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Degradation of hydroxypropylcellulose by *Rhizomucor*: effects on release from theophylline–hydroxypropylcellulose tablets

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Abstract

The stability of several varieties of hydroxypropylcellulose was monitored during 3 years of storage (1) under the conditions recommended by manufacturers and official pharmacopoeias (simple storage in closed containers) and (2) at zero relative humidity. After 1 year, severe degradation of the varieties with lower initial pH and particle size stored at ambient relative humidity was shown by changes in their molecular weight and in the pH and apparent viscosity of 2% aqueous dispersions. Microbiological analyses showed the observed degradation to be attributable to the action of fungi of the genus *Rhizomucor*. The changes in apparent viscosity significantly affected the release of theophylline from direct compression tablets formulated with the degraded excipients.

Keywords: Hydrophilic matrices; Hydroxypropylcellulose; Microbiological contamination of excipients; *Rhizomucor*; Stability of cellulose ethers

1. Introduction

Cellulose ethers are hydrophilic polymers that are widely used as pharmaceutical excipients (Doelker, 1993). They are generally considered to be stable in the solid state when kept in closed containers under normal environmental conditions (Handbook of Pharmaceutical Excipients, 1994) and the norms established by official pharmacopoeias for their storage are accordingly not particularly stringent: The United States Pharmacopeia (1995) and the British Pharmacopoeia

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Table 1
Characteristics of HPCs upon opening the containers in which they were supplied

Polymer[a]	DS	MS	Mean diameter (μm)	Moisture content (%)	pH[b]	Mean molecular weight	Apparent viscosity[c] (mPa·s)
Klucel® GF	2.3	3.86	286.06 (1.91)	3.27 (0.01)	6.9 (0.1)	478900	178.0 (0.6)
Klucel® MF	2.4	3.89	245.21 (1.98)	4.51 (0.02)	7.3 (0.1)	1228500	3749 (62.3)
Nisso® M-BJ	2.2	3.48	142.80 (1.56)	2.88 (0.14)	6.5 (0.1)	599800	372.4 (5.8)
Nisso® M-DC	2.2	3.56	132.33 (1.61)	2.85 (0.09)	6.1 (0.1)	569800	348.0 (2.9)
Nisso® M-JD	2.2	3.37	149.69 (1.59)	3.16 (0.12)	6.4 (0.1)	537300	257.6 (1.4)
Nisso® H-BJ	2.3	3.42	136.32 (1.63)	4.64 (0.01)	6.4 (0.1)	1070400	2760 (43.5)
Nisso® H-JE	2.2	3.44	143.13 (1.63)	4.18 (0.06)	6.2 (0.1)	1130100	2809 (8.9)

[a] M-BJ, lot BJ-031; M-DC, lot DC-631; M-JD, lot JD-471; H-BJ, lot BJ-141; H-JE, lot JE-161.
[b] Of 1% aqueous solutions.
[c] Of 2% aqueous solutions.

(1998) merely require that they be stored in closed containers, without specifying further measures for prevention of water uptake or microbiological contamination.

The microorganisms most frequently isolated from pharmaceutical raw materials are those with very frugal nutrient requirements and good tolerance to dryness: notably *Bacillus*, *Streptococcus*, Gram-negative bacteria, yeasts and moulds (De la Rosa et al., 1995). The risks they pose for the integrity of cellulose ethers have hitherto received little attention (Banker et al., 1982; Kasulke et al., 1987), even though cellulose ethers with a moderate degree of substitution are often used in culture media for cellulase-producing fungi and bacteria because they constitute a suitable source of carbon for these microorganisms (Arai et al., 1987; Shambe and Ejembi, 1987; Masková et al., 1988; El-Naghy et al,. 1991). The importance of the risk of excipient contamination derives from the likelihood that it will significantly alter the properties of the dosage forms in which the excipient is subsequently incorporated (Blair et al., 1991; Beveridge, 1992; De la Rosa et al., 1995).

In the work described here we set out to study the stability of several varieties of hydroxypropylcellulose (HPC) during long-term storage, concentrating on the properties that are most important for their use as pharmaceutical excipients (Dahl et al., 1990; Acquier et al., 1992; Vázquez et al., 1992; Mitchell et al., 1993) and investigating the effects of any changes in these properties on drug release from direct compression tablets formulated with the affected HPC (the test drug employed was theophylline). In the event, microbiological analyses were included in the study to account for the observed severe degradation of some HPC varieties under officially permitted storage conditions.

2. Materials and methods

2.1. Materials

Hydroxypropylcelluloses (HPCs) were supplied by Aqualon, Hercules Inc. (USA) (Klucel® GF, lot FP10-10293, nominal viscosity 100–400 mPa·s; and Klucel® MF, lot 7857, nominal viscosity 1000–4000 mPa·s) and by Nippon Soda Co. (Japan) (Nisso® M, lots BJ-031, DC-631 and JD-471, nominal viscosity 100–400 mPa·s; and Nisso® H, lots BJ-141 and JE-161, nominal viscosity 1000–4000 mPa·s).

2.2. Characterization of the polymers

2.2.1. Moisture content

Moisture content was determined on the basis of weight loss after 3 h at 105°C (USP23–NF18; United States Pharmacopeia, 1995).

Table 2
Moisture content and pH of HPCs stored for 1, 2 or 3 years in closed containers at room temperature and zero relative humidity

Polymer[a]	Moisture content (%)			pH[b]		
	1 year	2 years	3 years	1 year	2 years	3 years
Klucel® GF	0.13 (0.01)	0.11 (0.01)	0.12 (0.01)	6.9 (0.1)	7.0 (0.1)	6.9 (0.1)
Klucel® MF	0.10 (0.01)	0.09 (0.01)	0.09 (0.01)	7.3 (0.1)	7.3 (0.1)	7.2 (0.1)
Nisso® M-BJ	0.15 (0.02)	0.14 (0.02)	0.13 (0.02)	6.5 (0.1)	6.4 (0.1)	6.5 (0.1)
Nisso® M-DC	0.15 (0.02)	0.13 (0.02)	0.12 (0.02)	6.1 (0.1)	6.1 (0.1)	6.0 (0.1)
Nisso® M-JD	0.10 (0.01)	0.10 (0.01)	0.10 (0.01)	6.3 (0.1)	6.4 (0.1)	6.3 (0.1)
Nisso® H-BJ	0.12 (0.01)	0.11 (0.01)	0.12 (0.01)	6.4 (0.1)	6.2 (0.1)	6.2 (0.1)
Nisso® H-JE	0.09 (0.01)	0.09 (0.01)	0.08 (0.01)	6.2 (0.1)	6.3 (0.1)	6.2 (0.1)

[a] See Table 1 for key.
[b] Of 1% aqueous solutions.

2.2.2. Degree of substitution and molar substitution

The substitution patterns of the various lots were evaluated by ^{13}C nuclear magnetic resonance (NMR) spectroscopy of their hydrolysates, as follows. First, 1.0 g of HPC was added to 30 ml of 6 M sulphuric acid, and stirred for 1.5 h at 20°C. The mixture was then made up to 90 ml with deionized water, autoclaved at 2 atm (120°C) for 1 h, allowed to cool to room temperature, neutralized with barium carbonate, filtered, and concentrated to 2 ml in a rotary evaporator at 40°C. A 1-ml sample was then made up to 2 ml with $^{2}H_2O$ and centrifuged at $3575 \times g$ for 5 min; 1 ml of the resulting supernatant was analysed by NMR in a Bruker AMX-300 apparatus at 75 MHz. All shifts were referred to external chromium(III) acetylacetonate in dimethylsulphoxide (3 mg/ml) at 40 ppm (Ibbett et al., 1992). Spectra were interpreted, and the degree of substitution (DS) and molar substitution (MS) were estimated as described by Lee and Perlin (1982).

2.2.3. Mean molecular weight

The viscosity of 0.015; 0.030, 0.045, 0.060 and 0.075% aqueous solutions at 25°C was measured in a Cannon–Fenske capillary viscometer (six determinations per lot). Intrinsic viscosity was estimated by fitting Martin's equation (Bardet and Alain, 1975) to the results thus obtained, and mean molecular weight (M) was estimated from the Mark–Houwink equation:

$$[\eta] = KM^a$$

where $[\eta]$ is intrinsic viscosity and K and a are constants assigned values of 6.25×10^{-5} and 0.84 respectively (Wirick and Waldman, 1970).

2.2.4. Particle size analysis

Martin diameters were determined on the basis of measurement of 625 particles of each lot under an Olympus BH-2 light microscope. The geometric mean and geometric standard deviation were determined after logarithmic transformation of the data.

2.2.5. pH

The pH of 1% (w/w) dispersions was determined using a Crison pH-meter with a combined glass–calomel electrode.

2.2.6. Apparent viscosity

The apparent viscosity of 2% (w/w) dispersions was determined by rotational viscometry in a Brookfield DVII apparatus with the shear rate set at 10 s^{-1} (USP23–NF18, 1995).

2.2.7. Microbiological analysis

Solutions containing 0.5 g of HPC in 9.0 ml of sterile water or 9.0 ml of peptone–NaCl buffer of pH 7.0 (European Pharmacopoeia, 1995) were prepared in a laminar flow cabinet. After 15 min had elapsed for dissolution of the polymer, Petri dishes containing the media Liver Broth (LB), Yeast Extract Mycological Peptone Glucose Agar

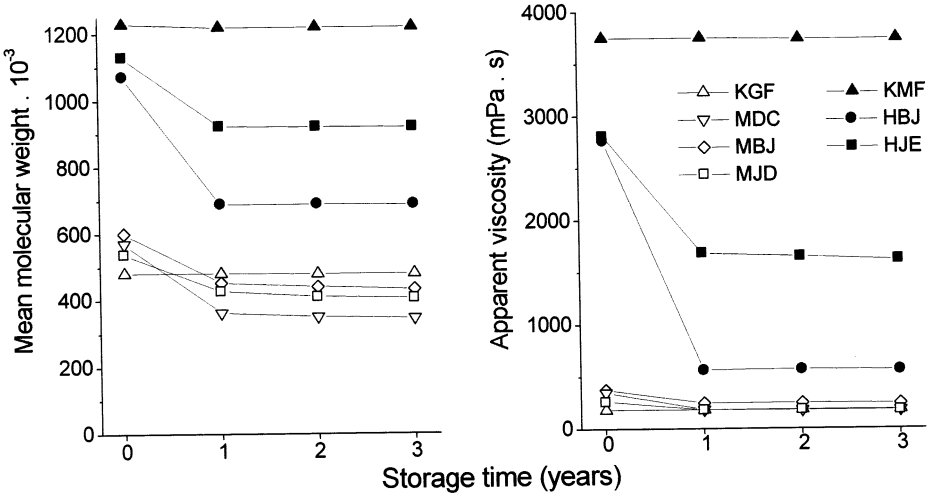

Fig. 1. Mean molecular weights of HPCs and apparent viscosities of 2% solutions of HPCs (see Table 1 for the key) plotted against the time for which the HPCs had been stored in closed containers at ambient relative humidity.

(YEPD), Lactobacilly MRS Agar (MRS), Trypticase Glucose Yeast Agar USP (PCA), Sabouraud Dextrose Agar (SDA) and Trypticase Soy Agar (TSA) (Dawson et al., 1990) were seeded with 1 ml of the solutions and incubated for 15 days. The colonies were quantified according to the plate method (USP23–NF18, 1995).

2.3. Effects of aging on polymer structure

Samples of each HPC lot were stored at room temperature in the dark in the containers in which they were supplied under (1) the relative humidity conditions specified by USP23–NF18 (1995), i.e. ambient relative humidity, or (2) a relative humidity of 0% achieved by storing the HPC containers in hermetically sealed boxes containing silica gel. Samples for analysis were taken with due care at the beginning of storage and after 1, 2 and 3 years; their moisture contents, hydroxypropoxyl group contents, particle size and molecular weights, and the pH and apparent viscosities of their aqueous solutions, were determined as described in Sections 2.2.1, 2.2.2, 2.2.3, 2.2.4, 2.2.5 and 2.2.6. Samples taken at the beginning of the study and after 3 years were also tested for contamination by microorganisms as described in Section 2.2.7.

2.4. Effects of HPC degradation on drug release by HPC-based theophylline tablets

At the beginning of the study and after 1 year's storage under both sets of storage conditions, samples of Klucel® MF and of both lots of Nisso® H were taken (nine samples in all) and were dried for 24 h at 70°C before being mixed with an equal weight of theophylline in a Turbula T2C9 mixer (15 min at 30 rpm). Direct compression tablets weighing 100 mg were obtained from the mixtures using 9-mm flat punches and a compression force of 2600 N in a Korch Eko eccentric tablet press equipped with a pressure-recording system. The release of theophylline from the tablets so prepared was characterized in a Turu–Grau apparatus complying with USP23–NF18 (1995) specifications for type II dissolution testers, using 900 ml of distilled water at 37°C as medium and a stirring rate of 50 rpm; the concentration of theophylline in samples withdrawn periodically from the test medium was determined spectrophotometrically at 271 nm, and the dissolution profiles so constructed were characterized in terms of the release rate constant of the Higuchi (1963) equation, K_H.

Table 3
Moisture contents and pH of HPCs stored for 1, 2 or 3 years in closed containers at room temperature and ambient relative humidity

Polymer[a]	Moisture content (%)			pH[b]		
	1 year	2 years	3 years	1 year	2 years	3 years
Klucel® GF	3.27 (0.01)	3.27 (0.01)	3.27 (0.01)	6.9 (0.1)	7.0 (0.1)	6.9 (0.1)
Klucel® MF	4.51 (0.02)	4.51 (0.02)	4.51 (0.02)	7.3 (0.1)	7.3 (0.1)	7.3 (0.1)
Nisso® M-BJ	2.88 (0.14)	2.88 (0.14)	2.88 (0.14)	5.3 (0.1)	5.2 (0.1)	5.2 (0.1)
Nisso® M-DC	2.85 (0.09)	2.85 (0.09)	2.85 (0.09)	5.6 (0.1)	5.5 (0.1)	5.6 (0.1)
Nisso® M-JD	3.16 (0.12)	3.16 (0.12)	3.16 (0.12)	5.7 (0.1)	5.5 (0.1)	5.5 (0.1)
Nisso® H-BJ	4.64 (0.01)	4.64 (0.01)	4.64 (0.01)	4.0 (0.1)	4.0 (0.1)	4.0 (0.1)
Nisso® H-JE	4.18 (0.06)	4.18 (0.06)	4.18 (0.06)	4.7 (0.1)	4.7 (0.1)	4.6 (0.1)

[a] See Table 1 for key.
[b] Of 1% aqueous solutions.

3. Results and discussion

Table 1 lists the characteristics of the various HPC varieties as determined at the beginning of the study, immediately after the containers in which they were supplied were first opened. All had similar degrees of substitution, although the higher total hydroxypropoxyl contents of the Klucel® varieties showed them to have more ramified side-chains than the Nisso® varieties. The latter also had smaller particle size, and their aqueous solutions somewhat lower pH, than the Klucel® varieties. No contamination by microorganisms (< 18 colonies/g) was detected.

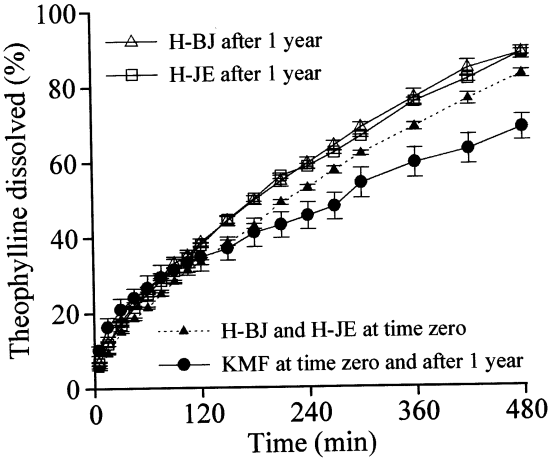

Fig. 2. Dissolution profiles of theophylline tablets formulated with HPCs upon receipt of the latter or after the HPC had been stored for 1 year at room temperature and ambient relative humidity. See Table 1 for key.

At no time during the following 3 years did any of the HPC varieties exhibit significant changes in particle size or degree of substitution under either of the humidities at which they were stored. All the samples stored at zero relative humidity underwent significant loss of moisture during the first year of storage, but little further change in moisture content occurred during the following 2 years, and at no time was their molecular weight or the pH or apparent viscosity of their aqueous solutions affected (Table 2).

None of the samples stored under ambient humidity conditions underwent any significant change in moisture content during storage, and for the Klucel® varieties molecular weight and the pH and

Table 4
Dissolution rate constants (K_H) obtained by fitting the Higuchi (1963) equation to the dissolution profiles of theophylline tablets formulated with HPCs upon reception of the latter (A) or after 1 year's storage in closed containers at room temperature and ambient relative humidity (B)[a]

Formulation	K_H	
	A	B
Klucel® MF	3.11 (0.03)	3.15 (0.05)
Nisso® H-BJ	3.45 (0.03)	4.21 (0.08)
Nisso® H-JE	3.49 (0.03)	4.17 (0.09)

[a] For all fits, $r^2 > 0.99$ and $p < 0.01$; the S.E.s of the fits are shown in parentheses.

apparent viscosity of aqueous solutions also remained unchanged (Table 3 and Fig. 1). However, the molecular weights of the Nisso® varieties fell by 20–30% during the first year of storage under these conditions, indicating cleavage of the polymer; as a result, the apparent viscosities of their aqueous solutions fell by 40–80%; and the acidities of their aqueous solutions increased by 0.5–2.4 pH units. No further changes occurred during the following 2 years.

The microbiological tests performed at the end of the study showed the cause of the degradation of the Nisso® varieties stored under ambient conditions to have been severe contamination by fungi (540–900 colonies/g) that were identified under the microscope in YEPD medium as being zygomycetes of the genus *Rhizomucor*. These fungi are widely distributed in the environment, especially in soil, grow rapidly at temperatures below 37°C (Jones et al., 1981; Larone, 1995), and attack cellulose-based substrates by means of hydrolytic enzymes which they release into the environment or which remain associated with their external cell wall. The proven up-regulation of enzyme synthesis by cellulose, which cannot cross the fungal cell wall, is thought to be mediated by the products of its hydrolysis by small amounts of spontaneously released enzyme (Singh and Hayashi, 1995). El-Naghy et al. (1991) reported that contamination of sodium carboxymethylcellulose by *Rhizomucor pusillus* reduced the apparent viscosity of 10% aqueous solutions by much the same amount as was observed in this work.

The interaction between cellulose-degrading enzymes and their substrate is thought to involve the formation of hydrogen bonds with the cellulose hydroxyl groups (Kasulke et al., 1987; Singh and Hayashi, 1995). This suggests that one of the main causes of the Nisso® varieties being more susceptible to attack by *Rhizomucor* species than the Klucel® varieties may have been the greater specific surface area associated with their smaller particle size (Shambe and Ejembi, 1987). Additional causes may have been the rather lower initial pH of the Nisso® varieties (the hydrolytic enzymes produced by *Rhizomucor* species exhibit peak activity at moderately acid pH; Kasulke et al., 1987) and the lower degree of side-chain ramification reflected by their lower hydroxypropoxyl contents, which implies easier access to their glucoside linkages (Parfondry and Perlin, 1977; Ma et al., 1989). The non-occurrence of any further degradation during the second and third years of storage may be attributed to the pH of the degraded varieties having fallen to values at which the cellulase-degrading enzymes of *Rhizomucor* species are no longer active (Kasulke et al., 1987).

In view of the finding of Banker et al. (1982) that the usefulness of aqueous HPC solutions as culture media increases with the molecular weight of the HPC, the fact that Nisso® H was more susceptible to fungal attack than Nisso® M (Table 1 and Fig. 1) may be attributed to its greater molecular weight. The absence of any degradation of any of the samples stored at zero relative humidity is attributable to the inability of any contaminating spores to germinate in the absence of moisture, which in turn probably explains why the microbiological analyses only detected contamination of the degraded samples.

Fig. 2 shows the dissolution profiles of theophylline tablets formulated with samples of freshly received Nisso® H and Klucel® MF and with samples stored for 1 year at ambient relative humidity (the profiles of tablets formulated with HPC samples stored for 1 year at zero relative humidity were identical to those corresponding to the freshly received products). For Klucel® MF, storage of the HPC at ambient relative humidity had no effect on drug release, but for Nisso® H release was more rapid from tablets formulated with the 1-year-old (degraded) HPC than from those formulated with the freshly received product. The degradation of Nisso® H was in fact associated with an increase in the dissolution constant K_H that was both statistically significant (Kruskal–Wallis $KW = 3.857$, 1 d.f., $p < 0.05$) and quantitatively significant (19% for lot JE-161, 22% for lot BJ-141; see Table 4).

4. Conclusions

The above results show that care must be taken to prevent the contamination and degradation of HPCs during handling and storage, and suggest

the desirability of stricter official recommendations and/or requirements concerning storage, pH, moisture content and microbiological testing.

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