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Effect of particle size and sorbed moisture on the compression behaviour of some hydroxypropyl methylcellulose (HPMC) polymers

S. Malamataris, T. Karidas and P. Goidas

Laboratory of Pharmaceutical Technology, Department of Pharmacy, University of Thessaloniki, Thessaloniki 54006 (Greece)

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Summary

A study has been made of the moisture sorption-desorption and the compressional characteristics of some powdered HPMC polymers with different particle size, methoxy/hydropropoxy substitution and molecular size. Moisture sorption-desorption isotherms, at 25°C, have been measured and analysed according to the Young and Nelson and the GAB equations, which distinguish moisture distribution in different physical forms. Compression data were obtained after storage at various environmental relative humidities by two methods: the tablet-in-die and the ejected-tablet method. The rearrangement or packing of HPMC particles and their deformation under pressure during tableting were determined by means of the Heckel equation. The externally adsorbed and normally condensed moisture were found to decrease with the particle size increase and the methoxy/hydropropoxy substitution ratio while the internally absorbed moisture increased mainly due to the particle size increase. No simple and general change due to molecular size was observed in the moisture distribution results. The particle packing and deformation of the HPMC powders were found to be related with the moisture distribution effects due to the particle size and the methoxy/hydropropoxy substitution ratio changes while no correlation was observed with the molecular size alteration.

Introduction

Hydroxypropyl methylcellulose (HPMC) polymers are widely used as excipients to control the release of drugs from tablet matrices. The interaction of these polymers with water, either in vapour or in liquid form, is a major factor in formulation, processing and sustaining the drug release. The ability to hydrate rapidly when in

contact with liquid water and thus to form a protective gel around the tablet matrix is an essential property for drug release. Therefore, various grades of HPMC are available of varying molecular size (viscosity), chemical substitution (hydropropoxy or methoxy groups) and particle size, while the sorption and desorption isotherms of vapour water (moisture) have been proposed as quality assurance specifications (USP XXI, 1985; Handbook of Pharmaceutical Excipients, 1986).

Moisture can be present in powders in different forms: as adsorbed monolayers or multilayers

Correspondence to: S. Malamataris, Dept of Pharmacy, University of Thessaloniki, Thessaloniki, Greece.

or as actual water layer on the surface; as physically absorbed water within the particles; or as strongly bound chemisorbed water (Chan and Pilpel, 1983; Van Campen et al., 1983; Zografí and Kontny, 1986). In cellulose derivatives moisture can exist in at least three thermodynamic states: (i) water directly and tightly bound to the cellulose structure, (ii) bulk water and (iii) water in an intermediate state or states (Zografí et al., 1984; Sadeghnejad et al., 1986). The amount and distribution of moisture in the different forms together with the chemical nature or substitution and the particle properties such as size and porosity may alter the compression behaviour of the HPMC polymers, i.e., packing and binding in tablet matrices.

The packing and binding of HPMC particles may account for differences in drug release from tablet matrices, especially for very soluble and very insoluble drugs. For the first case extremely fast hydration is required for the rapid development of the release barrier (gel) around the tablet matrix. For the second case a certain binding of the matrix components is necessary to relieve the internal stress that can occur during swelling. Therefore, in the present work it was considered appropriate to determine whether the moisture sorption and distribution is affected by the particle size and chemical nature of the different grades of hydroxypropyl methylcellulose polymers. Furthermore, it was decided to measure the possible alterations in the compaction characteristics, namely, the compressibility index and the Heckel parameters during compression of HPMC polymers after their storage at various environmental relative humidities (% RH). The compressibility index and the Heckel parameters are related to the rearrangement and packing of particles and to the ability of the materials to deform plastically under pressure during tabletting.

Experimental

Materials

Five grades of hydroxypropyl methylcellulose (HPMC) polymers (Methocel Products, Dow

TABLE 1

Hydroxypropyl methylcellulose (HPMC) polymers and their properties according to the supplier

HPMC product	USP type	Viscosity (2%) (cP)	Methoxy (% w/w)	Hydropropoxy (% w/w)	Methoxy/hydropropoxy ratio
K100M	2208	99100	22.0	10.8	2.0
K15M	2208	18699	22.2	8.3	2.7
K4M	2208	5100	21.7	8.2	2.6
E4M	2910	5202	28.9	8.2	3.5
F4M	2906	4606	29.4	6.6	4.5

Chemicals or Colorcon, Orpington, U.K.) with different molecular size (viscosity of 2% aqueous solution) and chemical substitution were employed. They were classified using a Multiplex zig-zag classifier (Alpine, Augsburg, Germany) to give three particle size fractions: less than 120 μm , 120–320 μm and more than 320 μm . A list of the HPMC polymers is given in Table 1 together with their properties.

Moisture sorption and desorption isotherms

Samples of the HPMC powders were dried over phosphorus pentoxide and then were exposed in thin layers to atmospheres of controlled humidity (11–93% RH) which were provided by saturated solutions in tightly closed desiccators at 25°C (Callahan et al., 1982). The moisture contents after 15 days equilibration were determined in triplicate to the nearest 0.1 mg. The results yielded the sorption isotherms. A similar procedure was followed for obtaining the desorption isotherms, the samples now being first equilibrated over saturated potassium nitrate (RH 93% at 25°C).

Determination of packing properties

Powders were stored in desiccators at controlled relative humidities (0–93%) under sorption conditions for not less than 15 days and their density (true, bulk and tap) was determined. The true density (ρ_g) was determined on an air comparison pycnometer (Beckman, Model 930). The bulk density (ρ_b) and the tap density (ρ_t) were measured in a 50 ml cylinder using a J. Engelmänn volumeter, Model JEL ST2 (Ludwigshafen,

Germany). The changes occurring in packing arrangement during the tapping procedure are expressed as the compressibility index:

$$\text{Compressibility index} = [(\rho_t - \rho_b) / \rho_t] \times 100$$

Samples of the equilibrated materials (known moisture content) corresponding to 500 mg of dry HPMC polymer were weighed in small glass vials, stored in the same desiccators for more than 3 days and then were compressed. Compression was carried out using a mechanical testing machine (T30K, J.J. Lloyd Instruments, Southampton, U.K.) fitted with a force recorder, a compression cage and a 13 mm diameter flat-faced punch and die set which was previously lubricated with a suspension of magnesium stearate in chloroform. The samples were quickly transferred into the die and compression pressure up to 100 MPa was applied. The platen movement was 5 mm min⁻¹ and the thickness of the compact inside the die was determined under load (tablet in die method) at certain levels to an accuracy of 0.01 mm. After correction of punch deformation, the packing fraction (p_f = bulk density/true density) of the compacts was calculated and profiles were constructed of log reciprocal porosity (=

$1/(1 - p_f)$) vs applied pressure according to the Heckel equation (Heckel, 1961). These profiles were evaluated in two ways by dividing the compression range into two parts, from 10 to 50 MPa and from 50 to 100 MPa. Firstly, on the basis of the difference between the tap density of the powders and the corresponding packing fraction at zero pressure for the two parts of the profiles and secondly, on the basis of the yield pressure, i.e., the reciprocal of the slope value (Paronen and Juslin, 1983).

Tablet preparation

Tablets were prepared after equilibration under sorption conditions of each HPMC fraction of known moisture content by applying compression pressure from 10 to 120 MPa. Compression was carried out using a hydraulic press and a 13 mm diameter punch and die set. The pressure was applied to the upper punch by lowering the hydraulic ram at a rate of 1.5 mm s⁻¹. The tablets were weighed to the nearest 0.1 mg and their thickness and diameter were measured after ejection of the die to the nearest 0.01 mm. The packing fraction of the tablets was calculated and profiles were constructed of log reciprocal poros-

TABLE 2

Moisture content (% w/w) of HPMC products after equilibration at different % RH under sorption conditions

HPMC product	Particle size (μm)	Moisture content (% w/w) at RH %								
		11	23	33	43	52	64	75	83	93
K100M	< 120	2.6	4.1	5.0	7.0	8.4	11.3	15.1	18.7	27.4
	120–320	2.6	3.8	4.9	7.3	8.6	11.1	15.2	18.2	24.0
	> 320	3.0	3.9	5.0	6.7	7.8	10.4	13.4	17.9	23.1
K15M	< 120	2.5	4.1	5.0	7.8	8.8	12.8	14.7	18.1	24.0
	120–320	2.6	3.8	4.9	7.3	8.7	11.4	14.7	17.3	20.4
	> 320	2.7	3.4	4.4	6.3	7.4	9.6	11.8	15.8	19.8
K4M	< 120	2.6	4.6	5.0	7.3	8.6	11.3	14.9	18.1	24.9
	120–320	2.8	4.1	5.2	7.7	8.8	11.6	14.5	18.0	21.0
	> 320	3.3	4.1	5.2	7.2	8.4	11.0	13.8	17.5	21.1
E4M	< 120	1.8	2.7	3.6	5.4	6.4	9.1	12.2	16.1	23.8
	120–320	1.8	2	3.4	5.4	6.4	8.9	12.4	15.6	19.8
	> 320	2.7	3.1	3.8	5.5	7.7	9.7	10.8	15.1	20.5
F4M	< 120	1.1	1.9	2.7	4.5	5.3	7.9	11.2	14.9	20.4
	120–320	1.9	2.8	3.5	5.3	6.3	9.0	12.0	15.0	19.5
	> 320	2.0	2.5	3.2	4.8	5.6	7.6	10.5	14.7	19.1

TABLE 3

Moisture content (% w/w) of HPMC products after equilibration at different % RH under desorption conditions

HPMC product	Particle size (μm)	Moisture content (% w/w) at RH %								
		11	23	33	43	52	64	75	83	93
K100M	< 120	3.0	4.6	5.9	8.4	9.5	12.3	15.3	18.8	27.4
	120–320	2.9	4.2	5.6	7.9	9.3	11.9	15.9	18.6	24.0
	> 320	3.1	4.9	6.0	8.7	9.8	12.7	15.4	19.0	23.1
K15M	< 120	3.2	5.1	6.2	8.7	9.6	13.6	15.2	18.2	24.0
	120–320	2.8	4.5	6.0	8.2	9.3	11.7	15.4	17.4	20.4
	> 320	2.9	3.9	5.3	8.0	9.2	11.4	13.7	16.7	19.8
K4M	< 120	2.7	4.8	5.8	8.4	9.5	12.3	15.1	18.3	24.9
	120–320	3.1	4.8	6.1	8.5	9.7	12.5	15.3	18.3	21.0
	> 320	3.4	4.9	6.3	8.9	9.8	13.0	14.4	18.3	21.1
E4M	< 120	2.2	3.3	4.4	6.7	7.8	10.6	13.4	16.5	23.8
	120–320	2.0	3.2	4.3	6.3	7.6	10.1	12.8	16.3	19.8
	> 320	2.7	3.6	4.8	7.2	8.4	11.4	12.7	16.5	20.5
F4M	< 120	1.5	2.6	3.7	5.8	6.7	9.2	12.1	15.1	20.4
	120–320	2.2	3.4	4.4	6.3	7.5	9.7	12.5	15.4	19.5
	> 320	2.1	3.0	4.2	6.5	7.1	10.3	12.2	15.3	19.1

ity ($= 1/(1 - p_f)$) vs applied pressure according to the Heckel equation (ejected-tablet method).

Results and Discussion

The experimental results of moisture content for the different size fractions of the HPMC

products after their equilibration under sorption and desorption conditions are given in Tables 2 and 3, respectively.

The product K100M with particle size smaller than 120 μm showed the greatest tendency to moisture uptake (27.4% w/w at 93% RH), and the corresponding size fraction of product F4M the least (20.4% w/w at 93% RH). The moisture

TABLE 4

Computed values of parameters in the Young and Nelson equations and fit of moisture sorption desorption data

HPMC product	Particle size (μm)	E	A	B	(r)	Average deviation (%)	
						Sorption	Desorption
K100M	< 120	0.472	0.059	0.023	0.999	4.1	2.5
	120–320	0.334	0.054	0.027	0.998	3.4	5.5
	> 320	0.417	0.043	0.059	0.997	5.3	3.7
K15M	< 120	0.268	0.054	0.033	0.998	4.3	3.4
	120–320	0.242	0.046	0.038	0.994	5.8	6.0
	> 320	0.355	0.038	0.051	0.996	4.3	3.9
K4M	< 120	0.312	0.057	0.021	0.999	4.7	1.4
	120–320	0.237	0.047	0.040	0.994	4.5	4.9
	> 320	0.255	0.044	0.045	0.995	2.9	3.6
E4M	< 120	0.736	0.045	0.045	0.999	4.1	2.4
	120–320	0.494	0.039	0.046	0.997	5.0	4.7
	> 320	0.424	0.040	0.043	0.995	5.4	5.0
F4M	< 120	0.795	0.036	0.058	0.999	4.7	3.5
	120–320	0.443	0.040	0.037	0.998	4.2	4.5
	> 320	0.778	0.029	0.076	0.996	5.2	4.8

sorption-desorption data (Tables 2 and 3) exhibited hysteresis and a trend of decrease in moisture content with the increase in the methoxy/hydropropoxy substitution ratio ($K4M < E4M < F4M$, Table 1) but no simple and general change due to particle size and molecular size alterations was observed throughout the range of RH.

The sorption-desorption isotherms were analysed for three locations of moisture: monolayer adsorbed moisture ($A \cdot \theta$), externally adsorbed and condensed moisture ($A \cdot (\theta + \beta)$), and internally absorbed moisture ($B \cdot \psi$). The analysis was carried out by using a combination of iteration and multiple regression technique as described in detail by Young and Nelson (1967). The computed values of the parameters E , A and B in the Young and Nelson equations are given in Table 4 together with the highest correlation coefficient (r) of the iteration and multiple regression and the average deviation of the theoretical from the experimental values. In Table 5 are given the calculated values of $A \cdot \theta$, $A \cdot (\theta + \beta)$ and $B \cdot \psi$, for the mean environmental (52%) and the maximum experimental relative humidity (93%).

The moisture sorption data were also analysed according to the GAB equation by applying polynomial regression analysis. The GAB equation

TABLE 5

Moisture distribution (% w/w dry basis) for the mean environmental (52%) and the maximum experimental (93%) relative humidity

HPMC type	Particle size (μm)	52% RH			93% RH		
		$A \cdot \theta$	$A \cdot (\theta + \beta)$	$B \cdot \psi$	$A \cdot \theta$	$A \cdot (\theta + \beta)$	$B \cdot \psi$
K100M	< 120	4.2	7.5		0.8	5.7	2.0
	120–320	3.6	6.8		1.3	5.3	2.5
	> 320	3.1	5.6		2.2	4.2	5.3
K15M	< 120	4.3	7.7		1.4	5.3	3.0
	120–320	3.8	6.7		1.6	4.5	3.5
	> 320	2.9	5.1		2.0	3.7	4.7
K4M	< 120	4.5	8.0		0.9	5.6	1.9
	120–320	3.9	6.9		1.7	4.6	3.6
	> 320	3.6	6.4		1.9	4.3	4.1
E4M	< 120	2.7	4.9		1.4	4.3	4.0
	120–320	2.4	4.4		1.6	3.8	4.1
	> 320	1.9	3.4		2.4	3.8	3.9
F4M	< 120	2.9	5.2		1.4	3.9	3.3
	120–320	2.1	3.8		1.8	3.4	5.1
	> 320	1.7	3.0		2.3	2.7	6.7

takes into account three states of sorbed water: tightly bound or monomolecular water (W_m), less tightly bound and bulk water. The calculated values of W_m and the parameters C_G and K which are related to the heat of sorption are

TABLE 6

Computed values of parameters in the GAB equation and fit of moisture sorption data

HPMC type	Particle size (μm)	$W_m (\times 100)$	C_G	K	(r)	Average deviation (%)
K100M	< 120	5.3	6.48	0.883	0.973	3.8
	120–320	5.7	5.65	0.848	0.920	5.4
	> 320	4.8	9.22	0.876	0.955	4.3
K15M	< 120	6.8	4.53	0.802	0.877	5.4
	120–320	6.5	5.04	0.785	0.827	6.4
	> 320	4.6	8.12	0.852	0.902	5.9
K4M	< 120	5.7	6.34	0.848	0.942	4.0
	120–320	6.5	5.61	0.788	0.862	5.2
	> 320	5.4	9.10	0.834	0.913	5.4
E4M	< 120	4.1	5.14	0.915	0.949	6.9
	120–320	4.3	4.46	0.883	0.904	7.2
	> 320	4.2	8.07	0.877	0.836	6.5
F4M	< 120	4.2	2.42	0.895	0.964	5.8
	120–320	4.2	5.26	0.882	0.905	7.1
	> 320	3.3	7.44	0.922	0.925	8.8

listed in Table 6 together with the correlation coefficients (r) of the polynomial regression analysis and the average percent deviation of the theoretical from the experimental values. Full details of the fitting procedure have been described elsewhere (Malamataris et al., 1991).

It can be seen from Tables 4–6 that the curve fitting procedure was valid and the values of the monomolecular water parameter, W_m , from the GAB equation and the amount of monolayer water, $A \cdot \theta$ at 93% RH, obtained from the Young and Nelson equations tend to be comparable. Furthermore, the moisture distribution results in Tables 5 and 6 indicate that for all the HPMC products under investigation the values of $A \cdot \theta$, $A \cdot (\theta + \beta)$ and W_m decrease with the particle size increase and the methoxy/hydropropoxy substitution ratio while the values of $B \cdot \psi$ increase. No simple and general change due to molecular size can be observed in the moisture distribution results.

In order to ascertain how each one of the variables under investigation (particle size, methoxy/hydropropoxy substitution ratio and molecular size) affects the present moisture sorption and distribution results, a standard method of multifactor analysis of variation has been used. Each of the variables was employed at three levels (low, medium and high). The three size levels were: less than 120 μm , 120–320 μm and more than 320 μm . The ratios of methoxy/hydropropoxy substitution were 2.6 (K type), 3.5 (E type) and 4.5 (F type) and for the three levels of molecular size only HPMC products of K type

were used. The three K type products had molecular sizes corresponding to the viscosity of a 2% aqueous solution: 99 100 (K100M), 18 699 (K15M) and 5 100 cP (K4M) and mean substitution ratios: 2.0, 2.7 and 2.6, respectively (Table 1). The values of the F ratio, which provide a quantitative measure of the effect of each particular variable or of the variables in combination on the measured properties, are given in Table 7 together with the values of % probability.

The results in Table 7 show that the particle size variable has a significant effect (95–99% probability level) on all the moisture distribution parameters. The methoxy/hydropropoxy substitution ratio has a significant effect on the external moisture ($A \cdot \theta$, $A \cdot (\theta + \beta)$ and the tightly bound monomolecular water W_m) for both the RH levels (52 and 93%), however, it has very little influence on the internally absorbed moisture ($B \cdot \psi$) for RH 93% and negligible for RH 52%. These results can be attributed to various factors which have been proposed as possible explanations of the mechanisms of moisture sorption hysteresis. These are the differences in advancing and decreasing contact angles between adsorbent and adsorbate, the role of surface pore shape and volume, and the phenomenon of multilayer adsorption followed by capillary condensation in cylindrical pores (Gregg, 1961).

The molecular size variable does not show any significant effect on the moisture distribution results except for the externally adsorbed and condensed moisture ($A \cdot (\theta + \beta)$) at 93% RH. The latter effect may be irrelevant to the molecu-

TABLE 7

Multifactor analysis of variation in the computed parameters of moisture distribution due to the experimental variables (particle size, substitution ratio and molecular size)

Parameter (at % RH)	Particle size		Substitution ratio		Molecular size	
	F ratio	% Prob.	F ratio	% Prob.	F ratio	% Prob.
$A \cdot \theta$ (52)	4.35	94.7	13.53	99.7	0.43	33.3
$A \cdot \theta$ (93)	9.85	99.3	11.51	99.5	1.75	86.4
$A \cdot (\theta + \beta)$ (52)	4.46	95.0	13.33	99.7	0.44	34.2
$A \cdot (\theta + \beta)$ (93)	16.22	99.8	9.81	99.9	4.02	93.8
$B \cdot \psi$ (52)	7.34	98.5	0.83	52.8	0.59	42.3
$B \cdot \psi$ (93)	4.87	95.8	2.74	87.6	0.23	20.3
W_m (GAB)	6.19	97.4	15.49	99.2	1.79	77.2

TABLE 8

Compressibility index and tap density of HPMC powders for three representative environmental relative humidities

HPMC type	Particle size (μm)	Compressibility index at RH %			Tap density at RH %		
		33	52	75	33	52	75
K100M	120–320	29.7	28.9	31.1	0.37	0.35	0.34
K15M	120–320	30.2	28.9	29.8	0.37	0.34	0.33
K4M	< 120	38.6	33.4	33.0	0.40	0.37	0.35
	120–320	32.1	32.4	30.7	0.42	0.39	0.37
	> 320	20.1	19.7	18.3	0.46	0.42	0.41
E4M	< 120	39.9	38.8	37.8	0.45	0.44	0.42
	120–320	27.1	24.2	25.8	0.54	0.51	0.50
	> 320	19.4	21.4	22.3	0.61	0.58	0.57
F4M	< 120	42.0	38.0	39.2	0.46	0.43	0.42
	120–320	28.4	28.5	28.3	0.49	0.47	0.46
	> 320	21.5	23.7	23.8	0.57	0.55	0.53

lar size of the HPMC products since it may be related to the small variation in the ratio of methoxy/hydropropoxy substitution (2.0–2.7) between the three HPMC products of type K with different molecular size.

The packing properties of the HPMC products during the tapping procedure expressed as compressibility index are given in Table 8 for three representative environmental relative humidities together with the tap density results. The com-

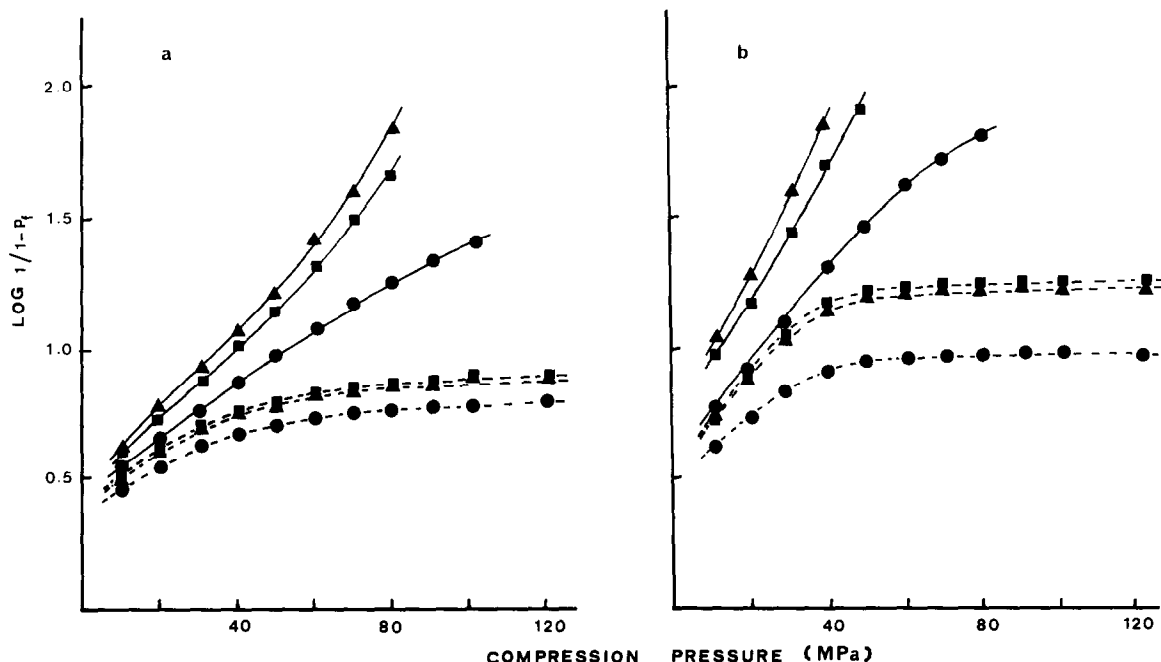


Fig. 1. Heckel plots for different types of powdered HPMC polymers (K100 M (Δ), K4M (\blacksquare) and F4M (\bullet)) of particle size 120–320 μm at two representative RH values (a, 33%; b, 75%) obtained from the tablet-in-die (continuous line) and the ejected-tablet (broken line) methods.

pressibility index results, in Table 8, show the expected decrease due to particle size increase, but no significant difference is observed due to alterations in the substitution ratio, the molecular size and the RH during storage, despite the pronounced changes in the tap density results. This may be attributed to the absence of moisture in the form of liquid bridges between the particles which are mainly responsible for cohesiveness and flowability changes of powders.

The slippage and rearrangement of the HPMC particles and their ability to deform plastically during the initial and later stages of compression were quantified on the basis of parameters in the Heckel plots. Figs 1 and 2 show typical Heckel plots obtained from the tablet-in-die and the ejected-tablet methods for different types of powdered HPMC polymers (Fig. 1) and for different particle size fractions (Fig. 2), all of them equilibrated under sorption conditions at two representative environmental relative humidities.

The plots obtained from the two compression methods differ as a result of the elastic recovery

of the tablets after their ejection from the die. Also, the plots in Figs 1 and 2 differ due to changes in the methoxy/hydropropoxy substitution, the particle size and the relative humidity of storage while no significant difference is observed due to the molecular size of the HPMC polymers. These changes in the compressional characteristics appear to be related to the moisture distribution alterations mentioned above and are attributed to various mechanisms of moisture sorption-desorption hysteresis. The observed independence of the moisture distribution and the compressional characteristics from the molecular size of the HPMC polymers is in agreement with the molecular models of moisture uptake for cellulose derivatives suggesting the existence of tightly bound water with a stoichiometry of one molecule per anhydroglucose unit (Zografis and Kontny, 1986) and the sorption of water in a stepwise process of hydrogen bonding (Khan and Pilpel, 1987).

The extent of particle packing during each of the two compression stages (< 50 and > 50 MPa)

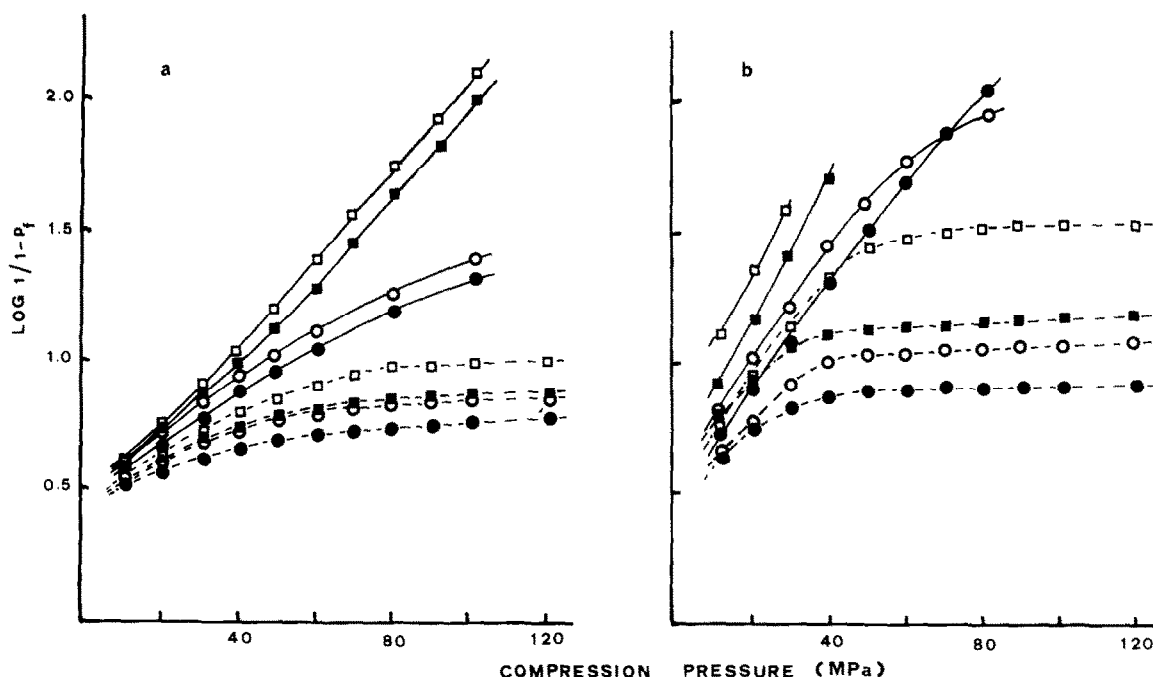


Fig. 2. Heckel plots for different size fractions of HPMC powders (K4M $< 120 \mu\text{m}$ (\square), K4M $> 320 \mu\text{m}$ (\blacksquare), F4M $< 120 \mu\text{m}$ (\circ) and F4M $> 320 \mu\text{m}$ (\bullet)) at two representative RH values (a, 33%; b, 75%) obtained from the tablet-in-die (continuous line) and the ejected-tablet (broken line) methods.

TABLE 9

Densification due to slippage and rearrangement of HPMC powders determined from the intercept of Heckel plots for two compression methods and load ranges at two representative environmental relative humidities

HPMC type	Particle size (μm)	Densification at compression range (MPa) and relative humidity (%)							
		Tablet-in-die method				Ejected-tablet method			
		< 50 MPa		> 50 MPa		< 50 MPa		> 50 MPa	
		(33)	(75)	(33)	(75)	(33)	(75)	(33)	(75)
K100M	120–320	0.31	0.54	–	–	0.29	0.45	0.47	0.59
K15M	120–320	0.31	0.45	–	–	0.30	0.46	0.46	0.61
K4M	< 120	0.20	0.44	0.06	–	0.23	0.36	0.37	0.55
	120–320	0.27	0.43	0.11	–	0.28	0.41	0.43	0.57
	> 320	0.28	0.41	0.13	–	0.28	0.50	0.42	0.57
E4M	< 120	0.22	0.28	0.31	0.45	0.17	0.30	0.37	0.48
	120–320	0.11	0.23	0.21	0.30	0.11	0.25	0.26	0.38
	> 320	0.04	0.19	0.16	–	0.06	0.21	0.20	0.30
F4M	< 120	0.21	0.33	0.33	0.47	0.20	0.34	0.36	0.47
	120–320	0.16	0.30	0.24	0.40	0.15	0.29	0.30	0.42
	> 320	0.09	0.22	0.19	0.07	0.09	0.25	0.22	0.34

was obtained from the difference between the packing fraction calculated from the intercept of the extrapolated Heckel plots (p_{fA}) and that corresponding to the tap density (p_{ftap}). p_{ftap} describes the die filling and the difference $p_{fA} - p_{ftap}$ is a parameter of densification due to slippage and rearrangement of particles. Results for two representative relative humidities are given in Table 9.

The results in Table 9 show that particle slippage and rearrangement increases, as expected, with the relative humidity and the compression range increase while it decreases with the particle size increase, except for the type K products and particularly for the tablet-in-die method. In general, the particle slippage and rearrangement increase can be attributed to the easier movement of particles under pressure and to the greater

TABLE 10

Yield pressure of HPMC powders equilibrated at two representative environmental relative humidities determined with two methods from the slope of Heckel plots for two compression ranges

HPMC type	Particle size (μm)	Yield pressure at compression range (MPa) and relative humidity (%)					
		Tablet-in-die method				Ejected-tablet method	
		< 50 (33)	< 50 (75)	> 50 (33)	> 50 (75)	< 50 (33)	< 50 (75)
K100M	120–320	74	52	46	–	135	97
K15M	120–320	73	33	47	–	151	83
K4M	< 120	68	39	55	–	118	60
	120–320	75	42	59	–	155	85
	> 320	80	37	62	–	171	167
E4M	< 120	84	40	105	61	123	87
	120–320	88	55	99	62	162	125
	> 320	87	58	125	41	182	174
F4M	< 120	89	49	134	79	139	118
	120–320	95	62	115	83	168	137
	> 320	96	63	139	48	202	196

plastic deformation at the earlier compression stages. The particle movement (flow) is facilitated by the lubricating action of moisture and the softening effect on particles. Both phenomena make it easier for the particles to slide past each other during the process of compression. The unexpected results for the type K products can be attributed to partial dissolution and/or crystallinity changes of these polymers resulting in almost transparent tablets and in Heckel plots of considerable curvature in the opposite direction to that of the other materials (Figs 1 and 2). As the type K HPMC polymers dissolve under load or change in crystallinity, the compacts' density approaches the true density of the powder and $\log(1/(1 - p_f))$ approaches infinity leading to rapid curvature in the plots.

The ability of the HPMC powders to deform plastically during the two compression stages was quantified as yield pressure derived from Heckel plots (reciprocal of slope, P_y) and the results for two representative relative humidities are given in Table 10. It is seen from Table 10 that the P_y values increase due to increase in the methoxy/hydropropoxy substitution ratio and decrease with moisture content and particle size. The P_y values, as expected, are greater for the ejected-tablet method than for the tablet-in-die method and for the

higher compression range (> 50 MPa), except in the case of K type products which show reverse curvature in the Heckel plots. P_y values became extremely high for the ejected-tablet method at compression pressure above 50 MPa probably due to involvement of the elastic recovery and are not included in Table 10.

The ability of the tableted HPMC powders to recover elastically after their ejection from the die was determined from the Heckel plots, at a fixed loading level (50 MPa), as the percentage increase in the tablet packing fraction compared with that in the die under load. The results for three representative relative humidities are given in Table 11 and show that elastic recovery, in general, is inversely related to the yield value, P_y , but is affected mainly by the particle size of the HPMC products under investigation. No correlation can be observed between elastic recovery and methoxy/hydropropoxy substitution ratio or molecular size of HPMC.

From the above, it can be concluded that the compressional characteristics of powdered HPMC polymers, namely, the particle packing and deformation, are related with the moisture distribution effects mainly due to the particle size changes and to some extent due to the methoxy/hydropropoxy substitution ratio changes while no dependence on the molecular size is evident.

TABLE 11

Elastic recovery of HPMC powders equilibrated at three representative environmental relative humidities determined as percentage increase in p_f after compression at 50 MPa

HPMC type	Particle size (μm)	Elastic recovery (%) at relative humidity (RH %)		
		33%	52%	75%
K100M	120–320	8.4	8.6	—
K15M	120–320	9.7	7.7	—
K4M	< 120	8.9	4.9	—
	120–320	9.3	7.6	—
	> 320	9.9	9.4	6.3
E4M	< 120	7.5	6.9	5.8
	120–320	9.4	8.2	7.0
	> 320	9.6	9.1	8.6
F4M	< 120	8.1	7.5	7.3
	120–320	9.4	8.1	7.7
	> 320	9.8	9.0	8.8

References

- Callahan, J.C., Cleary, G.W., Elephant, M., Kaplan, G., Kensler, T. and Nash, R.A., Equilibrium moisture content of pharmaceutical excipients. *Drug Dev. Ind. Pharm.*, 8 (1982) 355–369.
- Chan, S.Y. and Pilpel, N., Absorption of moisture by sodium cromoglycate and mixtures of sodium cromoglycate and lactose. *J. Pharm. Pharmacol.*, 35 (1983) 477–481.
- Fell, J.T. and Newton, J.M., Determination of tablet strength by the diametral compression test. *J. Pharm. Sci.*, 59 (1970) 688–691.
- Gregg, S.J., In *The Surface Chemistry of Solids*, 2nd Edn, Chapman and Hall, London, 1961, pp. 80–83.
- Handbook of Pharmaceutical Excipients*, American Pharmaceutical Association, Washington, DC and The Pharmaceutical Society of Great Britain, London, 1986, p. 138.
- Heckel, R.W., Density-pressure relationships in powder compaction. *Trans. Metall. Soc. AIME*, 221 (1961) 671–675.
- Khan, F. and Pilpel, N., An investigation of moisture sorption

- in microcrystalline cellulose using sorption isotherms and dielectric response. *Powder Technol.*, 50 (1987) 237–241.
- Malamataris, S., Goidas, P. and Dimitriou, A., Moisture sorption and tensile strength of some tableted direct compression excipients. *Int. J. Pharm.*, 68 (1991) 51–60.
- Paronen, P. and Juslin, M., Compressional characteristics of four starches. *J. Pharm. Pharmacol.*, 35 (1983) 627–635.
- Sadeghnejad, G.R., York, P. and Stanley-Wood, N.G., Water vapour interaction with pharmaceutical cellulose powders. *Drug Dev. Ind. Pharm.*, 12 (1986) 2171–2192.
- USP XXI, Mack, Eaton, 1985, pp. 516–517.
- Van Campen, L., Amidon, G.L. and Zografi, G., Moisture sorption kinetics for water-soluble substances. Theoretical considerations of heat transport control. *J. Pharm. Sci.*, 72 (1983) 1381–1388.
- Young, J.H. and Nelson, G.L., Theory of hysteresis between sorption and desorption isotherms in biological materials. *Trans. Am. Soc. Agric. Eng.*, 10 (1967) 260–263.
- Zografi, G., Kontny, M.J., Yang, A.Y.S. and Brenner, G.S., Surface area and water vapour sorption of microcrystalline cellulose. *Int. J. Pharm.*, 18 (1984) 99–116.
- Zografi, G. and Kontny, M.J., The interaction of water with cellulose-starch-derived pharmaceutical excipients. *Pharm. Res.*, 3 (1986) 187–194.