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Temperature dependence of the disintegration times of compressed tablets containing hydroxypropylcellulose as binder

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The dependence of the disintegration times of placebo and active tablets containing hydroxypropylcellulose (HPC), as binder on the temperature of the test medium in the region of 37° is reported. The degree of temperature dependence varied with the HPC lot and concentration in the formulations. These dependences could be accentuated by the presence in the formulation of certain drugs, such as caffeine. The extent of the temperature dependence could be diminished by reducing the HPC concentration in the formulations. Corresponding trends were observed in drug release behaviour from some of these formulations. The effects observed were interpreted in terms of the thermodynamic behaviour of HPC systems and a specific drug-HPC interaction.

Published data on the use of alkyloxy-substituted celluloses as binders in various granulation processes have provided a number of references to hydroxypropylcellulose (HPC). In a comparison of HPC with other alkyloxy celluloses, Selmeczi, Garamvolgyi-Horvath & Keresztes (1975) concluded that HPC as binder in an active formulation performed best in terms of good mechanical properties and shortness of disintegration time of tablets. In an article by Davies & Gloor (1972), the data show that tablets of excellent properties, in terms of hardness and disintegration times, could be made from formulations containing low concentrations of HPC as binder although disintegration times increased strongly with HPC concentration for little improvement in the tablet strength. Using alkyloxy celluloses as film coating agents, Schwartz & Alvino (1976) demonstrated a strong temperature dependence at 21° and 37° of aspirin release from coated tablets.

The work reported here comprises part of a study to characterize the properties of HPC as a granule binding agent in pharmaceutical formulations and its influence on the temperature dependence of the tablet disintegration time and related dissolution rate. Within the range of 35–39° permitted by the U.S.P. disintegration time measuring specification, the nature and extent of such a temperature dependence has obvious implications in setting limits for disintegration time, drug release rate and stability control parameters for tablets.

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MATERIALS AND METHODS

Materials

Powders used were lactose (200 mesh, DMV Holland), corn starch (Hoffmann, Germany), hydroxypropylcellulose (Klucel LF, Hercules Powder Co. Ltd, U.S.A.), magnesium stearate (Schweizerhall Chem. Fab. AG, Switzerland), stearic acid (Steingels AG. Switzerland) and colloidal silicon dioxide (Aerosil 200, Degussa, Germany).

Drug substances included anhydrous caffeine B.P., coarse and fine grades, a barbiturate, a pyrazolone and a benzodiazepine derivative.

Methods

The dry powders (including HPC, which was always incorporated dry) were blended and wet-massed in a conventional planetary mixer (model PLV 50, Dominici Italy) and screened first through a 3 mm perforated plate and then through a 1·2 mm mesh sieve. A two-phase drying procedure in a fluidized bed (model WSG 5 or WSG 15, Glatt Lufttechnische Apparate, Germany) was used to minimize fines content. Unless otherwise stated, the granulation liquid was water. Placebo and active formulations were tableted on rotary machines (model B2, Stokes Corp., U.S.A. or Betapress, Manesty Machines Ltd, England). Depending on formulation, the punches used were 7, 9 or 10 mm flat-faced or shallow concave for tablet weights of 120, 240 and 350 mg, respectively. Typical placebo formulations are given in Table 1, with representative tablet properties as in Table 2.

Table 1. *Typical placebo formulations.*

Lactose	74–92%
Corn starch	5–20%
Hydroxypropyl cellulose	2– 5%
Magnesium stearate	1%

Tablet disintegration times in water were measured according to the U.S.P. procedure with the following amendments: (*a*) Measurements were made at constant, fixed (±0·1°) temperature, and not over the usually allowed temperature range of 35–39°. (*b*) Plastic discs were not used since entrapment of disintegrated material in the disc channels tended to confuse the end points. Constant temperatures were maintained by monitoring with a calibrated digital electronic thermometer (Mettler, Switzerland), with the probe inserted in one of the six glass tubes of the tablet holder. Observation of disintegration behaviour of six tablets showed that the disintegration behaviour of the tablet in the tube containing the probe was not influenced by the presence of the probe.

Table 2. *Typical tablet properties.*

	Placebo	Active
Hardness, kp (Heberlein)	~4	5–8
Friability, % (Roche Friabilator, 400 rev)	<1	<1
Weight, mg	120	120, 240, 350
Wt. s.d. (%, for 50 tablets)	<2	<2

Dissolution rates were measured either by the U.S.P. rotating basket method or by the flow-through cell previously described by Cakiryildiz, Mehta & others (1975).

Turbidity was measured using a spectrophotometer (type PMQ 3, Zeiss, Germany) with 420 μm wavelength monochromatic light with distilled water as reference. The HPC solution was continuously circulated at 80 ml min^{-1} through a flow-through cuvette from a reservoir in a thermostated bath. The cuvette holder was heated by water circulated from the same water bath. The temperature of the test solution was continuously monitored in the fluid exit from the measuring cuvette. Measurements of turbidity were taken at frequent intervals and the solution temperature was increased at the rate of 8° h^{-1} over the range of 35–50°. 1% by weight HPC solutions were used, and where present, other additives were also at 1% by weight.

RESULTS AND DISCUSSION

Tablet disintegration times at temperatures in the range of 34–39° for a placebo formulation including HCP, lot 3630 at 2–3% concentrations, with either water or ethyl alcohol as granulation liquid, are shown in Fig. 1. The significant dependence of tablet disintegration time on the temperature of the water in the test is a function of HPC concentration. This dependence is influenced to a lesser extent by the nature of the granulating liquid.

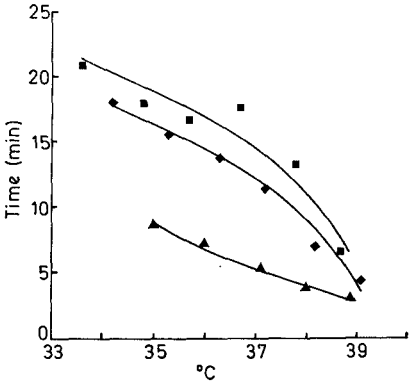

FIG. 1. Variation of disintegration time (min) (modified U.S.P.) with temperature for a placebo formulation. Tablets were 7 mm flat-faced and the HPC was f lot 3630. Each datum point represents the mean of six values. ■ 3% HPC granulated with water; ◆ 3% HPC granulated with ethanol; ▲ 2% HPC granulated with ethanol.

The same accentuated disintegration time-temperature dependence with increasing HPC concentration is apparent with a low drug dosage proprietary formulation A, in Fig. 2. The data

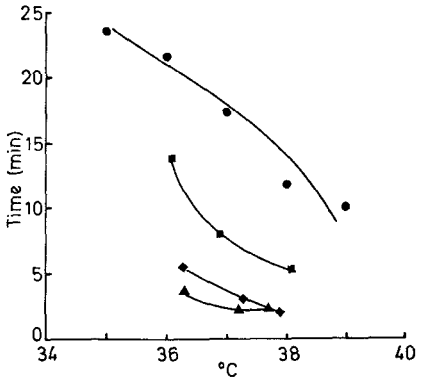

FIG. 2. Change in disintegration time (min) (modified U.S.P.) with temperature for the low dosage proprietary formulation A. The tablets were 7 mm flat-faced and each datum point represents the mean of six values. ● 4% HPC from lot 3630; ■ 3% HPC from lot 3630; ◆ 3% HPC from lot 3326; ▲ 2% HPC from lot 3630.

show that the disintegration time-temperature dependence varies not only with HPC content but also from HPC lot to HPC lot as given by the significant difference at the 3% levels of lots 3630 and 3326 (numbers being those of the manufacturer). Similar variations with regard to HPC concentration and lot number are apparent with a high drug dosage proprietary formulation B, Fig. 3. This behaviour is also repeated with a medium drug dosage proprietary formulation C, Fig. 4.

Although the degree of disintegration time-temperature dependence for the different HPC lots is strongly influenced by these tablet formulations,

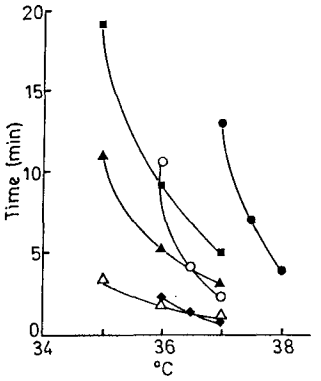

FIG. 3. Plot of disintegration time (min) (modified U.S.P.) against temperature for shallow convex 10 mm tablets made from a high dosage proprietary formulation B. Each datum point is the mean of six values. ● 3·57% HPC from lot 3630; ■ 3·14% HPC from lot 3630; ○ 3·57% HPC from lot 3326; ▲ 2·57% HPC from lot 3630; ◆ 3·57% HPC from lot 9660; △ 3·57% HPC from lot 3407.

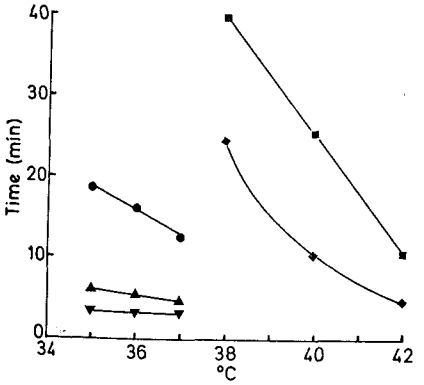

FIG. 4. Variation of disintegration time (min) (modified U.S.P.) with temperature for shallow convex 9 mm tablets from a medium dosage proprietary formulation C. Each datum point is the mean of six values. ■ 2·5% HPC from lot 3630; ◆ 2·5% HPC from lot 3326; ● 2·08% HPC from lot 3630; ▲ 1·67% HPC from lot 3630; ▼ 2·5% HPC from lot 9660.

the rank order of temperature dependence within the HPC lots is maintained (Figs 3 and 4). Thus at all concentrations lot 3630 imparts greater temperature dependence to tablet disintegration time than lot 3326. Results for tablets made with lots 3407 and 9660 indicate that with certain HPC lots it is possible to prepare rapidly disintegrating tablets with virtually no temperature dependence even at relatively high HPC content.

In addition, the temperature dependence of the disintegration time of formulations containing HPC can be accentuated by certain drug substances, such as caffeine, to a degree dependent on the particle size of the drug. For example, the proprietary formulation D, containing caffeine and HPC gave the results shown in Fig. 5.

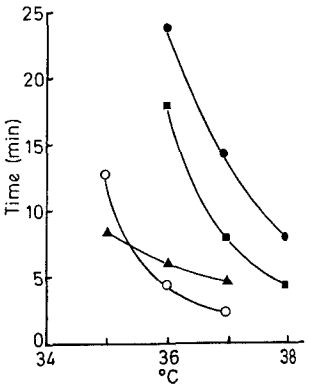

FIG. 5. Change in disintegration time (min) (modified U.S.P.) with change in temperature for shallow convex 10 mm tablets from a caffeine-containing high dosage proprietary formulation D. Each data point gives the mean of six values. ● 3·57% HPC from lot 3630 with fine caffeine; ■ 3·57% HPC from lot 3630 with coarse caffeine; ○ 3·57% HPC from lot 3326 with coarse caffeine; ▲ 2·57% HPC from lot 3630 with fine caffeine; mean particle sizes (Alpine jet sieve) of caffeine: fine 32 μm, coarse 106 μm.

The adverse effects of high concentrations of certain HPC lots, and the effect of finely divided caffeine on disintegration times was mirrored in drug dissolution rate from proprietary formulation A measured by the flow-through cell (Table 3) and from proprietary formulations B and D, measured by the U.S.P. rotating basket (Table 4).

It is readily apparent that temperature dependence of the important tablet properties, disintegration time and drug release rate, occurs within the critical temperature range, 35–39°. For HPC concentrations in the various formulations which were necessary to give adequate mechanical properties, this temperature dependence was most acute with one of the four HPC lots tested in this program.

Table 3. *Drug dissolution rates determined with the flow through cell. Each value represents the mean of six measurements.*

Formulation	A	A	A	A
HPC concentration, %	2	3	3	4
HPC lot number	3630	3630	3326	3630
Mean drug dissolution, %				
After 5 min	16·7	11·4	15·0	9·7
15 min	58·1	43·6	56·0	30·4
30 min	79·6	76·7	81·5	60·2
60 min	96·2	96·0	97·0	93·3

The effects of various HPC lots at different concentrations on drug dissolution rate and tablet distintegration time observed in this work could not be correlated with any of the parameters supplied by the manufacturer of the HPC used (Table 5). The cloud points given are claimed to be within experimental error of each other. Single viscosity measurements are notoriously bad indicators of actual polymer molecular weights,

Table 4. *Drug dissolution rates determined by the rotating basket method.* Each value represents the mean of 18 measurements. Mean particle sizes of caffeine, coarse 106 μm, fine 32 μm.

Formulation	B	B	B	B	B	D	D	D
HPC concn	2·57	1·57	3·57	3·57	3·57	3·57	3·57	3·57
HPC lot No.	3326	3630	3407	3326	3630	3326	3630	3630
Caffeine	—	—	—	—	—	Cse	Cse	Fine
Mean drug dissolution (%)								
After 5 min	49	46	93·3	32·5	11·7	36·6	10·8	9·5
15 min	100	99	100	96	54·7	99	49·3	44
30 min	100	100	100	100	89	100	95	84·7
60 min	100	100	100	100	100	100	100	100

particularly when measured on modified polymers varying in degree of substitution to the extent shown in Table 5, and especially with regard to viscosity behaviour of these systems, which are no longer Newtonian at the concentrations specified. The cloud point of a macromolecular solution occurs when the solution becomes thermodynamically unstable and separates into two phases. One of these phases, known as the gel phase, can, according to concentration and nature of the polymer demixing, give rise to a 'gelled' gel phase, gelled being used here in terms of the conventional rigid non-fluid meaning. This thermodynamic demixing is not a thermal gelation in the sense used, e.g. with respect to aqueous gelatin solutions which do not thermodynamically demix at the gel point.

Schwartz & Alvino (1976) observed modified drug release from alkyloxy cellulose film coated tablets over a wide temperature range. However, in converse to the results reported here for the use of an

Table 5. *Hydroxypropylcellulose specifications for various lot numbers.* Data supplied by manufacturer.

Lot No.	3407	3630	9660
Molar degree of substitution (of isopropoxy units)	3·1	3·8	3·7
Aqueous (5%) solution viscosities (cps)	123	107	90
Cloud point, °C	42	44	NA*

* Not available.

alkyloxy cellulose derivative as a binding agent, drug release rates were reduced at the higher temperature. They attributed the adverse drug dissolution rates to thermal gelation effects near 37°, although these types of polymers do not thermally gel, but thermodynamically demix in aqueous solutions.

Oligomeric and polymeric alkyloxy derivatives are known to exhibit complex miscibility behaviour in aqueous media (Morawetz, 1965).

Solutions exhibiting a lower critical solution temperature (LCST), a not uncommon phenomenon with macromolecular solutions, demix above the LCST. Systems which are polymolecularly dispersed, i.e. most polymers, demix over a temperature range, this range being greater the wider is the molecular weight distribution of the macromolecule. When the polymer is also substituted to different degrees, as apparent with HPC, then the molar degree of substitution of isopropoxy units will also affect the LCST. The cloud point is a convenient method of measuring the demixing temperature, and an accurate method of determining the temperature range at which demixing occurs was developed as described in the experimental section. Cloud point data for three different HPC lots, with and without caffeine, are shown in Figs 6 and 7.

If thermodynamic phase separation at the LCST is a contributing factor to the temperature dependence of the tablet disintegration time and dissolution rate, then cloud point data probably give the most direct information on this process. The cloud points of aqueous HPC solutions in the absence of caffeine show phase separation at higher temperature for HPC lot 3630, the HPC lot showing strongest temperature dependence of disintegration time. HPC lot 3326 has a significantly lower cloud point than lot 3630 but a much broader curve than either lots 3630 or 3407, suggesting that its behaviour lies between these two lots. On the other hand, the sharpest cloud point curve, at lower temperature, indicative of a narrower molecular weight distribution, is obtained with HPC lot 3407. Formulations

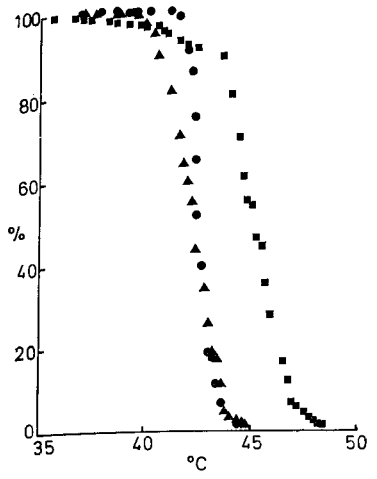

FIG. 6. Turbidity method of determining cloud point. The percentage transmission is plotted against the solution temperature for 1% HPC solutions. ■ HPC from lot 3630; ● HPC from lot 3407; ▲ HPC from lot 3326.

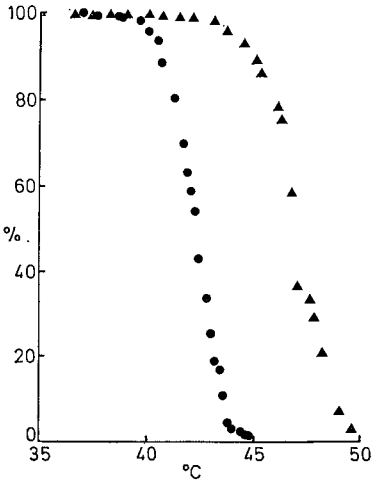

FIG. 7. Cloud point determined by turbidity for a 1% HPC solution from lot 3326 as altered by caffeine. ● HPC solution alone; ▲ HPC plus 1% caffeine solution. The percentage transmission is plotted against solution temperature.

containing HPC lot 3407 show least temperature dependence of disintegration time and faster dissolution rate of drug in the formulation even when used at higher HPC concentrations in the formulation. Indeed, there is evidence to suggest that the nearer the LCST of the HPC in water is to the 35-39° disintegration measurement range, the more HPC actually takes on the character of a disintegrant (Stafford, to be published).

In addition, a sharp shift of cloud point to higher temperature is observed when caffeine is added to the aqueous HPC solutions. During conventional wet massing, fine caffeine is more likely to partially dissolve in the granulation liquid water, than coarse caffeine. The chances of interaction of caffeine with the HPC present in the formulation, which must also partially or totally dissolve in the granulation fluid under the same conditions in order to act as binder, are consequently greater for fine than for coarse grade caffeine. Further evidence of this interaction between fine grade caffeine and HPC was observed in that formulations containing fine caffeine produced a wet mass consistency more dough-like than was the case when the caffeine was more coarse. Such an effect was not observed when other coarse grade material in the formulation was substituted by finer grade material. The type of interaction observed here is considered similar to the previously reported influence of HPC on caffeine in the promotion of whisker formation (Yamada, Nishinura & Matsuzaki, 1976).

CONCLUSION

A temperature dependence of tablet disintegration times and drug release rates in the region of 37° was observed with tablets containing HPC as a binder. It has been suggested that a major factor contributing to this effect is the phase separation of HPC which has an LCST for aqueous solutions near to 37°. Reduction of HPC concentration in the formulation reduces this temperature dependence, probably by reducing the amount of polymer separating as gel phase near the LCST. Finally, the effect of finely divided caffeine on the temperature dependence of the disintegration time of HPC containing tablets is attributed to a definite interaction between caffeine and HPC in aqueous systems. This temperature dependence could also be considerably reduced by reduction of the HPC concentration in the formulation.

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