(5) R. H. Waldman, T. C. Shipp, S. H. Wood, J. H. London, and F. M. Wigley, *Diabetes*, **20**, 552(1971).
(6) S. A. Berson and R. S. Yellow, *Methods Biochem. Anal.*, **12**, 69(1968).
(7) "The United States Pharmacopeia," 18th rev., Mack Publishing Co., Easton, Pa., 1970, p. 882.
(8) D. F. Waugh, R. E. Thompson, and R. J. Weimer, *J. Biol. Chem.*, **185**, 85(1950).
(9) G. M. Grodsky, *Biochem. J.*, **68**, 142(1958).
(10) R. R. Porter, *ibid.*, **53**, 320(1953).
(11) J. Porath and C. H. Li, *Biochim. Biophys. Acta*, **13**, 268(1954).
(12) W. Dickinson, *Nature*, **178**, 994(1956).
(13) F. A. Robinson and K. L. A. Fehr, *Biochem. J.*, **52**, 298(1952).
(14) G. Grodsky and H. Tarver, *Nature*, **177**, 223(1956).
(15) A. Light and M. V. Simpson, *ibid.*, **177**, 225(1956).
(16) E. L. Fenton, *Biochem. J.*, **71**, 507(1959).
(17) G. M. Grodsky and P. H. Forsham, *J. Clin. Invest.*, **39**, 1070(1960).
(18) W. E. Baum, W. F. Brown, and R. E. Crabtree, *J. Pharm. Sci.*, **53**, 738(1964).
(19) G. W. Probst, W. F. Brown, and H. J. Henry, *ibid.*, **55**, 1408(1966).
(20) W. O. Storvick and H. J. Henry, *Diabetes*, **17**, 499(1968).
(21) J. J. Sciarra, P. McGinly, and L. Izzo, *J. Soc. Cosmet. Chem.*, **22**, 385(1969).
(22) J. J. Sciarra and D. Adelman, *ibid.*, **22**, 867(1971).
(23) I. Porush, C. Thiel, and J. Young, *J. Amer. Pharm. Ass., Sci. Ed.*, **49**, 70(1960).

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Effect of Thermal Gelation on Dissolution from Coated Tablets

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Abstract □ Tablets with a methylcellulose coating were found to exhibit lower dissolution profiles than those coated with a hydroxypropyl methylcellulose coating at 37°, and the cause was investigated. The differences are attributed to thermal gelation of the methylcellulose at temperatures near 37°, which creates a barrier to the dissolution process and essentially changes the dissolution mechanism. This mechanism is substantiated by the fact that at temperatures below the gel point and at increased agitation, the effect disappears. The retarded dissolution effect is not peculiar to the drug involved.

Keyphrases □ Thermal gelation—effect on dissolution of methylcellulose-coated tablets □ Dissolution—methylcellulose-coated tablets, effect of thermal gelation □ Dosage forms—tablets, methylcellulose coated, effect of thermal gelation on dissolution □ Methylcellulose—tablet coating, effect of thermal gelation on dissolution

Polymers, particularly the cellulose polymers, are used in pharmacy as film formers for tablet coatings and as binding agents in a granulation step.

During the development of a coated tablet, several different polymers may be evaluated for various properties and their effects on the dosage form. Ideally, unless applied for a specific purpose, the coating used for a drug delivery system should not affect the efficiency with which the drug is delivered to the target site (1).

During a coating investigation, it was observed that identical core tablets coated with two different polymers exhibited widely different dissolution profiles. Differences in the polymers, methylcellulose[1] and hydroxypropyl methylcellulose[2], were investigated in an attempt to rationalize the observed dissolution differences.

EXPERIMENTAL

Core tablets containing the following components were prepared by standard direct compression techniques: dibasic calcium phosphate dihydrate, lactose USP, starch USP, purified wood cellulose[3], colloidal silicon dioxide[4], stearic acid, and magnesium stearate. Active ingredients included either aspirin or amitriptyline hydrochloride.

The coating consisting of only the polymer, and a yellow lake was applied by normal film-coating techniques. Approximately 2.9 mg of polymer was deposited per tablet. Dissolution measurements were carried out in the USP apparatus at 150 rpm, unless noted otherwise, in 0.1 *N* HCl. Solubility was measured according to the USP procedure.

RESULTS AND DISCUSSION

The dissolution profiles (Fig. 1) for the aspirin core tablet and the two corresponding coated tablets at 37° illustrate the difference in the methylcellulose coating. Aside from the lag time for the tablet coated with the hydroxypropyl polymer, the profile parallels that of the core tablet. The methylcellulose-coated tablet exhibits a slower release profile.

[1] Methocel MC 25 cps.
[2] Methocel 60 HG.
[3] Solka-Floc, B.W. 2030.
[4] Cab-O-Sil.

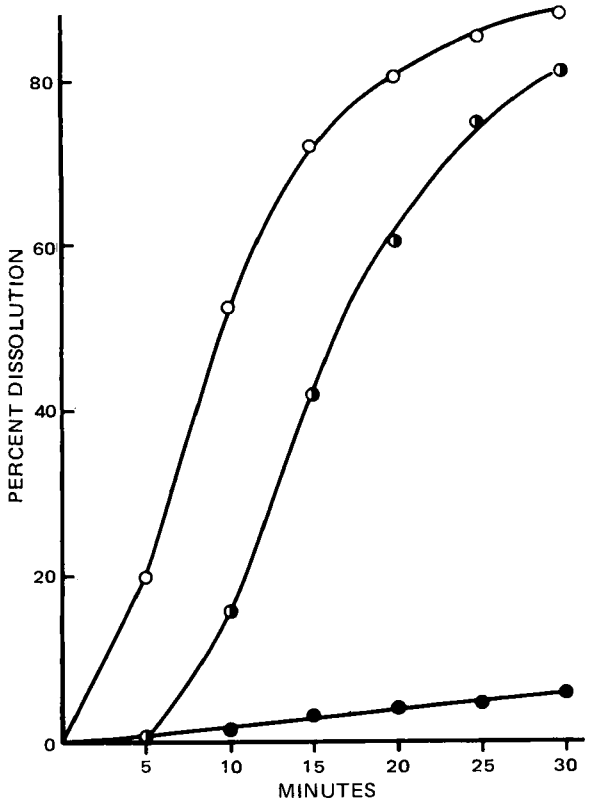

Figure 1—*Dissolution profiles for aspirin tablets at 37°. Key:* ○, *core tablet;* ◑, *hydroxypropyl methylcellulose coating; and* ●, *methylcellulose coating.*

Although both polymers are water soluble and the coating should not interfere with the dissolution process, these products do exhibit the property of thermal gelation, the phenomenon of gelation resulting from the application of heat. According to the product information (2), solutions of these cellulose derivatives gel on heating, whereas other gums, such as gelatin, gel only on cooling. Thermal gelation of these materials is a function of (among other factors) temperature and the type and concentration of polymer used.

If thermal gelation does occur, the gel formed by the tablet coating material may create a barrier to the dissolution process, *i.e.*, a change in the mechanism caused by a diffusion layer of polymer gel or by a very viscous polymer solution as it approaches the gel state. As the temperature of a methylcellulose solution is raised, hazing of the solution occurs just prior to gelation and viscosity may start to rise (2).

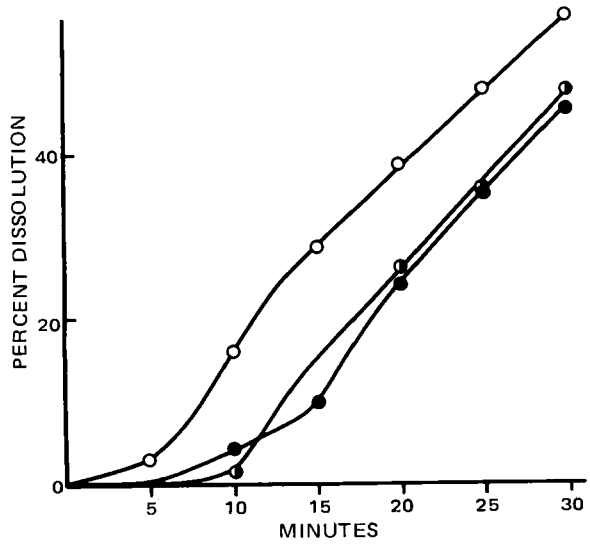

Figure 2—*Dissolution profiles for aspirin tablets at 21°. Key:* ○, *core tablet;* ◑, *hydroxypropyl methylcellulose coating; and* ●, *methylcellulose coating.*

If the phenomenon of thermal gelation is responsible for the slow dissolution rate of methylcellulose-coated tablets at 37°, then tablets coated with either polymer should give essentially the same profile at a temperature below the thermal gel point. Figure 2 shows the dissolution profiles for the aspirin tablets at 21°. Although the profiles for the core tablet and the hydroxypropyl polymer tablet are lower than those at 37°, as expected because of reduced solubility, the two coatings appear to yield equivalent results. However, the release from the methylcellulose-coated tablet is increased significantly over that at 37°.

Additional dissolution runs were also made at 26 and 31°. The 30-min dissolution figures are shown in Table I for all runs.

According to the Noyes–Whitney equation:

$$\frac{dw}{dt} = DS(C_s - C) \qquad \text{(Eq. 1)}$$

where w is the amount dissolved, t is the time, D is the diffusion coefficient, S is the surface area of the dissolving solid, C_s is solubility, and C is the concentration in the bulk.

At very low solute concentration in the dissolution medium, C may be ignored (3) and, by assuming D and S to be constant (*i.e.*, for initial dissolution rates), Eq. 1 may be integrated to yield:

$$w = kt \qquad \text{(Eq. 2)}$$

where $k = DSC_s$.

The slope of the initial points from a plot of percent released *versus* time for a given dissolution run yields the constant k', which equals $100k/w_0$, where w_0 is the initial amount of drug in the tablet. These values were calculated for the various dissolution runs (Table II).

The effect of temperature can be illustrated by the use of an Arrhenius plot (log k' *versus* the reciprocal of the absolute temperature). However, the term k' does contain the solubility term, C_s, which changes significantly with temperature (Table III).

Table I—Aspirin Dissolution at 30 min

Sample	Percent Released[a] at: 21°	26°	31°	37°
Core	56.41	66.22	73.84	88.01
Methylcellulose	45.19	10.35	7.62	5.82
Hydroxypropyl methylcellulose	47.56	63.95	77.28	81.08

[a] Mean of four runs.

Table II—Dissolution Rate Constants[a]

Temperature	Core Tablet (k')	Methylcellulose Coating (k')	Hydroxypropyl Methylcellulose Coating (k')
21°	2.539	0.985	1.526
26°	3.206	0.492	2.419
31°	3.067	0.290	3.034
37°	5.205	0.231	4.168

[a] See text.

Table III—Aspirin Solubility in 0.1 *N* HCl

Temperature[a]	Solubility × 10^2, moles/liter
21°	3.88
26°	4.82
31°	5.93
37°	7.55

[a] Measurements were made at 21 and 37°. Intermediate values were calculated by the Van't Hoff equation.

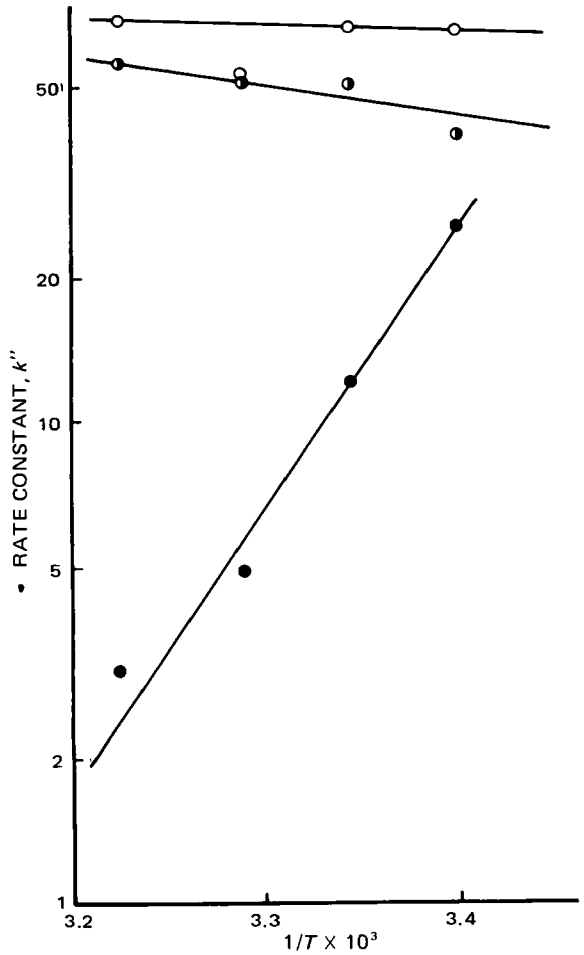

Figure 3—*Arrhenius plot showing effect of temperature on the rate constant k'' (see text). Key: ○, core tablet; ◑, hydroxypropyl methylcellulose coating; and ●, methylcellulose coating.*

The solubility effects can be separated by plotting the log k'' *versus* the reciprocal temperature (Fig. 3):

$$k'' = k'/C_s = 100\frac{DS}{w_0} \qquad \text{(Eq. 3)}$$

Changes noted in such a plot cannot then be attributed to a change in solubility when the solvent is assumed to be 0.1 *N* HCl.

The slopes in Fig. 3 for the core tablet and the hydroxypropyl polymer-coated tablet show slight decreases in the dissolution rate constant k'', which could be explained by a decrease in D as temperature is decreased. However, the data on the tablet with the methylcellulose coating show not only a positive slope but widely different values for k'', especially at higher temperatures. These values, of course, cannot be attributed to changes in D as a function of temperature, again if the solvent is assumed to be 0.1 *N* HCl.

The change in the sign of the slope indicates a difference in the mechanism for release with the methylcellulose polymer. The decrease in the k'' value with temperature can be explained simply by an increase in the viscosity of the dissolution medium. In such a case, the dissolution medium or barrier is no longer the 0.1 *N* HCl but a methylcellulose solution or methylcellulose gel with a concentration sufficient to lower D by increasing viscosity. The solubility, C_s, could also be lower in the methylcellulose solution than in the normal dissolution medium; but since the same concentration of polymer should exist for each methylcellulose-coated tablet and the C_s of the drug should increase with increasing temperature, the viscosity and, hence, the diffusion coefficient considerations appear to predominate.

Thus, the change in mechanism is attributed primarily to the presence of a barrier to dissolution in the form of a polymer solution or gel where the diffusion coefficient is much higher than that in the normal dissolution medium.

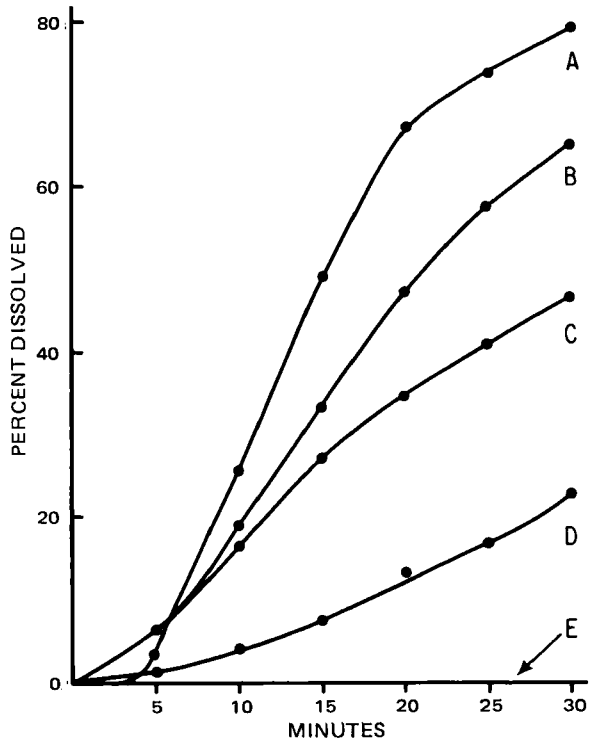

Figure 4—*Dissolution profiles for aspirin core tablets at 37° when methylcellulose has been added to the dissolution medium. Key (percent methylcellulose): A, 0.000387, B, 0.5; C, 1.0; D, 2.0; and E, 5.0.*

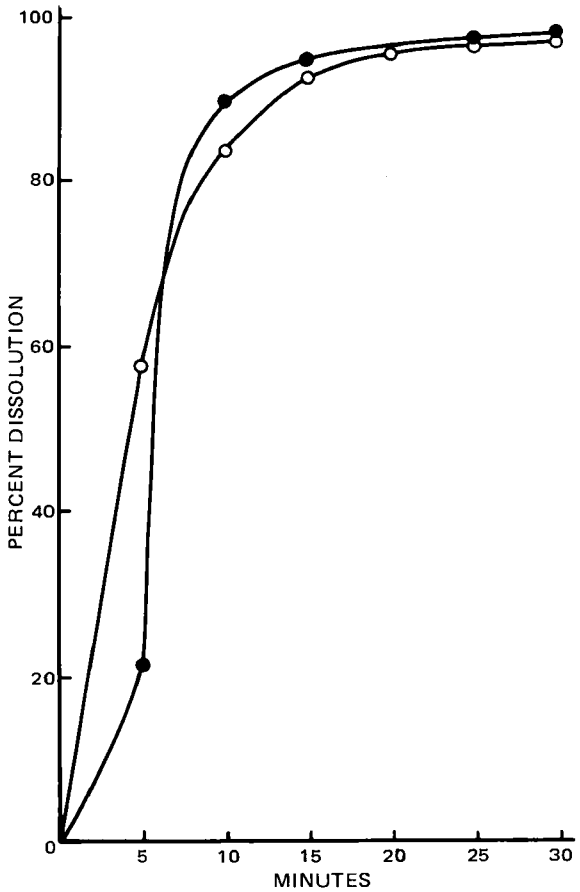

Figure 5—*Release profiles at 37° for aspirin tablets at 350 rpm. Key: ○, core tablet; and ●, methylcellulose coating.*

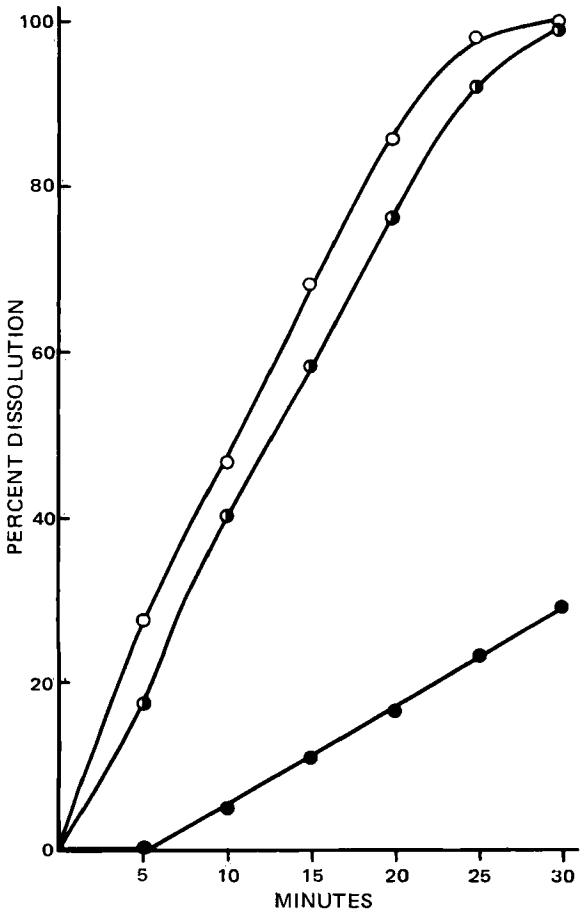

Figure 6—*Dissolution profiles at 37° for tablets containing amitriptyline hydrochloride. Key:* ○, *core tablet;* ◑, *hydroxypropyl methylcellulose coating; and* ●, *methylcellulose coating.*

To support this hypothesis, the effect on dissolution of the core tablet when the polymer concentration is increased in the dissolution medium is shown in Fig. 4. It is known that as the concentration of a given type of cellulose polymer increases, the thermal gel temperature decreases (2). The quantity of polymer in the coating of one tablet, when dispersed in the volume of solvent used for dissolution, is not sufficient to form a gel at the temperatures studied. The dissolution medium for curve A in Fig. 4 contains 2.9 mg of methylcellulose (0.000387%), and the profile is equivalent to that of the core tablet in the normal dissolution medium (Fig. 1).

As the concentration of methylcellulose is increased, the release rate decreases. At 5% polymer (Fig. 4, curve E), where gel structure was visually apparent, the gel-coated tablet was removed intact even after 15 min at a 500-rpm stirring rate.

These data indicate that it is not simply the presence of the polymer that retards dissolution but the concentration at the tablet surface. A very concentrated polymer solution probably exists at the surface of the methylcellulose-coated tablet—concentrated enough, in fact, to reduce the gel point to 37° or below. Even if gelation is incomplete, the polymer solution with its high viscosity provides a barrier to the dissolution process.

Agitation can affect the degree and apparent temperature of gelation, and continued agitation during gelation may break down the gel structure (2). The rotational speed of the dissolution basket was increased, and Fig. 5 shows that the release at 350 rpm for the methylcellulose-coated tablet is essentially equivalent to that of the core tablet.

To show that the decrease in release rate from the methylcellulose-coated product at 37° is not peculiar to the drug involved, the experiment was repeated using amitriptyline hydrochloride as the active ingredient. The release profiles for the core and coated tablets (Fig. 6) illustrate the differences.

The property of thermal gelation, although present in many polymers, is only of interest in this context when it occurs sufficiently near normal body temperatures to influence the rate of drug release. Where rapid release is required or where absorption might be controlled by the dissolution step, this phenomenon could be important and should be avoided.

REFERENCES

(1) L. C. Schroeter, in "Remington's Practice of Pharmacy," 14th ed., Mack Publishing Co., Easton, Pa., 1970, p. 1681.

(2) "Methocel Product Information," Dow Chemical Co., Midland, Mich., 1968.

(3) E. Nelson, *J. Amer. Pharm. Ass., Sci. Ed.*, **46**, 607(1957).

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