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RESEARCH PAPER

The Stability of Theophylline Tablets with a Hydroxypropylcellulose Matrix

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ABSTRACT

The behavior of 40:60 anhydrous theophylline/hydroxypropylcellulose (HPC) direct compression tablets obtained using a variety of hydroxypropylcelluloses with low or medium-high degrees of substitution (L-HPCs and HPCs, respectively) was determined immediately following their preparation and after storage for 6 months at 20°C and a relative humidity (RH) of either 70.4% or 93.9%. The lower relative humidity did not bring about hydration of the active principle in any formulation, but the higher relative humidity totally hydrated the drug in all except one L-HPC formulation, in which hydration remained incomplete. Both relative humidities caused significant tablet swelling, with L-HPC formulations being more affected than HPC formulations. Drug release was slowed by hydration of the active principle, but accelerated with tablet swelling. The lower relative humidity caused significant alteration of drug release characteristics in only two L-HPC formulations, release from which was accelerated, while the higher relative humidities only failed to cause such alterations in two HPC formulations, with release from all except one of the others slowed (in the exceptional formulation, which exhibited incompletely hydrated theophylline and the greatest swelling of all, release was accelerated).
***Key Words*:** *Anhydrous theophylline; Hydrophilic matrices; Hydroxypropylcellulose; Stability; Theophylline monohydrate.*

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INTRODUCTION

The drug theophylline is available in one monohydrated and two anhydrous crystalline forms; one of the two anhydrous forms (I) is obtained by cooling a solution from above the melting point of the crystals; the other (II) is obtained by vacuum dehydration of the monohydrate (1,2). These three crystalline forms differ considerably as regards their physical and chemical properties; in particular, the anhydrous theophyllines dissolve in water more rapidly than the monohydrate one (1,3). These differences can give rise to corresponding differences among the drug release profiles of dosage forms in which they are used (3–7); the ability of the monohydrate to form hydrogen bonds with hydrophilic matrix polymers via its hydration water is thought to be a contributory cause to its slower release from such matrices than the release of anhydrous theophylline (5). As a result of these differences, the properties of theophylline dosage forms can be affected by transformations between one form of the drug and another during the preparation of the dosage form (5) and/or its storage (8,9).

The transformation of anhydrous theophylline to the monohydrate form in humid atmospheres occurs through recrystallization following dissolution of the anhydrous form in sorbed water (10). Powder of form I undergoes transformation to the monohydrate form at relative humidities greater than 88%, and powder of form II undergoes transformation at relative humidities greater than 75% (2,10). In theophylline tablets formulated with the anhydrous forms, the rate of transformation to the monohydrate is influenced considerably by the nature of the excipients used, particularly the presence of small quantities of highly hygroscopic compounds (9,11).

In oral dosage forms for controlled release of theophylline (12), the major excipient is often a cellulose ether (9,13–15). The high capacity of cellulose ethers for water uptake and gelling (16) and for the formation of hydrogen bonds can crucially affect the hydration and recrystallization of the drug during storage (17).

In this work, we examined the changes in drug hydration and release profiles of direct compression anhydrous theophylline tablets formulated with a number of hydroxypropylcelluloses (HPCs), differing in degree of substitution and water-binding characteristics, during storage for 6 months under relative humidities above and below the anhydrous theophylline hydration thresholds.

MATERIALS AND METHODS

Materials

The following materials were used: anhydrous theophylline (Sigma, St. Louis, MO; batch 97F-0733); hydroxypropylcelluloses with low degrees of substitution (L-HPCs) (LH-20 [batch 405117], LH-21 [batch 506157], and LH-31 [batch 502032]; Shin-Etsu Chemical Co., Tokyo, Japan); hydroxypropylcelluloses with medium-high degrees of substitution (HPCs) (Nisso® M [batch DC] and Nisso H [batch BJ]; Nippon Soda Co., Tokyo, Japan); and Klucel® GF (batch FP10-10293) and Klucel MF (batch 7857) (Aqualon, Wilmington, DE).

Characterization of the Polymers

Degree of Substitution and Molar Substitution

The substitution patterns of the various hydroxypropylcelluloses were evaluated by ^{13}C nuclear magnetic resonance (NMR) spectroscopy of their hydrolysates as follows. First, 1.0 g of polymer was added to 30 ml of 6 M sulfuric acid, and the mixture was stirred for 1.5 hr at 20°C. The mixture was then made up to 90 ml with deionized water, autoclaved at 2 atm for 1 hr, cooled and 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 D_2O and centrifuged at 3575*g* for 5 min, and 1 ml of the resulting supernatant was analyzed by NMR spectrometry in a Bruker AMX-300 apparatus (Karlsruhe, Germany) at 75 MHz. All shifts were referred to chromium(III) acetylacetonate (3 mg/ml in dimethylsulfoxide) at 40 ppm (18). Spectra were interpreted, and degree of substitution (DS) and molar substitution (MS) were estimated as per Lee and Perlin (19) and Alvarez-Lorenzo et al. (20).

Particle Size Analysis

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

Enthalpy of Hydration

The enthalpy of hydration of each polymer at 25°C was determined in duplicate in a Tronac 458 isoperibol microcalorimeter (Orem, Utah) using 50 ml of distilled

water and 0.05–0.10 g samples dried for 1 hr at 70°C. The reactivity of each polymer was defined as the measured enthalpy divided by the time taken for complete dissolution (21).

Water-Binding Capacity

Exactly weighed quantities of distilled water were added to exactly weighed quantities of dry hydroxypropylcellulose in 6 mm aluminum crucibles, which were then sealed. After equilibration for 48 hr at 20°C, the quantity of unbound water was determined by differential scanning calorimetry (DSC) (22) in a Shimadzu DSC-50 apparatus (Kyoto, Japan); the samples were cooled to −30°C at a rate of 5°C/min to freeze all free water and were then heated to 30°C at 5°C/min (23). Water-binding capacity was defined as the greatest water content such that all water was bound, as estimated by extrapolation to zero enthalpy of melting (24).

Characterization of Theophylline

The infrared (IR) spectrum of theophylline in KBr disks was recorded in a Mattson Cygnus 100 spectrophotometer (Karlsruhe, Germany), and its X-ray diffraction pattern was determined in a Philips PW 1710 diffractometer (Eindhoven, Holland) using CuK_α radiation and scanning over the range $5° < 2\theta < 40°$ at a rate of 1.5°/min. The enthalpy of hydration was determined as described above.

Preparation, Characterization, and Stability of Tablets

After drying for 24 hr at 70°C, anhydrous theophylline and HPC in a 40:60 ratio were mixed for 15 min at 30 rpm in a Türbula T2C apparatus (Basel, Switzerland), and tablets with a nominal weight of 125 mg were then pressed with 9-mm flat punches at a compression force of 2600 N in a Korch Eko tableting machine equipped with a pressure-recording system. For each formulation, 10 tablets were individually weighed, and their diameters and thicknesses were measured with a digital micrometer (Mitutoyo, Tokyo, Japan). The IR spectra of powdered tablets and the X-ray diffraction patterns of whole tablets were recorded as described above.

Drug release profiles were obtained using a USP 23 type II apparatus (25) as modified by Pérez-Marcos et al. (26). Six tablets were stirred at 50 rpm, each in 900 ml of distilled water at 37°C. The concentration of the active principle in samples periodically taken was determined spectrophotometrically at 271 nm. The profiles of L-HPC formulations were characterized in terms of 1-hr dissolution efficiency (27) and those of the HPC formulations by the rate constants estimated in fitting Higuchi's equation (28).

To study stability, tablet samples were stored for 6 months at 20°C and a relative humidity of either 70.4% or 93.9% and were then characterized as to weight, size, drug release profile, and the hydration of the active principle (as determined by X-ray diffraction). In addition, a sample of anhydrous theophylline was stored for the same period under the same conditions and then was characterized as described in the section on characterization of theophylline. Before storage and after storage characteristics were compared using Student *t* tests, except for the Higuchi rate constants, for which the Wilcoxon rank sum test was used.

RESULTS AND DISCUSSION

Table 1 lists the characteristics of the hydroxypropylcelluloses used. The HPCs release significantly more energy than the L-HPCs on hydration, but the shorter reaction time of the latter makes their reactivities greater than those of the HPCs. The lower enthalpies of hydration of L-HPCs can be attributed to their smaller hydrophilic substituent content (29), and their shorter reaction times can be attributed to their smaller particle size (30). The L-HPCs varied little from each other as regards either enthalpy of hydration or reactivity, but among the HPCs, the Nisso products were more exothermic and reactive than the Klucel products. Since all four HPCs have very similar degrees of substitution, the enthalpy differences must be due to the greater ramification of the hydroxypropoxy groups in the Klucel products (31,32); their lower reactivities are attributable mainly to their larger particle size. The same pattern of differences emerged as regards water-binding capacity, reflecting the smaller hydroxypropyloxy content of the L-HPCs and the difference in enthalpy of hydration between the Klucel and Nisso products.

The IR spectrum of the theophylline used and its enthalpy of hydration ($17.53\ kJ \cdot mol^{-1}$) were identical, to within experimental error, to the reported IR spectrum (33) and enthalpy of hydration (34) of anhydrous theophylline. Its X-ray diffraction pattern (Fig. 1) showed peaks at 7°, 12°, and 25° 2θ, characteristic of anhydrous form II. These properties were unaltered by storage for 6

Table 1

Properties of the Hydroxypropylcelluloses Used

Polymer	Nominal Viscosity (mPA · s)	Degree of Substitution	Molar Substitution	Particle Size (μm)	Enthalpy of Hydration ($J \cdot g^{-1}$)	Reactivity ($J \cdot g^{-1} \cdot min^{-1}$)	Water-Binding Capacity (% Dry Polymer)
L-HPC LH-20	—	0.30	0.33	25.5 (2.4)	−69.97 (2.90)	69.97	36.78 (1.20)
L-HPC LH-21	—	0.25	0.25	22.0 (2.1)	−69.95 (2.71)	66.62	35.30 (1.70)
L-HPC LH-31	—	0.25	0.25	13.9 (1.9)	−71.35 (0.17)	67.95	42.47 (1.61)
HPC Nisso M-DC	150–400	2.2	3.56	132.3 (1.6)	−97.11 (1.34)	23.03	94.25 (1.96)
HPC Klucel GF	150–400	2.3	3.86	286.1 (1.9)	−83.84 (1.87)	15.72	79.60 (2.11)
HPC Nisso H-BJ	1000–4000	2.3	3.42	136.3 (1.6)	−97.69 (1.23)	26.17	98.69 (3.09)
HPC Klucel MF	4000–6500	2.4	3.89	245.2 (1.9)	−82.95 (0.54)	15.08	87.06 (3.38)

months storage at a relative humidity of 70.4%, but after 6 months at a relative humidity of 93.9%, total conversion to the monohydrate was shown by an increased enthalpy of hydration (28.54 $kJ \cdot mol^{-1}$; cf. the value of 28.6 $kJ \cdot mol^{-1}$ reported for theophylline monohydrate by Suihko et al. in Ref. 34) and by the appearance or strengthening of X-ray peaks at 9°, 11°, and 27° 2θ. This difference between the responses to the higher and lower relative humidities is in keeping with reports that form II is not hydrated at relative humidities below 75% (2,10).

The prestorage X-ray diffraction patterns of the tablets (Fig. 1) show that the theophylline was still in anhydrous form II after tableting. As reported by others (35), the active principle was released rapidly from tablets

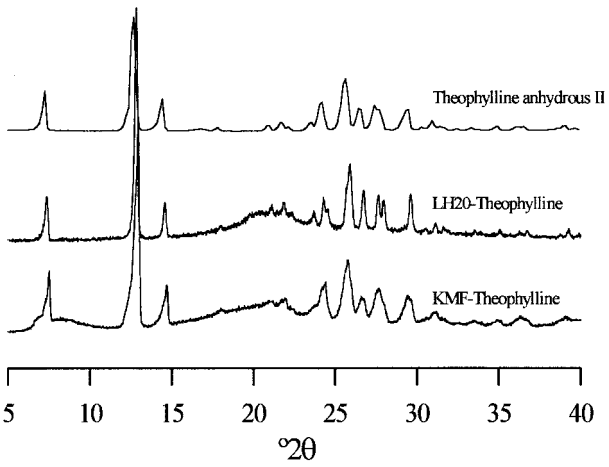

Figure 1. Prestorage X-ray diffraction patterns of anhydrous theophylline II and 40:60 theophylline:hydroxypropylcellulose tablets formulated with the LH-20 and Klucel MF.

prepared with L-HPCs; HPCs, as with other cellulose ethers with medium-high degrees of substitution (36–38), brought about much slower, steadier release (Fig. 2). Table 2 lists the dissolution efficiencies of the L-HPCs and the Higuchi rate constants of the HPCs.

Storage at a relative humidity of 70.4% increased the size and weight of the tablets of almost all the formulations studied ($\alpha < 0.05$), the L-HPC formulations especially (Table 3). The moisture contents of 3.5–5.1% that were acquired amount to about 6.0–8.5% of the dry HPC content, that is, about 16–18% of the water-binding capacity of the L-HPCs and about 7–9% of that of the HPCs (Table 1). However, only the formulations prepared with the L-HPCs LH-20 and LH-31 suffered significant alteration of their drug release profile, with release being accelerated in both cases (Fig. 2, Table 2). Since no peaks indicative of conversion to monohydrate appeared in the X-ray diffraction patterns of the tablets stored under these conditions (as was expected given the relative humidity threshold [75%] for hydration of anhydrous theophylline II; see Ref. 10), the altered release characteristics of the LH-20 and LH-31 tablets must be attributed to changes in their physical properties associated with moisture-induced swelling. These results appear to contrast with those of Adeyeye et al. (6), who found that, if relative humidity was greater than 52%, storage for 3 months at room temperature caused significant conversion of anhydrous theophylline to its monohydrate form (and a consequent marked alteration of drug release profiles) in tablets prepared by direct compression from anhydrous theophylline (42%), microcrystalline cellulose (48%), and the hydroxypropylmethylcellulose Methocel® E10 (10%).

When stored at a relative humidity of 93.9%, the tab-

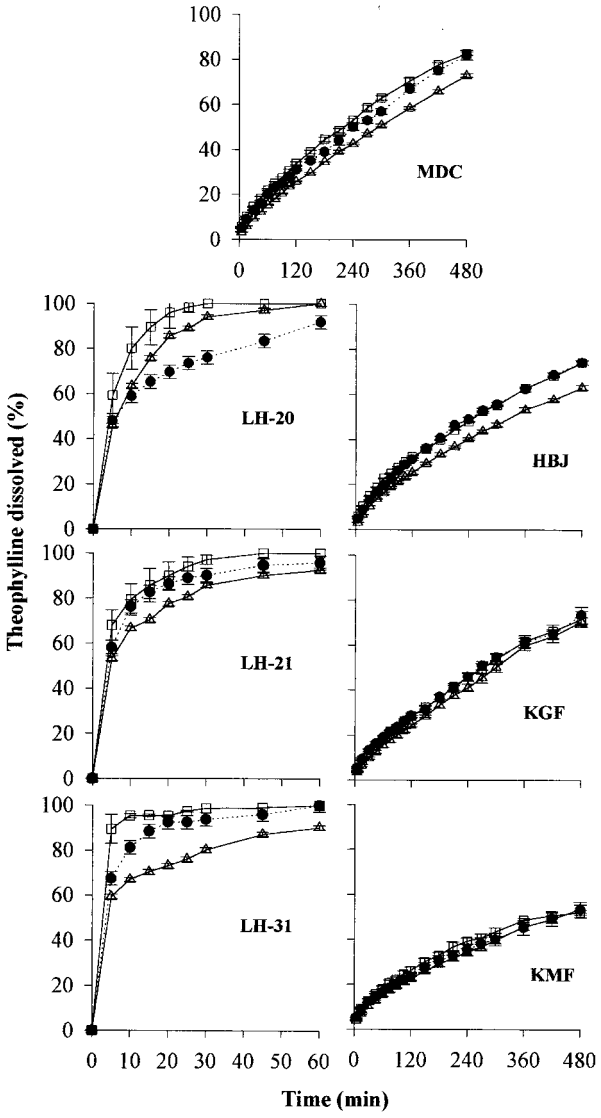

Figure 2. Drug release profiles of direct compression tablets formulated with anhydrous theophylline II and various hydroxypropylcelluloses in a 40:60 ratio before (●) and after storage for 6 months at 20°C and relative humidities of 70.4% (□) or 93.9% (△).

lets of all the formulations increased in size and weight ($\alpha < 0.05$), acquiring water contents of 17.6–24.2%; as at the lower relative humidity, L-HPC formulations swelled considerably more than HPC formulations (Table 1). X-ray diffraction patterns (Fig. 3) showed total conversion of anhydrous theophylline to the monohydrate form except in the case of the LH-20 formulation, for which anhydrous form II peaks were still visible; however, unlike Ando and colleagues (11), we found no theophylline monohydrate crystals visible to the eye. Since anhydrous theophylline can bind up to 8.9% of its weight as hydration water (39), the total hydration of the theophylline content of the tablets implies a hydration water content of 4.45 mg; this in turn implies that the water that was absorbed by the tablets but did not hydrate their theophylline content was equivalent to about 80–84% of the water-binding capacity of the polymer in the LH-21 and LH-31 formulations and to about 26–36% of the water-binding capacity of the polymer in the HPC formulations. The fact that, in the HPC formulations, theophylline was totally hydrated even though the HPC was far less than totally hydrated may be attributed largely to the slowness with which HPCs bind water (reflected in Table 1 by their low reactivities), which will favor water-theophylline binding. Among the L-HPC formulations, drug release accelerated in the presence of LH-20, but slowed in the presence of LH-21 or LH-31; among the HPC formulations, drug release was slowed in the presence of the Nisso products, but was hardly affected in the presence of the Klucel products (Fig. 2). However, in neither the L-HPC nor the HPC formulations was the release of theophylline so markedly altered as in Ando et al.'s (9,11) studies of release from tablets based on microcrystalline cellulose or in Adeyeye et al.'s (6) study of hydroxypropylmethylcellulose plus microcrystalline cellulose formulations.

The effects of storage at a relative humidity of 93.9% on drug release can be explained in terms of conflict between the tendency of tablet swelling to accelerate drug release and the tendency of theophylline hydration to slow drug release because of the slower dissolution of the monohydrate (1,3) and its ability to form additional hydrogen bonds with the hydroxypropylcellulose via its hydration water (5). In the LH-20 formulation, the acceleration of drug release due to tablet swelling would have been only partially offset by hydration of the active principle, which was incomplete, whereas in the other L-HPC formulations and the Nisso HPC formulations, slowing due to theophylline hydration appears to have overridden acceleration due to swelling. Only in the Klucel HPC formulations does it appear that slowing due to theophylline hydration was almost exactly compensated by the accelerational effects associated with swelling, probably because HPC gelling was visibly more intense in these formulations than in others, which would facilitate drug release (9). This greater propensity to gel is in turn attributable (24) to the greater particle size of the Klucel HPCs.

The finding that, in the case of the anhydrous theophylline formulations studied in this work, the presence of HPCs does not prevent hydration at high relative humidities as it does in the case of carbamazepine formulations

Table 2

Dissolution Efficiencies and Higuchi Rate Constants for Release of Theophylline from Direct Compression Tablets Formulated with Anhydrous Theophylline II and Various Hydroxypropylcelluloses in a 40:60 Ratio Before and After Storage for 6 months at 20°C and Relative Humidities of 70.4% or 93.9%

Formulation	Start	70.4%	93.9%
Dissolution efficiency			
L-HPC LH-20	71.5 (5.52)	89.42[a] (3.42)	82.39[a] (1.60)
L-HPC LH-21	83.8 (3.34)	88.42 (3.54)	77.45[a] (1.80)
L-HPC LH-31	85.4 (5.19)	93.09[a] (0.75)	75.24[a] (2.01)
Higuchi constant			
HPC Nisso M-DC	3.86 (0.05)	3.99 (0.08)	3.55[a] (0.12)
HPC Klucel GF	3.35 (0.06)	3.39 (0.06)	3.29 (0.15)
HPC Nisso H-BJ	3.25 (0.02)	3.26 (0.02)	3.00[a] (0.07)
HPC Klucel MF	2.31 (0.02)	2.32 (0.03)	2.35 (0.05)

Values shown are means of six replicate experiments; standard deviations are in parentheses. $\alpha < 0.05$ with respect to prestorage (starting) values.
[a] Significant.

(17) may be due to the markedly different affinity by the water of these two drugs (40). The only partial conversion of theophylline to the monohydrate in the LH-20 formulation could be attributed to the high water-binding capacity and reactivity of this polymer.

CONCLUSIONS

When direct compression anhydrous theophylline/hydroxypropylcellulose tablets are stored at high relative humidity, the hydroxypropylcellulose does not protect

Table 3

Weights, Diameters, and Thicknesses of Direct Compression Tablets Formulated with Anhydrous Theophylline II and Various Hydroxypropylcelluloses in a 40:60 Ratio Before and After Storage for 6 Months at 20°C and Relative Humidities of 70.4% or 93.9%

	Weight (g)			Diameter (mm)			Thickness (mm)		
Formulation	Start	70.4%	93.9%	Start	70.4%	93.9%	Start	70.4%	93.9%
L-HPC-LH-20	0.1256 (0.0007)	0.1300[a] (0.0005)	0.1505[a] (0.002)	9.089 (0.029)	9.168 (0.016)	9.827[a] (0.008)	2.146 (0.026)	2.263 (0.018)	2.780[a] (0.006)
L-HPC LH-21	0.1265 (0.0004)	0.1312[a] (0.0004)	0.1531[a] (0.0003)	9.109 (0.021)	9.216 (0.009)	9.604[a] (0.017)	2.078 (0.037)	2.184 (0.035)	2.517[a] (0.006)
L-HPC LH-31	0.1242 (0.0002)	0.1299[a] (0.0002)	0.1542[a] (0.0006)	9.108 (0.012)	9.217 (0.003)	9.569[a] (0.015)	2.027 (0.008)	2.116 (0.008)	2.337[a] (0.007)
HPC Nisso M-DC	0.1232 (0.0010)	0.1295[a] (0.0009)	0.1484[a] (0.0007)	9.033 (0.017)	9.035 (0.038)	9.277[a] (0.031)	1.950 (0.026)	1.987 (0.022)	2.053[a] (0.031)
HPC Klucel GF	0.1256 (0.0009)	0.1308[a] (0.0004)	0.1513[a] (0.0005)	9.053 (0.020)	9.030 (0.008)	9.293[a] (0.032)	2.041 (0.011)	2.193 (0.007)	2.277[a] (0.019)
HPC Nisso H-BJ	0.1258 (0.0009)	0.1311[a] (0.0008)	0.1508[a] (0.0008)	9.043 (0.015)	9.129 (0.011)	9.303[a] (0.017)	1.988 (0.023)	2.135 (0.027)	2.179[a] (0.031)
HPC Klucel MF	0.1236 (0.0015)	0.1280[a] (0.0010)	0.1454[a] (0.0010)	9.101 (0.008)	9.121 (0.023)	9.358[a] (0.029)	2.095 (0.028)	2.150 (0.032)	2.302[a] (0.026)

Values shown are means of 10 tablets, with standard deviations in parentheses. $\alpha < 0.05$ with respect to prestorage (starting) values.
[a] Significant.

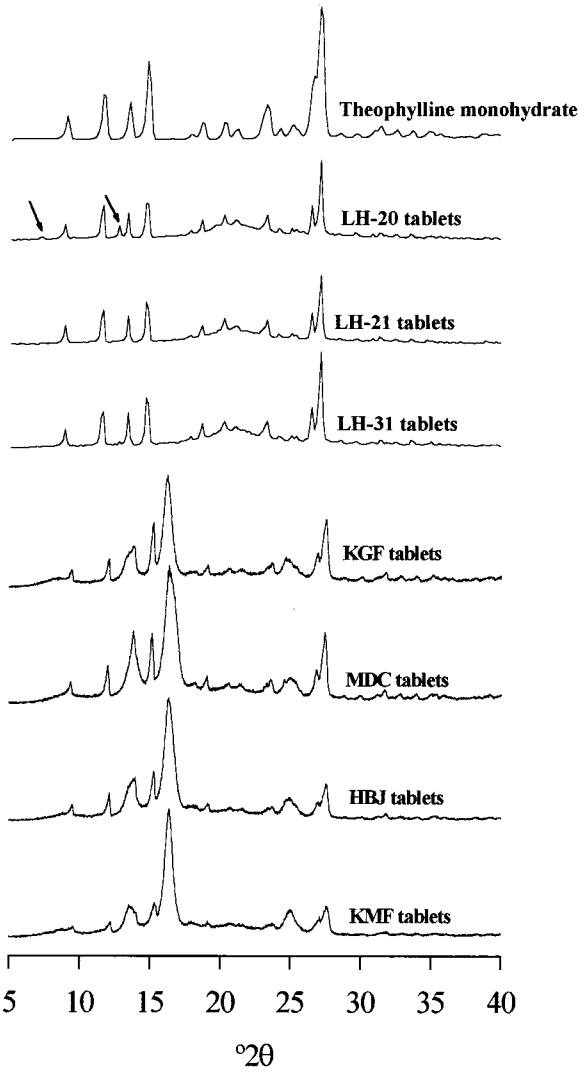

Figure 3. X-ray diffraction patterns of theophylline monohydrate and of direct compression tablets formulated with anhydrous theophylline II and various hydroxypropylcelluloses in a 40:60 ratio after storage for 6 months at 20°C and relative humidities of 70.4% (□) or 93.9% (△). Arrows mark peaks characteristic of anhydrous theophylline II.

the theophylline from hydration. The overall effect of hydration on drug release is the result of conflict between the tendency of tablet swelling to accelerate drug release and the tendency of theophylline hydration to slow drug release. The latter tendency generally predominates, but the two tendencies can cancel each other almost exactly in tablets formulated with HPCs with a particle size that favors gelling of the polymer.

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