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THE EFFECT OF MOISTURE CONTENT OF MICROCRYSTALLINE CELLULOSE ON THE COMPRESSIONAL PROPERTIES OF SOME FORMULATIONS

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ABSTRACT

The effect of moisture content of microcrystalline cellulose (MCC) on the compression properties of systems containing this diluent, has been examined. The formulations used included a product containing 97% MCC and two MCC based direct compression systems containing 49.5% paracetamol and 68% potassium phenethicillin. The MCC used contained moisture levels ranging from 0.6 - 7.3%. The tablets were made on an instrumented machine in conditions of relative humidity not exceeding 40%. The following tablet

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MCC are well documented, little has been published on the effect of moisture on its compressional characteristics. Also since it is common industrial practice to dry excipient before use with moisture sensitive drugs, a study of the effect of MCC on its compressional, disintegration and dissolution properties should be useful.

MATERIALS

The following materials were used:

Potassium phenethicillin (Broxil* batch no. 4277, Beecham Pharmaceutical, Worthing, UK),Microcrystalline cellulose Avicel PH102, (Honeywell and Stein, Surrey, UK),Magnesium Stearate (Durham Chemicals, Durham, UK), Paracetamol (Batch 57244, Greasser, Salicylates Deeside, UK).

METHODS

The following three formulations were used:

		%w/w	
a)	MCC	97	(moisture content: 0.6, 1.0,
	Potassium phenethicillin	2	2.5, 4.8 & 7.3%).
	Magnesium stearate	1	
		%w/w	
b)	MCC	49.5	(moisture content: 0.6, 2.5
	Paracetamol	49.5	and 4.8%)
	Magnesium stearate	1.0	

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properties were studied: weight variation, crushing strength, porosity, disintegration time and dissolution rate. The results show that a decrease in the moisture content of MCC reduces its compressibility. These results are discussed in terms of the compaction mechanism of MCC.

INTRODUCTION

The role of moisture in direct compression systems in general has not been properly investigated but the available evidence suggests that moisture can both increase or decrease the tensile strength of compacts depending upon the system used.[1,2,3] For sodium chloride[1,2] an increase in moisture content reduced the compact strength at higher pressures. It was suggested that the effect was caused by the hydrodynamic resistence to consolidation which reduced the strength of interparticulate bonds. However, the evidence obtained from the compressing of sodium chloride must be used with caution for other systems, particularly those involving water insoluble materials. These systems may have considerably larger surface area then the crystalline sodium chloride.

Microcrystalline cellulose (MCC) is water insoluble but hydrophilic and has a strong affinity for water demonstrated by monolayer coverage at approximately 20% relative humidity[4]. The powder is relatively porous with an internal surface area of 130 - 270m^2/g. This surface area represents at least 95% of the surface that interacts with water[4]. Although the tableting properties of

		%w/w	
c)	MCC	30	(moisture content: 0.6, 2.5
	Potassium phenethicillin	68	and 4.8%)
	Magnesium stearate	2	

Formulation A was used to examine the effect of moisture within MCC on its tableting properties. 2% potassium phenethicillin was added as a drug tracer to monitor the effect of moisture on dissolution.

Formulation B and C contained different drugs at relatively high concentrations; Potassium phenethicillin was chosen as a representative of a moisture sensitive and water soluble drugs where as paracetamol represented an insoluble drug system.

Processing

The initial moisture content of the batch of microcrystalline cellulose used was 4.8%. It was dried to various moisture levels down to 1.0% at 75°C by using a laboratory fluid bed dryer (PRL Engineering Ltd., Motsyn, Flintshire, UK). To dry MCC below 1% a temperature of around 100°C was used. The starting material was also exposed to 75% RH at 25°C (saturated solution of sodium chloride) until it absorbed 7.3% moisture. All moisture contents were determined using the Karl Fischer method.

The ingredients for each formulation were mixed by tituration followed by blending in a planetary mixer (Hobart bowl) for 15 minutes. The tablets were made, in an environment of controlled relative humidity of around 35%, using an instrumented single punch tablet machine[5] fitted with a 7/16" inch flat punches.

Granule and tablet properties

The true densities of the compression mixes were determined using an air comparison pycnometer (Beckman Model 938). To determine the weight uniformity of the tablets ten compacts were individually weighed and the coefficient of variation (CV) was calculated. The thickness of at least ten tablets was individually measured and the mean tablet volume was obtained. Tablet porosity was calculated from the knowledge of the true density of the compression mix, tablet weight and volume (apparent tablet density). Crushing strengths were determined using a Schleuniger hardness tester. The mean of ten tablets was obtained. Disintegration times were determined using the B.P. method except that 2 tablets were used in each tube and the mean of three determinations was obtained. The dissolution rate of the phenethicillin tablets (Formulation A) were examined using a method described elsewhere[5]. The concentration of phenethicillin in the dissolution medium was determined using a u.v. spectrophotometer at 268nm.

Moisture absorption and loss from tablets

In order to see if the absorption or loss of moisture from MCC tablets affects the properties of the tablets after manufacture, tablets containing 7.3% moisture were dried in a laboratory oven at 80°C and those containing 1.5% moisture were allowed to absorb moisture at 75% RH, 25°C (obtained using a saturated solution of sodium chloride). The moisture content, tablet strength and disintegration times were monitored at various time intervals.

RESULTS AND DISCUSSION

The compressional properties of Formulation A containing 97% MCC are shown in Table 1 and the crushing strength pressure profiles in Figure 1. Although the processing and tableting was carried out at around 35% relative humidity, the blends containing MCC dried to less than 2% moisture absorbed over 1% moisture during processing. The moisture content of tablets after compaction are given in the parenthesis in Figure 1. The crushing strength pressure profiles of Formulation A clearly shows that its compressibility progressively decreases with a reduction in the moisture contents of MCC (Figure 1).

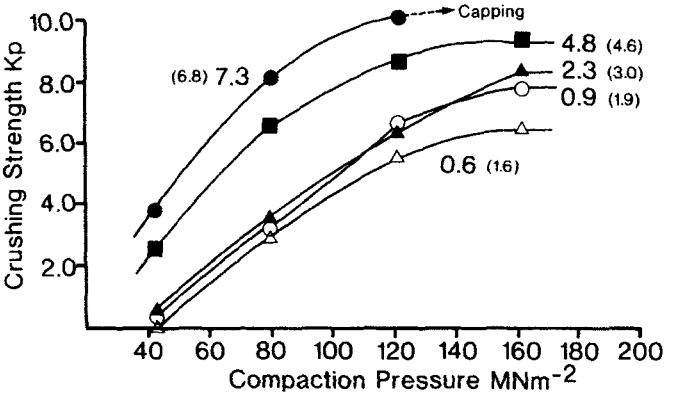

FIGURE 1 The compaction pressure/crushing strength profiles of tablets prepared from Formulation A containing MCC at various moisture levels (Figures outside parenthesis are the % moisture content of the compression mix and those inside the parenthesis refer to the % moisture contents of the tablets).

The strongest compacts were produced with MCC containing 7.3% moisture but they also capped when compressed at $163MNm^{-2}$. The capping is attributed to one or both of the following reasons: (i) compacts containing 7.3% already have a high relative density and further compaction might have exceeded the limiting density causing elastic rebound (ii) at higher pressures condensed moisture may be squeezed out on to the particle surface reducing inter particle bonding and increasing elastic recovery. This behaviour is similar to that reported by Rees and Hersey[2] who also found that sodium chloirde compacts containing higher moisture content had lower strength when compacted at higher pressures.

Table 1 also shows the effect of moisture content of MCC on the disintegration time of tablets prepared from formulation A. The disintegration times of tablets containing MCC up to 2.3% moisture are similar. However since an increase in moisture content above 2.3% significantly increases the tablet strength and reduces the porosity, the disintegration time increases particularly for the tablets made at higher pressure, due to the reduced penetration of water into the tablet structure. The dissolution rates were similarly affected. For example, the time for 90% dissolution of phenethicillin for tablets compressed at $163MNm^{-2}$ and containing MCC at 0.9, 2.3 and 4.8% were 38, 47 and 64 minutes respectively. The disintegration time results of tablets prepared from formulation B and C are also similar to those for formulation A (see Tables 2, 3 and Figure 1).

Table 2 and Figure 2 show the effect of moisture content of MCC on the tableting properties and crushing strength/pressure profiles

TABLE 1

Effect of Moisture within Microcrystalline Cellulose (MCC) on the Tableting Properties of a Formulation Containing MCC 97%, Potassium Phenethicillin 2% and Magnesium Stearate 1%

Moisture Content (%)	Compression Pressure (MNm^{-2})	Uniformity of Weight		Porosity %	D.T.* (min.)
		Mean g	C.V. %		
0.6	41	0.1835	1.703	45.58	0.11
	82	0.1913	1.512	31.45	0.34
	122	0.1897	1.033	22.76	1.24
	163	0.1899	1.063	17.89	2.12
0.9	41	0.1958	0.853	42.91	0.11
	82	0.1938	0.743	30.02	0.33
	122	0.1931	0.730	20.77	1.27
	163	0.1933	0.729	14.26	2.12
2.3	41	0.1884	0.753	40.64	0.23
	82	0.1884	0.552	26.87	0.30
	122	0.1884	0.833	17.96	1.56
	163	0.1881	0.404	12.68	2.23
4.8	41	0.1876	0.299	30.09	0.22
	82	0.1885	0.397	15.83	1.08
	122	0.1887	0.928	8.98	2.15
	163	0.1881	0.595	4.04	4.04
7.3	41	0.1886	1.039	24.74	0.63
	82	0.1876	0.677	10.62	2.10
	122	0.1867	0.734	6.51	8.74
	163	← Capping →			

*D.T. = Disintegration time

TABLE 2

The Effect of Microcrystalline Cellulose Containing Various Moisture Contents on the Properties of Paracetamol Tablets (Formulation B)

Moisture Content (%)	Compression Pressure (MNm^{-2})	Uniformity of Weight		Porosity %	D.T.* (min.)
		Mean g	C.V. %		
0.6	82	0.1992	0.677	21.67	0.35
	122	0.2009	0.271	15.25	1.23
	163	0.2029	0.278	10.98	8.80
	245	0.1979	0.451	7.52	28.56
2.5	82	0.1909	1.175	21.59	0.28
	122	0.1909	0.537	13.85	1.40
	163	0.9904	0.449	10.91	9.18
	245	0.1917	0.648	6.93	37.69
4.8	82	0.1945	0.804	17.83	0.31
	122	0.1938	0.260	12.90	1.49
	163	0.1946	0.377	8.99	14.32
	245	0.1950	1.244	5.38	52.79

*D.T. = Disintegration time

of paracetamol tablets containing 49.5% MCC. These results also show a progressive decrease in the compressibility of the paracetamol formulation reflected by an increase in porosity and a decrease in disintegration time with a decrease in the moisture content of the MCC. Similar results were obtained for potassium phenethicillin tablets containing 30% MCC (Table 3) except that the

TABLE 3

The Effect of Microcrystalline Cellulose Containing Various Moisture Contents on the Properties of Potassium Phenethicillin Tablets (Formulation C)

Moisture Content (%)	Compression Pressure (MNm^{-2})	Uniformity of Weight		Crushing Strength (Kp)	Porosity %	D.T.* (min.)
		Mean g	C.V. %			
0.6	82	0.1823	1.459	10.8	19.28	3.67
	163	0.1815	1.934	16.5	10.01	3.88
	327	0.1655	2.151	12.0	4.12	4.0
	490	0.1619	1.106	11.6	3.38	4.18
2.5	82	0.1846	0.602	11.1	16.34	3.74
	163	0.1814	0.794	16.7	8.09	4.30
	327	0.1773	1.252	12.3	3.97	4.33
	490	0.1650	2.430	12.9	1.69	4.62
4.8	82	0.1873	1.424	12.1	15.08	3.99
	163	0.1897	1.132	17.6	5.30	4.43
	327	0.1868	1.304	17.4	2.58	4.62
	490	0.1860	1.016	17.8	1.25	5.37

*D.T. = Disintegration time

crushing strength reaches a maximum value for tablets compacted at $163MNm^{-2}$ containing MCC at 0.6 and 2.5% moisture contents. This behaviour is attributed to incipient capping during strength testing caused by decompression.

The studies carried out by Hollenback *etal*[4] suggest that at its equilibrium moisture content of 5% most of the water will be within the porous structure of MCC and a large proportion of this bound

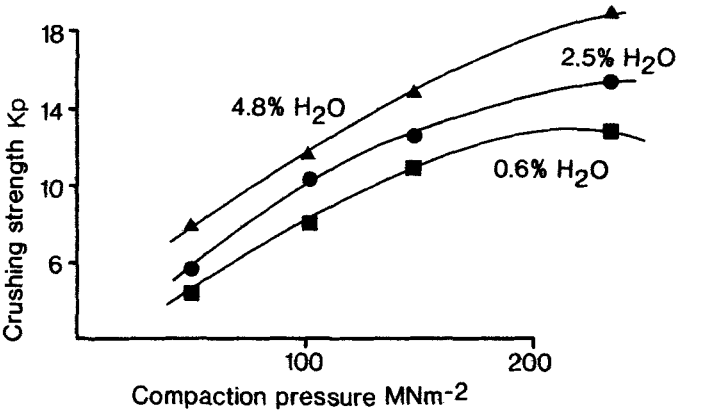

FIGURE 2 The compaction pressure/crushing strength profiles of paracetamol tablets (Formulation B) containing MCC at various moisture levels.

moisture is expected to be hydrogen bonded to small bits of cellulose within the particle. It is proposed that since MCC compacts by plastic deformation[6], the moisture within the pores acts as an internal lubricant and facilitates slippage and flow within the individual microcrystalls. If, as hypothesised[6] after plastic deformation the particles are so close that hydrogen bonding can occur, then the presence of an optimum amount of water will prevent elastic recovery by forming bonds through hydrogen bond bridges. These results are in agreement with those recently reported by Ritter and Sucker[7] who reduced the capping tendency of an MCC based (Avicel PH101) formulation by increasing its

moisture content from 3.2 to 6.1%. This was attributed to the strengthening of inter particle bonding forces and the reduction of elastic recovery by lowering of the yield point.

The results of loss and absorption of moisture from MCC tablets containing 7.3 and 1.5% moisture are presented in Tables 4 and 5. The drying of MCC tablets containing 7.3% moisture slightly decreases tablet strength and disintegration time. Therefore, as explained above that although the presence of an optimum amount of moisture is necessary to form strong particle to particle bond in compaction, the expulsion of that moisture by drying has little or no effect on the crushing strength of tablets. Similarly for the study in which tablets were allowed to absorb moisture, as the moisture content of tablets increased from 1.5 to 7.2% there was a gradual small reduction in tablet strength with a corresponding slight decrease in disintegration time (Table 5).

TABLE 4

Properties of Tablets (Formulation A) Containing 97% MCC at 7.3% Moisture after Drying at 80°C

Time of drying (hours)	Crushing Strength Kp	D.T.* (min.)	Moisture Content %
0	8.3	2.10	6.8
0.5	7.5	1.29	2.2
1	7.3	1.02	1.6
8	7.1	1.01	1.3
24	7.2	1.02	1.2

*D.T. = Disintegration time

TABLE 5

Properties of Tablets (Formulation A) containing 97% MCC at 1.5% Moisture after Exposure to 75% Relative Humidity at 20°C

Time of Exposure (hours)	Crushing Strength Kp	D.T.* (secs)	Moisture Content %
0	2.9	34	1.5
0.5	2.6	43	4.1
1	2.5	32	5.0
1.5	1.9	30	5.5
2	1.7	30	6.7
4	1.6	21	7.3
8	1.5	14	7.2

*D.T. = Disintegration time

This effect is attributed to the absorption of moisture into the hydrophilic particles of MCC causing particle swelling and some disruption of the hydrogen bonding.

In conclusion, it is suggested that if dried MCC is used to impart compressibility to a moisture sensitive product, its moisture content has to be controlled by tight specifications. This may be particularly relevant to a very poorly compressible drug which may not tablet once the moisture content of MCC is reduced below 2%.

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