ammonium thiocyanate				77	75
sodium formate	−40	55	66	70	73
sodium acetate	−70	-	59	67	73
sodium propionate	−50	46	64	67	73
sodium octanoate	+73	-	92	85	79
sodium benzoate	+39	91	80	76	74
sodium *o*-methoxybenzoate	+21	84	78	76	75
sodium salicylate	+77	-	90	83	76
tetracaine hydrochloride	> +77		-	90	78
chlorpheniramine maleate	> +77		-	90	78
benzoic acid				[c]	74
salicylic acid				[c]	69
p-hydroxybenzoic acid					70
dextrose			59	67	73
lactose	−25	62	70	72	74
sorbitol				50	73
sodium chloride [d]					
sodium salicylate				-	76

[a] Gelation temperature of polymer solution was 74°C

[b] Fig. 9.

[c] Insoluble.

[d] 2×10^{-2} M each.

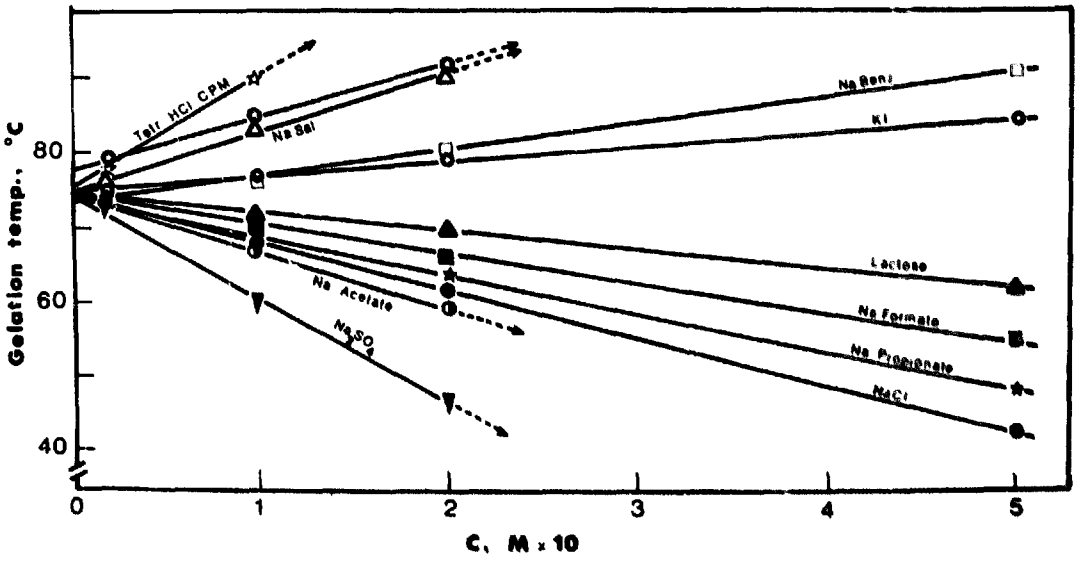

Fig. 8. Relation of gelation temperature of 2% methylcellulose to additive concentration.

absence of additive. The effects of the salts and acids studied are presented in Scheme 1.

Scheme 1

Classification of components according to effects on gelation temperature of aqueous methylcellulose.

(A)Depression of gelation temperature. Sodium sulphate > salicylic acid > *p*-hydroxybenzoic acid > sodium acetate > sodium chloride > sodium propionate > sodium formate > lactose

(B) Elevation of gelation temperature. Chlorpheniramine maleate > tetracaine-HCl > sodium salicylate > sodium octanoate > sodium benzoate > sodium *o*-methoxybenzoate > ammonium thiocyanate > potassium iodide.

It is immediately evident that the order of the effects of the inorganic salts on the methylcellulose gel point follow their order in the lyotropic series. Of particular interest, however, is the elevation caused by the large organic anions and cations, which has not previously been observed.

Gel point reduction is readily explained by salting-out of the polymer, the most effective of the ions studied, sulphate, causing substantial dehydration of the polymer (Bailey and Callard, 1959; Levy and Schwarz, 1958). Sulphate is followed by ions of short-chain (C1 to 4) organic acids and chloride. The lyotropic series order in fact reflects the dependence of salting-out on the radius and degree of hydration of the ion responsible.

Reduction of the gel point by salicylic and *p*-hydroxybenzoic acid may be due to formation of a complex of low solubility with the macromolecule (Tillman and Kuramoto, 1957).

The only salts on record as raising the solubility of methylcellulose are potassium thiocyanate and iodide (Heymann, 1938). The effect was explained on the basis of Katz's theory as arising from adsorption of the large ion of relatively low water-affinity on to the macromolecule, carrying with it water molecules raising the degree of hydration of the colloid. With polarizable ions or groups such adsorption may involve polarizing centres in the polymer (Savage, 1971); alternatively, adsorption may be thermodynamic in origin, involving hydrophobic bonding between polymer groups and ions which destructure the water. In any event polymer aggregation would be interfered with by intercalation of such ions, ionic repulsion forces, and the presence of a hydration sheath, though it is not clear at present which of these effects will be predominant. The large planar aromatic ions in Scheme 1B are indeed polarizable and readily adsorbed, while the long sodium octanoate chain would be expected to undergo hydrophobic interaction with suitable polymer groups.

Further evidence of hydration effects was obtained from viscosity data and Huggins constants, treated by the equation:

$$\eta_{sp}/C = [\eta] + K_H[\eta]^2C \qquad (6)$$

in which C is the polymer concentration, $[\eta]$ the intrinsic viscosity, K_H the Huggins constant and η_{sp}/C the reduced viscosity. The equation is applicable to linear

polymers in dilute solution, K_H changing with structure and rising with increasing heterogeneity of the system. A value somewhat larger than 0.35 for K_H characterizes an uncharged polymer in a 'poor' solvent, flexible coiled macromolecules being compressed in 'poor' solvents and stretched in 'good' ones. The reduced viscosity expresses the internal friction in the linear colloidal system, its value rising with increasing polymer concentration.

In Fig. 9, the linear relation between η_{sp}/C and C at low polymer concentration is shown: pronounced upward curvature occurs at higher concentrations due to mutual attraction of particles in close proximity, leading to aggregation. The value of $[\eta]$, obtained from $\lim_{C \to 0} \eta_{sp}/C$ by graphical extrapolation, was 7.26 dl/g in water, which interpolates with literature data (Savage, 1971). In 0.1 M salt concentrations, values were 6.80 in chloride, reflecting a compressed or coiled structure, and 8.50 in salicylate, suggesting a stretched or swollen structure. A similar decrease in intrinsic viscosity caused by sodium chloride was recorded for another hydrophilic polymer system, polyethylene glycol, and was explained by salting-out (Bailey and Callard, 1959).

K_H values were calculated using Eqn. 6 and found to differ considerably for the 3 systems studied, viz. polymer alone or with sodium salicylate or sodium chloride in dilute solution (Table 4). The high value for methylcellulose solution without additives points to poor solvation of the polymer. Sodium salicylate at low concentrations improved the solvation, K_H falling from 0.6 to 0.38, near the boundary value for a good solvent, in contrast to the increase to 0.80 in sodium chloride solution.

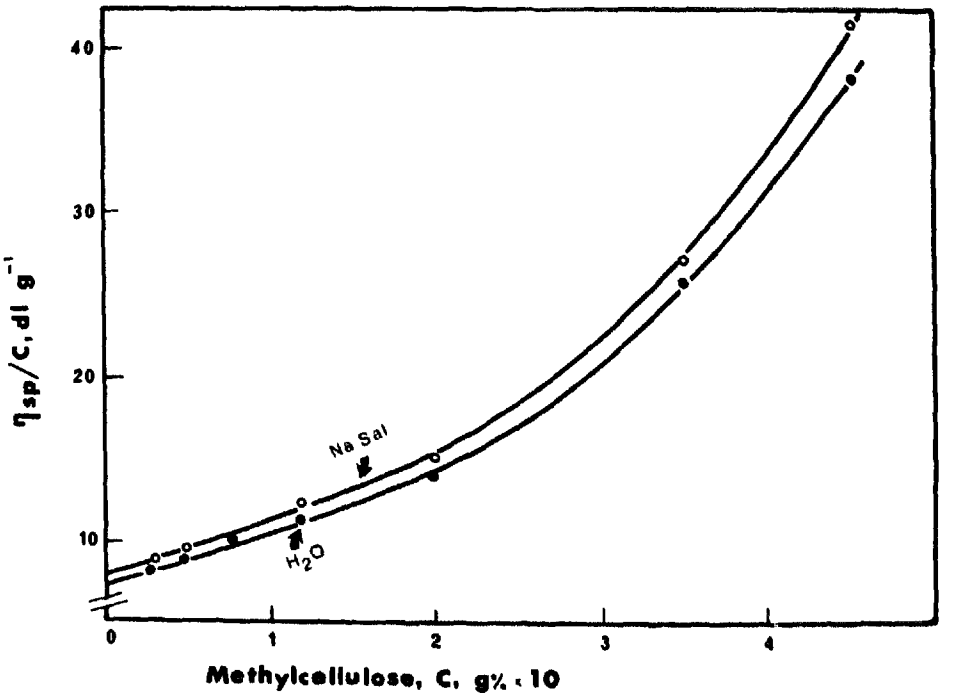

Fig. 9. Influence of sodium salicylate on the viscosity of methylcellulose solutions.

TABLE 4

INTRINSIC VISCOSITIES AND HUGGINS CONSTANTS OF 2% w/w METHYLCELLULOSE SOLUTIONS CONTAINING DIFFERENT ADDITIVES

Additive [a]	Concn. (M)	K_H [b]	$[\eta]$
-	-	0.60	7.26
chloride	0.05	0.82	6.87
chloride	0.10	0.81	6.84
salicylate	0.05	0.49	8.04
salicylate	0.10	0.38	8.49

[a] As sodium salt.
[b] Calculated by means of Eqn. 6.

The conclusion drawn from these experiments (which may be ascribed to apparent changes in the activity of water) accord with those presented earlier for gelation temperature in terms of improved polymer hydration with large organic ions such as salicylate and dehydration with components causing salting-out. The failure of compressed tablets containing these large ions to undergo attrition or disintegration, unlike the matrices from which these agents were absent, is evidence that these ions were the cause of stabilization of this matrix. While the physical evidence points to increased polymer hydration being involved in the maintenance of hydrophilic matrix integrity, the hypothesis may be put forward that the cohesiveness of such matrices is a function of the degree of hydration and stretching of the linear macromolecular chains; this is supported by the viscosity increase of aqueous systems in which integrity-maintaining additives are present and decrease with other types of additive, though other factors may also be present.

Finally, the pharmaceutical aspects which perhaps seem self-evident have not hitherto received adequate attention. Though Gibaldi and Weintraub (1968) did note that a dissolution model seemed to be applicable to release of salicylic acid from compressed discs of a polyvinylpyrrolidone matrix, it is generally accepted that diffusional release is the general pattern for whole compressed hydrophilic matrix tablets. The present work shows that this is by no means true, and that the type of drug and additive used together with their concentrations determines whether the tablet will behave as an intact delivery system in water, giving diffusional release, or will yield its drug by slow or rapid dissolution.

Acknowledgement

The authors are most appreciative of the technical assistance of Mrs. Dalia Gilhar.

References

Bailey, F.E., Jr. and Callard, R.W., Some properties of Poly(ethylene oxide) in aqueous solutions. J. Appl. Polym. Sci., 1 (1959) 56–62.

Bailey, F.E., Jr. and Kolske, J.W., Poly(ethylene oxide), Academic Press, NY, 1976 p. 31.

Borodkin, S. and Tucker, F.E., Drug release from hydroxypropyl cellulose-polyvinyl acetate films. J. Pharm. Sci., 63 (1974) 1359–1364.

Buri, P. and Doelker, E., Formulation des comprimes a liberation prolongee II Matrices hydrophiles. Pharm. Acta Helv. 55 (1980) 189–197.

Donbrow, M. and Touitou, E., The dissolution mechanism in a system undergoing complexation salicylamide in caffeine solution. J. Pharm. Pharmacol., 29 (1977) 524–528.

Gibaldi, M. and Weintraub, H., Dissolution of salicylic acid and polyvinylpyrolidone from compressed mixtures. J. Pharm. Sci., 57 (1968) 832–855.

Heymann, E., Studies on sol–gel transformations. Trans Faraday Soc., 31 (1936) 846–864.

Heymann, E., Bleakley, H.G. and Docking, A.R., Studies on the lyotropic series. J. Phys. Chem., 42 (1938) 353–368.

Higuchi, W.I., Analysis of data on the medicament release from ointments. J. Pharm. Sci., 51 (1962) 802–804.

Higuchi, W.I., Mir, N.A. and Desai, S.J., Dissolution rates of polyphase mixtures. J. Pharm. Sci., 54 (1965) 1405–1410.

Hixson, A.W. and Crowell, J.H., Dependence of reaction velocity upon surface and agitation. Ind. Engng. Chem., 23 (1931) 923–931.

Kassem, M.A. and Matha, A.G., Rheological studies on dispersion of methyl hydroxyethyl cellulose (Tylose MH 1000). Pharm. Acta Helv., 45 (1970) 345–367.

Lapidus, H. and Lordi, N.G., Drug release from compressed hydrophilic matrices. J. Pharm. Sci., 57 (1968) 1292–1301.

Levy, G. and Schwarz, T.W., The effect of certain additives on the gel point of methylcellulose. J. Am. Pharm. Ass., Sci. Edn., 47 (1958) 44–46.

Marriott, P.M. and John, E.G., Influence of electrolytes on the hydration of methylcellulose in solution. J. Pharm. Pharmacol., 25 (1973) 633–639.

Neely, W.B., Solution properties of polysaccharides. IV. Molecular weight and aggregate-formation in methylcellulose solutions. J. Polym. Sci., 1 (1963) 311–320.

Samsel, E.P. and Delap, R.A., Colorometric determination of methylcellulose with antrone. Anal. Chem., 23 (1951) 1795–1797.

Savage, A.B., Ethers. In Bikales, N.M. and Segal, L. (Eds.), Cellulose and Cellulose Derivatives, Vol. V, Wiley-Interscience, U.S.A. 1971, p. 796.

Tillman, W.J. and Kuramoto, R., A study of the interaction between methylcellulose and preservatives. J. Am. Pharm. Ass., Sci. Edn., 46 (1957) 211–214.

Wurster, D.E. and Taylor, P.W., Dissolution rates. J. Pharm. Sci., 54 (1965) 169–175.