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COMPARATIVE COMPACTION PROPERTIES OF VARIOUS MICROCRYSTALLINE CELLULOSE TYPES AND GENERIC PRODUCTS

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ABSTRACT

The purpose of this review is to compare the tableting properties of conventional microcrystalline cellulose (MCC) with those of other common direct compression diluents and of the numerous new MCC grades and brands recently made available. After a brief discussion of the mechanisms of consolidation involved in the formation of MCC tablets, the first section deals with the basic mechanical properties of powders important for compression. Values of parameters describing ductility, brittleness, elasticity and viscoelasticity are presented and discussed in relation with the degree of polymerization, the crystallinity, the moisture content and the morphological properties of the materials.

The tableting properties of the powders during the compression process (densification behavior, work of compression) and the mechanical strength of the finished products (compactibility) are examined. Special attention is given to the effects of moisture content, lubricants and other added substances on the performances of MCC products. Comparative tablet weight variation data are provided for several MCC types from different supplies.

Note : The symbols for registered names and trademarks have been systematically dropped for sake of simplicity.

Finally, aging of the MCC compacts is discussed in relation to environmental conditions, before warning the user in the conclusion on the considerable variability of MCC products currently available on the market.

INTRODUCTION

About ten different excipients are currently available for the production of tablets by direct compression. Among these, microcrystalline cellulose (MCC) exhibits the best compactibility (ability to produce strong compacts) and has gained widespread acceptance. The preparation of cellulose in a microcrystalline form was first disclosed in patents issued in 1961, 1962 and 1964 and was later decribed in several basic papers by Battista and Smith (1-3) of the American Viscose Corporation. The product was first commercialized in 1962 under the brand name Avicel®. Avicels are presently marketed by FMC Corporation. Soon after, articles were published reporting on the good tableting properties of these products as dry binders for direct compression formulations (4-20). The first compendium monograph of MCC was already published in 1966, in the 2nd Supplement to the 12th edition of the National Formulary.

MCC is derived from purified wood α-cellulose. The hinges of amorphous cellulose which link the naturally occuring microcrystals are preferentially removed by a severe acid hydrolysis, yielding a cellulose with a so-called "level-off degree of polymerization" or "D.P." of about 200 to 300. The microcrystals (with diameters ranging from 1 to 10 μm) are freed from their fibrous, packed structure by mechanical shearing of a water slurry and obtained as a powder by spray-drying. The microcrystals rebind together randomly as aggregates. By varying the hydrolytic, shearing and drying conditions, the particle size and the moisture content may be changed, and such changes give rise to different commercial MCC grades currently available. Note that the degree of crystallinity of the MCC products varies a lot and is not necessarily higher than that of the original cellulose because intensive agitation may destroy the crystal structure and short macromolecular chains are unfavorable to the formation of crystalline regions.

Up to the 1980's Avicel grades were the only MCC products available on the market but since then a variety of new products have been launched by various manufacters. Some of these MCCs are equivalent in their tableting properties to

the pioneer products but others are much inferior and the situation is further complicated by the existence of numberless resellers.

Here we propose to review the literature on the tableting characteristics of both the conventional and the new MCCs. The first section deals with the consolidation mechanisms involved in the formation of MCC tablets. Then, the basic mechanical parameters used for describing the ductility, brittleness, elasticity and visco-elasticity are discussed in relation with the chain length and alignment, the moisture content as well as the morphological properties of MCCs. Next, tableting properties during the compression process and the strength of the finished tablets are examined. Special attention is given to the effect of the moisture content, and to the addition of lubricants and other tableting excipients or active ingredients. Results illustrating the relationship between the flow properties of MCC products and weight variation of tablets are presented. The article closes with the problem of the aging of the MCC tablets as function of environmental conditions.

Beside its main function of dry binder for direct compression, MCC also acts as disintegrating agent, and as binding agent in wet granulation or extrusion, but this latter aspect will not be discussed here. However, it is worthwile noting that significant loss of plasticity of MCC has been found after wet granulation (21).

Although the article focusses on the tableting properties of the various types of MCC currently available a comparison is also made with other direct compression fillers such as powdered (microfine) cellulose, various lactose types, dicalcium phosphate dihydrate, sodium chloride and pregelatinized starch, compaction characteristics of which are well characterized, and basically very different. Data on paracetamol, a model of a very poorly compactible material, are also given, when available.

MECHANISMS OF TABLET FORMATION WITH MCC POWDERS

MCC powders are known to form tablets mainly through plastic deformation, but they are also quite elastic with a time dependent behavior (22). Some fragmentation of the particles under compression has been reported by Armstrong and Cham (23), but not by Sixsmith (24).

One feature of MCC powders is their intraparticle porosity. Approximately 90 to 95% of the total specific surface area is shown to be internal when comparing the geometric (25) and the BET surface areas (26-29). Note that a 10-fold

TABLE 1
Particle Sizes and Specific Surface Areas of Avicel Powders (25,29,30)

	Avicel PH-101	Avicel PH-102	Avicel PH-103	Avicel PH-105
Geometric mean diameter (μm)[1]	91	120	251	187
Coulter Counter median diameter (μm)	49.5	85.5	46	16.5
Median Stokes diameter (μm)	37	62	36	25
Permeametry median diameter (μm)	16	15.3	15.3	6.3
Geometrical surface area ($m^2 g^{-1}$)[2]	0.08	0.05	0.09	0.24
BET surface area ($m^2 g^{-1}$)[3]	1.22	1.12	-	2.45
Porosimetry surface area ($m^2 g^{-1}$)[4]	1.30	1.26	1.36	2.21
Apparent surface area ($m^2 g^{-1}$)[5]	1.39	117	-	173
S_{N_2}/S_{geo}	15.3	22.4	-	10.2
S_{H_2O}/S_{N_2}	114	104	-	71

[1] d_{gw}, measured using sieving; [2] S_{geo}, calculated from the Coulter Counter data; [3] S_{N_2}, measured using nitrogen adsorption data; [4] Calculated from the mercury intrusion porosimetry data; [5] S_{H_2O}, calculated from the water vapor adsorption data; [6] Sieving values for Avicel PH-103 and Avicel PH-105 are unreliable because of presence of aggregates.

systematic error was made by Marshall and Sixsmith (25) when calculating the specific surface area from nitrogen adsorption data. Note also that very high values for specific surface area have been reported using water vapor sorption (27-29) (about 100 times the BET surface area), but they reflect penetration into the amorphous portions of the cellulose structure and interaction with the individual anhydroglucose units rather than a true specific surface area (26).

Mercury intrusion porosimetry was used to evaluate the interparticulate pore structure of various MCC powders and gave modal values of 35 μm (Avicel PH-102), 20 μm (Avicel PH-101 and PH-103) and 5 μm (Avicel PH-105). Particle size distribution of these products was measured using a variety of techniques (25,30). Table 1 lists selected mean particle size values as well as specific surface area values obtained using various methods for four Avicel grades.

When comparing the BET to geometrical surface area ratios, it is seen that Avicel powders have a moderate microporosity, which varies with the product considered. Unfortunately no reliable data on the intraparticle pore distribution have been found in the literature.

The change in particle size and specific surface area with increasing compaction pressure has been investigated (23, 24). Sixsmith (24) used photosedimentometry and observed a slight increase in Stokes diameter. Armstrong and Cham (23) measured the equivalent volume diameter (Coulter Counter) of disintegrated Avicel PH-102 tablets and found a four-fold decrease in diameter by comparison with the original powder. As these authors sonicated the dispersions of the disintegrated tablets and probably no aggregates were therefore present, one can imagine that some fragmentation occurs during compaction, at least with this MCC grade. Sixsmith (24) also measured the specific surface area of the compacts using nitrogen adsorption and found only little change in the surface area (except for the fine grade Avicel PH-105), in accordance with the assumed consolidation mechanism by plastic deformation.

Beside the morphological aspect, many parameters (chemical composition, chain length and alignment, water content) may affect the mechanical properties of MCC materials and thus their compactibility. The effects of these factors on the compactibility will be discussed in the next section. First the mechanical properties of the powders will be addressed, but before that it is worthwhile to make some comments concerning the bonding mechanism of MCC. Neighbouring cellulose chains link predominantly through hydrogen bonds. This is supported by the solubility parameter data given by Phuoc et al. (31) which give a fractional polarity amounting to 0.76. However, it has been recently demonstrated, by testing compacts prepared under ambient conditions and in liquids with different dielectric constants, that besides intermolecular forces, mechanical interlocking of the particles plays a role in the strength of compacts (32).

MECHANICAL PROPERTIES OF MCC POWDERS

According to a recently developed theory (33,34) differences in bonding characteristics of materials are due principally to differences in their mechanical properties. In this respect, various parameters are known to favor the formation of strong compacts :

- high ductility (plastic deformation)
- low brittleness (fragmentation propensity)
- low elasticity (reversible deformation)
- high viscoelasticity (time-dependent behavior).

Numerous physical constants or indices, sometimes empirical, have been proposed to quantify these properties. Some of them are determined from the results of a single type of test, others combine the results of two types of tests. Table 2 lists the parameters which have been used for MCC products.

To facilitate understanding, these constants or indices are briefly defined before quoting the experimental values obtained for MCC products and other direct compression bases.

The yield stress, P_y, is usually calculated as the reciprocal of the slope, K, of the Heckel curve (50, 51) :

$$\ln[1/(1-D)] = KP + A \qquad \text{(Eq. 1)}$$

where D is the relative density, P is the compaction pressure and A is a constant.

Indentation hardness is the resistance to plastic deformation. It is approximately three times the uniaxial yield stress (52). The most widely used method is the static Brinell hardness test giving the Brinell Hardness Number, H, but dynamic or rebound hardness has also been measured on pharmaceutical materials (53). The compression susceptibility, γ, is derived from the Leuenberger equation (54) :

$$H = H_0[1-\exp(-\gamma P D)] \qquad \text{(Eq. 2)}$$

where H is the Brinell hardness at the compaction pressure P and relative density D, and H_0 denotes the theoretical maximum hardness attained as P approaches infinity and D unity (porosity is zero).

The Brittle Fracture Index, BFI, or Brittle Fracture Propensity, is one of the tableting indices proposed by Hiestand (38). It is a measure of the ability of a compact to relieve stress at a local region of stress concentration. Practically, it is obtained by comparing the tensile strength of compacts with (σ_T) or without (σ_{T_0}) a hole (stress concentrator) at their center :

$$BFI = [(\sigma_T/\sigma_{T_0})-1] / 2 \qquad \text{(Eq. 3)}$$

The stress intensity factor, K_{IC}, is a measure of the resistance of the material to cracking. A three-point or four-point bending test performed on rectangular beams is usually used and K_{IC} is calculated from (55) :

$$K_{IC} = 3 P_{IC} a^{1/2} (L_1-L_2) \gamma / 2 b h^2 \qquad \text{(Eq. 4)}$$

TABLE 2

Physical Constants and Indices for Characterizing the Mechanical Properties of Powdered Materials

Property	Index or constant	Reference [1]
Ductility	Yield strength	Hersey et al. (35)
	Indentation hardness	Ridgway et al. (36)
	Compression susceptibility	Leuenberger (37)
Brittleness	Brittle fracture index	Hiestand (38)
	Critical stress intensity factor	Mashadi and Newton (39)
Elasticity	Elastic modulus	Church and Kennerley (40)
	Elastic quotient	Aulton et al. (41)
	Strain index	Hiestand (38)
	Elastic recovery	Armstrong and Haynes-Nutt (42)
Viscoelasticity	Stress relaxation [2]	Shlanta and Milosovich (43)
	Strain recovery [2]	Baba and Nagafuji (44)
	Creep compliance	Staniforth et al. (45)
	Elastic and viscous moduli	Radebaugh et al. (46)
Combined indices	Bonding index	Hiestand (38)
	Plasto-elasticity ratio	Malamataris et al. (47)
	Elastic recovery index	Celik and Travers (48)
	Indentation hardness / Yield strength ratio	Roberts and Rowe (49)

[1] Name of the authors who first to our knowledge proposed the use of the index in the pharmaceutical literature; [2] Both dynamic and static measurements.

when P_{IC} is the load at fracture, a is the notch length, L_1 and L_2 are the outer and inner loading spans (in the four-point test), b and h are the beam width and thickness, respectively, and γ is here a value known as compliance.

The elastic modulus, or Young's modulus E, is given by Hooke's law :

$$E = \sigma / \varepsilon \qquad \text{(Eq. 5)}$$

where σ and ε are the axial stress and strain, respectively. It can be determined by using the bending test on rectangular compacts, compression testing of large cylindrical compacts or from indentation tests.

The elastic quotient, EQ, is defined as the fraction of the indentation which rebounds elastically on removal of the load (41) :

$$EQ = h_1 - h_2 / h_1 = \Delta h/h_1 \qquad \text{(Eq. 6)}$$

where h_1 is the depth of penetration under load and h_2 is the decreased penetration after load removal. The modulus of elasticity can also be calculated from (36) :

$$E = 0.268\ W / \Delta h/h_1^{1/2} \qquad \text{(Eq. 7)}$$

where W is the applied load.

The Strain Index, SI, has been defined by Hiestand (38) as the ratio of the indentation hardness, H, to the complex modulus E' :

$$SI = H / E' \qquad \text{(Eq. 8)}$$

E' being given by :

$$E' = E_1 / (1-\nu_1^2) \qquad \text{(Eq. 9)}$$

where E_1 is the elastic modulus of the compact and ν its Poisson's ratio.

The elastic recovery, ER, is defined here according to (42) as the percentage of axial expansion of the compact after ejection, relatively to its height at maximum pressure :

$$ER = \frac{h - h_c}{h_0} \cdot 100 \qquad \text{(Eq. 10)}$$

h_c and h being the heigths under compression and after ejection, respectively. Various models have been proposed to analyse the stress relaxation data. For instance, according to a Maxwell model the viscoelastic slope, k, can be derived from (23) :

$$\ln \Delta F = \ln \Delta F_0 - kt \qquad \text{(Eq. 11)}$$

where ΔF is the amount of compressional force left in the viscoelastic region at time t, and ΔF_0 is the total magnitude of this force at time zero.

Strain movements under constant stress can be analyzed in terms of creep compliance, J, which is defined as (56) :

$$J = \varepsilon / \sigma \qquad \text{(Eq. 12)}$$

Three compliance values can be calculated from the creep curve, namely the Newtonian or plastic compliance, J_N, the retarded or viscoelastic compliance, J_R, and the elastic compliance, J_0. The ratio of elastic to plastic deformation is given by J_0/J_N.

Several combined indices can be found in the literature. Hiestand (38) proposed the Bonding Index, BI, which estimates the persistence at decompression of areas of true contact (bonded areas) which were formed by compression. The BI is the ratio of the tensile strength, σ_T, (measured by transverse compression) to the indentation hardness, H, i.e. :

$$BI = \sigma_T / H \qquad \text{(Eq. 13)}$$

If the static indentation test is used, one obtains the best Bonding Index, BIb. The worst case Bonding Index is obtained from the dynamic test and is the best estimate of the bonding capacity of the material. A comparison of the two values indicates the extent of viscoelasticity.

Malamataris et al. (47) developed a creep test where the powder is maintained under a fixed load for a certain time and the compact is then ejected. They propose to calculate two parameters, plastic compression, PC, and elastic recovery, ER, according to:

$$PC = \frac{h_o - h}{h} \cdot 100 \qquad \text{(Eq. 14)}$$

$$ER = \frac{h - h_L}{h_L} \cdot 100 \qquad \text{(Eq. 15)}$$

where h_0 is the compact thickness when first formed, h_L at the end of the loading period and h after ejection. From these two quantities, a plasto-elasticity ratio can be estimated as :

$$\text{plasto-elasticity ratio} = ER / PC \qquad \text{(Eq. 16).}$$

Similarly, Celik and Travers (48) proposed to define an Elastic Recovery Index, ERI, from strain movements :

$$ERI = ER / SM \qquad \text{(Eq. 17)}$$

where ER is the elastic expansion within the die on load release and SM is the strain movement under a constant load.

TABLE 3

Basic Mechanical Properties of MCC Compared with those of other Common Bases for Direct Compression

Parameter	MCC[1]		Powdered cellulose[2]	Sodium chloride	Pre-gelatinized starch[3]	Lactose mono-hydrate	An-hydrous lactose	Spray-dried lactose	Dicalcium phosphate dihydrate[4]	Paracetamol	Ref.
	Type 1	Type 2									
Yield strength,	50, 46	-	-	108	72	123	-	152	345	74	57, 58
P_y (MPa)	29.8	-	-	-	-	-	-	-	-	299	59
	73	-	-	94	-	-	140	-	-	-	60
	48	-	-	62	45	92	-	103	294	-	61
	72	-	-	-	-	-	-	-	226	-	62
	-	49	-	60	-	-	149	-	431	-	49
	104	-	-	125	78	-	-	-	252	-	63
	56	-	72	-	-	-	-	-	-	-	-[5]
Brinell Hardness,	32.8	-	-	-	49.0	-	18.6	-	50.0	12.3	41
H (MPa)	26.2	-	14.8	-	-	-	-	-	-	-	64
	-	168.3	-	-	-	-	534.3	-	752.3	non measurable	65[6]
Compression susceptibility, $\gamma \times 10^2$ [MPa]	-	1.33	-	0.93	-	-	0.32	-	0.17	non measurable	65
Brittle Fracture Index, BFI	0.10	-	-	-	-	-	-	-	-	-	66
	-	0.04, 0.09	-	0.4	0.22, 0.27	-	-	0.18, 0.12, 0.16	-	-	38, 67, 68
	0.083, 0.055	-	-	-	-	-	-	0.073, 0.142	-	-	69

TABLE 3 (continued)

Parameter	MCC[1] Type 1	MCC[1] Type 2	Powdered cellulose[2]	Sodium chloride	Pre-gelatinized starch[3]	Lactose mono-hydrate	An-hydrous lactose	Spray-dried lactose	Dicalcium phosphate dihydrate[4]	Paracetamol	Ref.
Elastic modulus, E (GPa)	0.8-1.9	-	-	-	-	-	-	-	-	-	40[7]
	6.25	-	5.40	7.80	1.35	-	-	5.25	8.55	-	70[8]
	8.3		6.7	14.3	6.1	-	-	7.6	16.3	-	71[9]
	-	4.7	-	-	-	-	-	-	-	-	72[10]
	10.3	-	-	-	-	-	-	-	-	-	39[11]
	9.19	8.67	-	-	-	3.21	17.91	11.36	47.79	-	73[11]
	-	5.8	-	18	6.6	36	-	17	27	10, 11	72[12]
Elastic quotient, Q	0.61	-	-	-	0.51	-	0.53	-	0.41	0.51	41
	0.55	-	0.51	-	-	-	-	-	-	-	64
Strain Index, SI	0.025	-	-	0.75	0.023	-	-	0.021	-	-	38, 67, 68
Elastic recovery, ER (%)	6.7	-	-	0.9	-	3.2	-	-	-	-	44
	6.0	12.3	-	-	-	-	-	-	-	-	64
Viscoelastic slope,k (s^{-1})	0.332	-	-	-	0.336	-	-	-	0.182	-	23
	0.105	-	-	-	-	-	-	-	-	0.011	59
Elastic to plastic compliance ratio, J_O/J_N (s^{-1})	-	550	-	-	589	-	-	-	964	-	74[13]

TABLE 3 (continued)

Parameter	MCC[1] Type 1	MCC[1] Type 2	Powdered cellulose[2]	Sodium chloride	Pre-gelatinized starch[3]	Lactose mono-hydrate	An-hydrous lactose	Spray-dried lactose	Dicalcium phosphate dihydrate[4]	Paracetamol	Ref.
Bonding Index,											
BIw	0.05	-	-	-	-	-	-	0.005,			66
		0.04	-	0.022	0.013	-	-	0.006	-	-	38,67,68
BIb	-	0.051	-	-	-	-	0.024	-	0.019	-	75
Plasto-elasticity											
ratio, ER / PC	6.0	-	-	-	-	-	-	-	-	-	47
	4.1	-	-	-	-	-	-	-	-	14.1	76
	6.0	-	-	-	17.7	-	-	5.4	4.5	-	77
	0.3	-	-	-	-	-	-	-	-	1.92	78
Elastic Recovery											
Index, ER / SM	0.520	-	-	-	0.369	-	-	-	1.410	2.260	48[14]
H / P_y ratio		3.43,	-	3.42,							
	-	3.15 [15]		3.35 [15]	-	-	2.43 [15]	-	2.25[15]	-	49

[1] Avicel® PH-101 and Avicel® PH-102, FMC Corp., Philadelphia, USA; [2] Elcema® P 100, Degussa AG, Francfort, Germany; [3] Starch 1500®, Staley, Decatur, USA; [4] Emcompress® E. Mendell, New York, USA; [5]Unpublished data; [6] Values extrapolated to infinite pressure using Leuenberger's equation (54); [7] Four-point flexure testing of rectangular beams compacted at various pressures,; [8] Four-point flexure testing of rectangular beams of a relative density of 0.81; [9] Values reported by Church and Kennerley (70) and extrapolated to zero porosity; [10] Values obtained by compressing large cylindrical compacts and ectrapolated to zero porosity; [11] Value obtained using four-point flexure testing and extrapolated to zero porosity; [12] Values obtained from recovery during decompression and ecxrapolated to zero porosity; [13] Compacts prepared at 79 MPa; [14] 30 kN compression force and 10 s holding time; [15] Values obtained from elastic moduli using Marsh's equation (79).

Finally, Robert and Rowe (49) used the following ratios :

$$H / P_y \quad \text{(Eq. 18)}$$

and

$$E / P_y \quad \text{(Eq. 19)}$$

H being the indentation hardness, P_y the yield pressure and E the elastic modulus.

A number of results on direct compression bases and notably MCC products have been reported. One difficulty of comparing them is that different experimental conditions were used. A second source of variations in the values determined is that compacts were not necessarily prepared at the same void fraction (porosity). When possible, we will report constants and indices which had been extrapolated to zero void fraction (subscript o). Table 3 lists values for MCC products as well as those for selected common direct compression excipients. But for comparability's sake, the latter are mentioned only if determined in the same papers reporting on MCC products, i.e. measured in the same conditions.

MCC (Avicel PH-101 or PH-102) is the most plastic material among the cited bases as demonstrated by its P_y values. It has even a lower P_y than the typical plastically deforming sodium chloride. It is also more plastic than powdered (microfine) cellulose because of the random orientation of the crystallites. The discrepancy between P_y values comes from the fact that some values were determined at "zero pressure", others "under pressure", but also from differences in the choice of the boundary values limiting the linear segment of the Heckel profiles.

No trend can be observed from the hardness values. Brinell hardness is in fact a complex number reflecting both plasticity and elasticity. Further, some fragmentation is known to occur for certain materials under compression (lactose, dicalcium phosphate dihydrate, paracetamol) and the compacts tested are neither isotropic nor non-porous. The Brinell hardness numbers cannot either be compared to the indentation values reported by Jetzer et al. (65) which are calculated by extrapolation to zero porosity using Eq. 2 and which these authors call the compactibility of the powder material. Note, however, that the so-called compression susceptibilities rank in the same order as the yield pressure values.

MCC shows quite an unsignificant brittleness having a BFI inferior to 0.2. However it is very difficult to compare values obtained under different conditions. The elastic modulus, as determined using various techniques, and the elastic quotient, deduced from indentation testing, are fairly high but appear not to be very sensitive for discriminating between the various materials. Hiestand's

strain indices are similar for MCC, pregelatinized starch and SD lactose. In contrast, it is markedly higher for sodium chloride indicating a high proximity of the surfaces remaining in contact after decompression.

Elastic recovery is a simple measurement of the disruptive forces acting after compression. High ER values have been observed for MCC, but Krycer et al. (59) noted a maximum in elastic recovery at a given applied pressure followed by a decrease due to further interparticle bonding.

MCC shows a highly time dependent behavior and exhibits similar viscoelasticity properties, such as the viscoelastic slope or the elastic to plastic compliance ratio, to those of pregelatinized starch.

Viscoelastic materials have long been known to be sensitive to tableting speed, an increase in speed leading to a reduction in tablet strength. Differences have been explained in terms of time of exposure to compression. This is still true but recently Armstrong and Palfrey (80, 81) have shown that the primary effect of tableting speed on tablet strength was to change the porosity, which in turn is related to the consolidation mechanism. The decrease in tablet strength with increased tableting speed is thus basically due to increased porosity. Therefore, when preparing tablets at the same compaction pressure, differences in strength are observed, but these differences nearly disappear when correction for porosity is made. Table 4 presents data for four directly compressible diluents together with the observed yield pressure P_y (50, 51) and the strain rate sensitivity, SRS, as defined by Roberts and Rowe (82) :

$$SRS = \frac{P_{y_2} - P_{y_1}}{P_{y_2}} \cdot 100 \qquad \text{(Eq. 20)}$$

where here P_{y1} and P_{y2} are the yield pressures at the low and high machine speeds, respectively.

Fragmenting materials show very little speed dependency and correction for porosity has almost no effect. This is true for dicalcium phosphate and to a lesser extent for SD lactose. The strength of tablets prepared from plastic materials (MCC and pregelatinized starch) is very much affected by compaction speed but after correction for porosity differences, values are equivalent. It is to be noted that the strength sensitivity to the compaction speed does not parallel the SRS values as calculated here from the P_y values given by Armstrong and Palfrey (80). In contrast, these authors found a very good correlation (81) when taking

TABLE 4
Tablet Tensile Strengths (MPa) Achieved at the Pressure of 80 MPa, before and after Correction for Porosity (80, 81), and Strain Rate Sensitivity of Four Direct Compression Bases

	MCC [1]	Spray-dried lactose	Pregelatinized starch	Dicalcium phosphate
Machine speed (rev / s) Before correction				
0.33	5.4	0.77	0.28	0.63
0.63	5.2	0.76	0.25	0.62
2.63	3.9	0.68	0.15	0.60
% reduction [2]	28	12	47	0
Strain rate sensitivity (%)[2]	9.7	16.6	15.5	15.0
After correction				
0.33	5.4	0.77	0.28	0.63
0.63	5.3	0.77	0.27	0.62
2.63	5.4	0.79	0.24	0.64

[1] Avicel PH-102; [2] Based on 0.33 and 2.63 rev/s.

the SRS values given by Roberts and Rowe (82), but mention should be made that some of the materials differed.

Coming now to the combined indices (Table 3), MCC has the highest Hiestand's bonding index to date, and allied to a very low BFI, this ensures a problem-free material. The plasto-elasticity ratio of MCC is < 7-10 which suggests according to Pilpel at al. (47, 83) that it can form satisfactory compacts, but other values reported in Table 3 seem to fail to actually differentiate between "good" materials (lactose, dicalcium phosphate) and the excellent MCC. The same comment can be made on the elastic recovery index (48), which is very similar in essence to the previous index. Neither could the H/P_y ratio as determined by Roberts and Rowe (49) be related to the strength of the compacts, with MCC for example showing the same H/P_y value as sodium chloride, but forming much

TABLE 5
Basic Mechanical Properties of Several MCC Products

Material	P_y (MPa)		H (MPa)	K_{IC_0} (MPa $m^{1/2}$)	E_0 (GPa)	EQ[7] (%)	ER[7] (%)	
Avicel PH-105[1]	-	-	-	1.33	9.43	-	-	-
Avicel PH-101[1]	56	57.3	26.1	0.87	9.19	0.55	6.0	5.1
Avicel PH-102[1]	-	-	-	0.76	8.67	-	-	5.3
Emcocel 50M[2]	-	55.8	-	0.92	7.13	-	-	5.3
Emcocel 90M[2]	-	-	-	0.80	8.87	-	-	7.2
Unimac MG-100[3]	37	-	25.1	0.80	8.03	0.49	4.5	4.9
Unimac MG-200[3]	-	-	-	0.67	7.34	-	-	6.4
MCC type 101[4]	69	-	24.6	-	-	0.53	8.4	7.2
Indocel 80[5]	44	-	16.6	-	-	0.52	8.7	-
Reference	- [6]	84	64	85	73	64	64	86

[1] FMC Corp., Philadelphia, USA; [2] Finnish Sugar Ltd, Finland (E.Mendell, Regate, U.K..);
[3] Unikita Rayon, Osaka, Japan; [4] MingTai, Taipei, Taiwan (Trans-Medica, Hambourg, Germany);
[5] Neelkanth Chem., Ahmedabad, India (Dr. S. Saxena, Hofheim, Germany); [6] Unpublished data;
[7] For compacts prepared at 100 MPa.

stronger compacts. The reason for the lack of correlation between these three last indices and the compactibility of the materials is probably that the compression phase during the test is a combination of elastic, viscoelastic and plastic deformation, and not a purely permanent deformation.

Up to now, the pioneer Avicel products were compared to other well known bases for direct compression. When confronted with the new MCC products which are now proposed, it is very important to evaluate their basic mechanical properties because they can cause differences in tableting (Table 5).

One can hypothesize that one or several of the following composition related and morphological characteristics could explain the differences in the mechanical properties observed with MCC :

- chemical composition

- molecular mass (degree of polymerization)
- degree of crystallinity
- moisture content
- particle size and shape.

Table 6 lists selected data which characterize various MCC materials but which of course were not necessarily obtained on the same batches.

MCC products all come from softwood and as such possess very similar cellulose (and glucose) contents. The same is true for the hemicellulose sugars mannose and xylose (87). Therefore differences in mechanical properties cannot probably be ascribed to this factor. Concerning the molecular mass, one can note that one sample (Indocel 80) had probably undergone a mild hydrolysis and another one (Unimac MG-100) a very severe hydrolysis but all DP values fall slightly below the general accepted level-off degree of polymerization range of 200-300 (1-3, 92, 93) but inside the range of 100 to 200 which has also been reported by some authors (94). No relation could be observed between the mechanical properties and the degree of polymerization i.e. with the length of the crystallites, since the latter roughly follows the DP value. This is probably due to the random orientation of the crystallites of MCC products. There is also no apparent correlation between chain length and degree of crystallinity, i.e. the proportion of aligned and free macromolecules, but mention should be made that the values of crystallinity obtained are very much dependent on the technique used. In contrast, when considering the data for Avicel PH-101, Unimac MG-100, MCC type 101 and Indocel 80, some correlation seems to exist between the degree of crystallinity and the plasticity (as measured by the yield pressure) or the elasticity (see the elastic quotient from indentation measurements). However more data are needed for confirmation.

Because of insufficient data brittleness (see values of stress intensity factor) cannot be correlated to DP or to the degree of crystallinity. Brittleness is certainly related to particle size, the coarser materials being more prone to fragmentation, but this is in fact a consequence of the effect of the particle size of the powder on the properties of the beam specimen itself. No definite trend related to the effect of particle size on the Young's modulus can be identified, both increase and decrease in E_0 being observed with increasing particle size. The same holds true for plasticity when considering for instance the data of Roberts and Rowe (95, 96). P_y values are very close for Avicel PH-105, PH-101 and PH-102 and the

TABLE 6

Selected Characteristics of the MCC Products Analyzed for their Mechanical Properties

Material	Cellulose (%)	DP_V [1]		Degree of crystallinity[2] (%)				Moisture content (%)	Mean diameter (μm)		Index of circularity[3]
									Microscopy	Sieving	
Avicel PH-105	98.1	-	-	-	72.8	-	-	-	-	-	-
Avicel PH-101	96.5	166	167	77.7	77.0	82	62.7	4.7	44	34	0.233
Avicel PH-102	96.9	178	-	80.1	75.3	-	-	4.9	-	53	-
Emcocel 50M	97.8	-	-	-	-	-	66.9	5.0	-	35	-
Emcocel 90M	-	-	-	-	-	-	-	4.6	-	52	-
Unimac MG-100	-	-	113	-	-	53	-	3.7	55	31	0.350
Unimac MG-200	-	-	-	-	-	-	-	3.8	-	45	-
MCC type 101	-	-	151	-	-	74	-	3.5	52	30	0.360
Indocel 80	-	-	212	-	-	58	-	6.0	57	-	0.318
Reference	87	88	89	88	90	64	91	86	64	86	64

[1] Viscosity-average degree of polymerization; [2] X-ray diffraction; [3] Defined as 4 π area / (perimeter)^2.

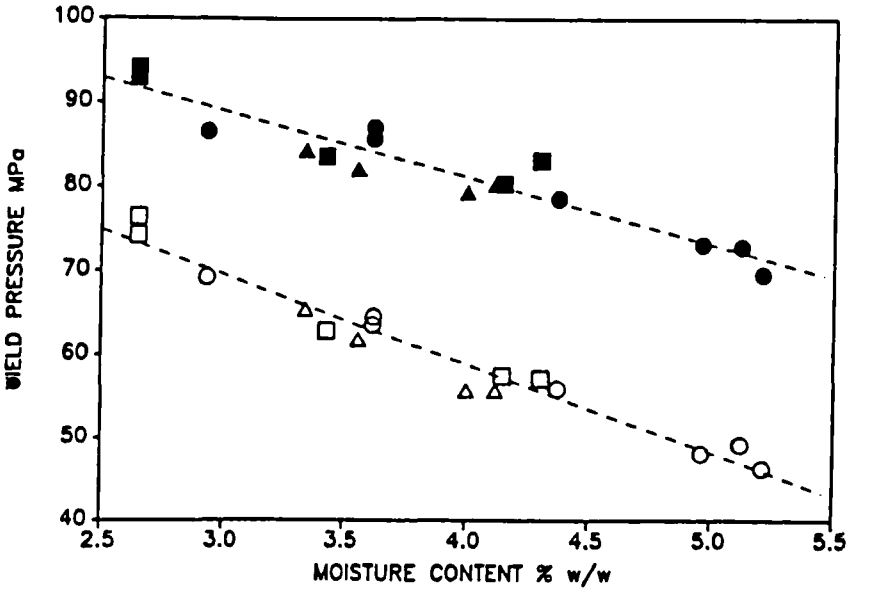

FIGURE 1
Yield pressures for samples of Avicel (○,●), Emcocel (△,▲) and Unimac (□,■) at 0.033 mm s^{-1} (open symbols) and 300 mm s^{-1} (closed symbols), plotted against moisture content. The dotted line represents the best fit for all of the samples (96).

sequence changes somewhat with the compaction velocity used. Neither did these authors note any logical sequence in strain rate sensitivity (52.4, 50.6 and 48.3 %, respectively).

By far the most important parameter for the mechanical properties is the moisture content of the material. Figure 1 shows that the yield pressure decreases linearly with increasing moisture content at both strain rates used. The different materials have all a similar behavior.

A similar effect has been noted by Ragnarsson and Sjögren for a batch of Avicel PH-101 (97). It can be explained by the plasticizing effect of water which renders the macromolecules less rigid and also by the lubricating action of water which facilitates the slippage and flow of individual microcrystals. The plasticizing effect of course also acts on the Young's modulus which reduces for Avicel PH-101 from 9.19 GPa when stored at 40 % relative humidity to 6.55 GPa at 76 % relative humidity (73).

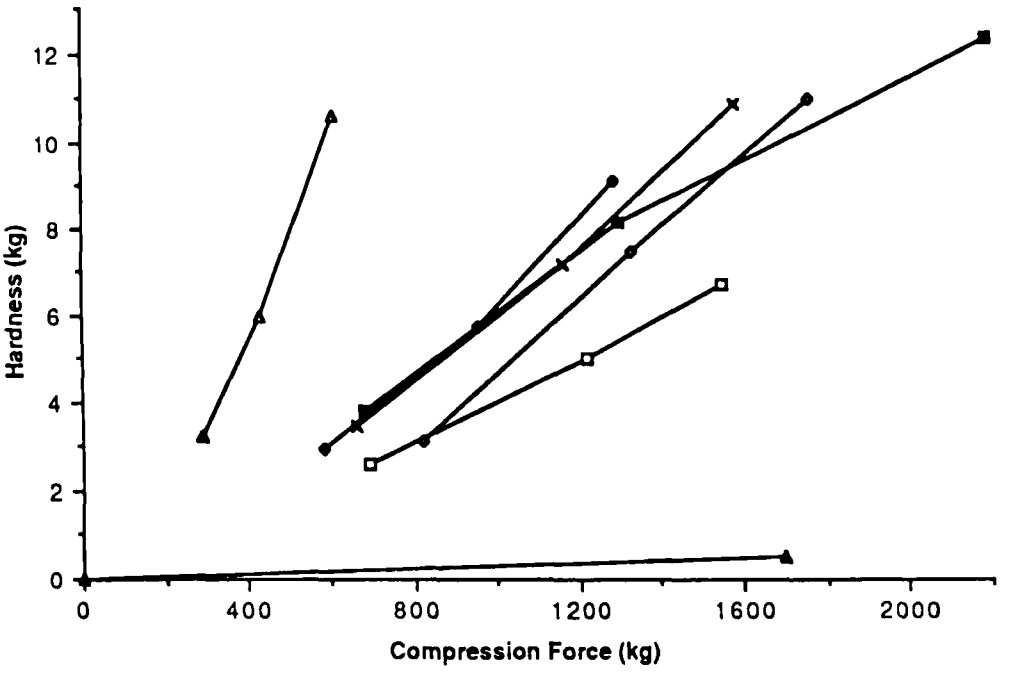

FIGURE 2
Excipient compactibility with 0.75 % magnesium stearate as lubricant (100). Key : △, MCC (Avicel PH-101); ◆, SD lactose (Fast-Flo); ✖, anhydrous lactose; ◇, DC sucrose (Di-Pac); ■, DC sucrose (Nu-Tab); □, dicalcium phosphate dihydrate (Emcompress); ▲, granular form of powdered cellulose (Elcema G 250).

The effect of the moisture content on the mechanical properties of Avicel PH-101 has been extensively investigated by Khan et al. (98) and Malamataris et al. (99). The former authors observed a continuous decrease in yield pressure P_y and plastic compression PC with increased in moisture content. Elastic recovery slightly decreases so that on the whole the plasto-elasticity ratio ER / PC increases with increasing moisture content. The elastic modulus first increases but above about 3 % water (condensation water) diminishes because moisture begins to disrupt bonds. This work will be discussed further in the next section (Fig. 4). As for Malamataris et al. (99), they observed a very slight decrease in yield pressure with moisture content, while the brittle fracture index and tensile strength isotropy values remained steady.

TABLE 7

Evaluation of Different Excipients without Lubricant (-) and with 0.5 % Magnesium Stearate (+) (adapted from (12))
Criteria : G, good; A, adequate; I, inadequate.
* : these excipients could not be tableted without lubricant.

Material	Weight variation		Lubrication ratio[1]		Ejection force		Crushing force		Disintegration time	
	-	+	-	+	-	+	-	+	-	+
Avicel PH-101	I	I	I	G	G	G	G	G	I	G
Avicel PH-102	I	A	I	G	G	G	G	G	I	G
Granular cellulose[2]	G	G	I	G	G	G	G	I	I	G
Pregelatinized starch[3]	I	I	I	G	G	G	G	A	A	G
Dicalcium phosphate [4]	*	G	*	G	*	G	*	G	*	I
Dextrates[5]	*	G	*	A	*	I	*	G	*	G
Dextrose monohydrate	*	G	*	A	*	I	*	A	*	G
Lactose anhydrous	*	A	*	G	*	A	*	G	*	A
Lactose monohydrate	*	G	*	G	*	G	*	A	*	A
Lactose spray-dried	*	G	*	G	*	G	*	G	*	A

[1] The lubrication ratio is the ratio of the force transmitted to the lower punch by the upper punch and is thus an indication of the force lost to the die by friction; [2] Elcema G 250; [3] Starch 1500; [4] Emcompress special; [5] Celulab (Emdex).

TABLETING PROPERTIES OF MCC POWDERS

The tableting properties of MCCs, i.e. the densification behavior, the work of compression and lastly the mechanical tensile strength of the tablets, will be discussed in relation with the effects of :

- moisture content
- added lubricants
- added diluents or active ingredients.

Before doing this, we will compare the compactibility and tableting properties of the pioneer MCC products with those of other selected DC bases. Figure 2 presents the crushing force vs applied force for such materials.

MCC is by far the most compactible material. The effect of magnesium stearate to decrease compactibility varies according to the excipient but the tendency remains the same. MCC is thus the best dry binder and can add significant hardness to compacts at levels as low as 3 to 5 % (100).

Another good comparison of the caracteristics of common DC excipients with MCC is that of Bohluis and Lerk (12). Table 7 presents the conclusions of their study. Note that several excipients could not be tableted without lubricant.

With the criteria used by the authors (weight variation < 0.5 %, lubrication ratio > 0.9, ejection force < 75 kg, crushing force > 7 kg and disintegration time < 300 s at a compression force of 1500-3000 kg), MCC products failed in some aspects. Weight variation was satisfactory only for Avicel PH-102 with magnesium stearate. Without lubricant too much friction was observed for both grades at compression whereas the lubricating properties were always excellent at ejection. The mechanical strength of the tablets was good for the two grades, but the crushing strength was lower in presence of magnesium stearate. This is reflected in the disintegration times which were shorter for the lubricated tablets.

The compacts prepared with powdered cellulose in the granular form exhibited much less weight variation than both MCC grades because of superior flow properties, but gave softer tablets. The other excipients were inferior in several aspects, except pregelatinized starch which is well known for its good disintegrating properties.

A complete comparative study of conventional CD materials (and paracetamol) was carried out at the University of Geneva (101). Table 8 lists the various parameters measured using an instrumented single-punch machine. Force-displacement data were interpreted in terms of Heckel equation (Eq. 1) and work of compression. Heckel plots were published elsewhere (57) and the precise definition of the various parameters used here can be found in ref. 102.

Based on Heckel analysis, MCC possesses, as already mentioned, the lowest yield value, but also a very small densification term assigned to particle fragmentation. Viscoelastic (MCC) and plastic (sodium chloride) materials offer much more resistance to densification (high compression work values) than the brittle materials do, but they also retain more energy in the tablets (high W_N and PL values). The lactose of the quality used in the study and paracetamol, with 67% plasticity, are poorly compactible substances. When combining parameters

TABLE 8

Compression Caracteristics of Various Materials (Size Fraction : 0-63 µm, Prelubricated Die, Applied Pressure : 140 MPa) (57, 101)

Parameter	MCC[1]	Sodium chloride	Lactose mono-hydrate[2]	Dicalcium phosphate dihydrate[3]	Paracetamol[4]
Heckel equation					
P_y (MPa)[5]	46	108	161	333	79
D'_B [6]	0,061	0,065	0,096	0,150	0,158
Work of compression					
W_U [7] (J)	7.92	6.43	3.31	4.97	3.21
W_{ED}[8] (J)	1.09	0.32	1.10	0 .98	1.05
W_N[9] (J)	6.88	5.81	2.22	3.72	2.08
PL[10] (%)	86	95	67	79	67
F_x[11] (N)	> 200	> 200	45	101	capping

[1] Avicel PH-101; [2] Lactose DT (Merck, Darmstadt, Germany); [3] Calipharm (Albright & Wilson, Oldbury, U.K.); [4] Compressed at 120 MPa; [5] Yield pressure; [6] Densification by fragmentation; [7] Upper punch work; [8] Work of elastic deformation; [9] Net work; [10] Plasticity index = W_N/W_L x 100 (W_L = lower punch work); [11] Diametrial crushing force.

given by various analyses, one can, according to Wiederkehr - von Vincenz (103), categorize materials according to their compaction properties as follows :

- viscoelastic materials : MCC, dextrates
- plastic materials : potassium chloride, sodium chloride
- brittle materials : dicalcium phosphate dihydrate, lactose
- poorly compactible materials : paracetamol, phenacetin.

Firm compacts can be obtained with the first three classes, brittle materials giving generally a lower mechanical strength (with the exception of dicalcium phosphate dihydrate).

The data given in Table 8 were all obtained using a prelubricated die, but it is important to note that MCC is not "self-lubricating" despite low ejection forces measured even in absence of lubricant (104). For instance the lubrication ratio R

TABLE 9
Frictional Parameters of Unlubricated Materials Compressed at 150 MPa (106)

Material	F_D[1] (kN)	μ_1[2]	F_E[3] (kN)	μ_2[4]
Avicel PH-101	3.49	1.97	0.245	1.29
Sodium chloride	3.63	1.37	1.79	0.83
Anhydrous Lactose	5.29	2.25	3.19	2.68
Paracetamol	3.07	1.55	1.12	1.72

[1] Force lost to the die (upper punch force less lower punch force); [2] Coefficient of friction at maximum compression (FD / maximum die wall force at compression); [3] Ejection force; [4] Friction coefficient at ejection (FE / die wall force at ejection).

was 0.804 for unlubricated Avicel PH-101 and 0.927 when 1% magnesium stearate was added (105). A more complete example is provided by Hölzer and Sjögren (106). Table 9 lists values of several parameters related to friction either during compression or at ejection for some materials.

The value of the friction coefficients (and thus the force lost to the die and the ejection force) depends largely on the conditioning of the die. Values given in Table 9 are for a conditioned die, i.e. are equilibrium values after the preparation of several tablets. Fig. 3 comparing the evolution of the friction coefficient μ_1 for sodium chloride and MCC illustrates this point.

When 20 tablets of sodium chloride were prepared (at 115 MPa) starting with a cleaned die, μ_1 increased to a constant value of 1.4. When subsequently 20 tablets of lubricated sodium chloride were pressed (at the same pressure), μ_1 decreased rapidly to a constant value of 0.3. Finally, 30 tablets of unlubricated material were needed to return to the initial value of 1.4.

When compressing pure MCC (at 60 MPa) in an initially clean die, μ_1 increased progressively to a constant value of 2.5 at 20 tablets. This constant value was maintained when preparing further tablets at 60 or 150 MPa. Cleaning the die after 50 tablets did not affect the μ_1 value. No data with lubricant were given but magnesium stearate would certainly have lowered μ_1. A lubricant is thus absolutely necessary for MCC to act as an antifriction agent at the compression stage, and Avicel is probably more an antiadhesive than a true lubricant.

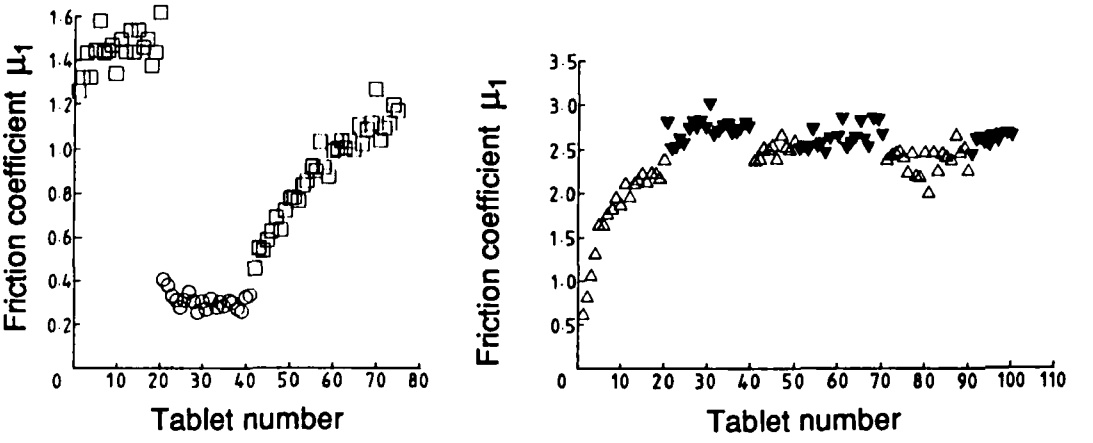

FIGURE 3

Friction coefficient at compression μ_1 for consecutive sodium chloride (left) and MCC (right) tablets (106).

Key :□, sodium chloride at 115 MPa; ○, sodium chloride with 1 % magnesium stearate at 115 MPa; △, Avicel PH-101 at 60 MPa; ▼, Avicel PH-101 at 150 MPa.

It has been shown that the compression characteristics of MCC differ in many respects from those of other common DC diluents, but it is also important to assess whether their properties vary to any large extent between different MCC grades from different sources. Some partial comparisons on a few products had been published in the literature (64, 84, 91, 107-112). Thus, we compared four model MCC materials for their basic compressional properties, their frictional properties and the mechanical strength of the finished tablets. (Table 10). Some of the characteristics (cristallinity index, moisture content, particle size) of the tested products can be found in Table 6.

For a fixed compression pressure, the higher the crystallinity of the material, the more work of compression, W_U, seems to be required, giving less dense compacts (higher porosity). The plasticity indices of the four samples are however very close and no trend is discernable for the elastic recovery.

Note in particular that the two materials which differed the most in crystallinity, i.e. Avicel PH-101 and Unimac MG-100, give compacts of similar tensile strength and Brinell hardness, but that their work of failure (the so-called toughness) differs by a factor of more than 2. Incidentally, it also should be

TABLE 10
Compared Compression Properties and Characteristics of the Tablets Prepared from Various MCC Brands at 100 MPa (64).

Parameter[1]	Avicel PH-101	MCC type 101	Indocel 80	Unimac MG-100
Powder characteristics				
Crystallinity index (%)	82	74	58	53
Moisture content (%)	5.6	3.5	6.0	3.8
Basic compression properties (prelubricated die)				
W_U (J)	10.75	10.97	8.42	8.55
W_{ED} (J)	1.15	1.33	1.16	0.90
PL (%)	85.1	86.0	84.7	88.0
η^2	0.52	0.53	0.54	0.56
$P_{R_O}{}^3$ (MPa)	3.8	2.8	2.9	2.4
ER[4] (%)	6.0	8.4	8.7	4.5
Porosity (%)	15.2	19.3	11.8	7.0
Frictional properties (unlubricated die)				
W_L (J)	12.56	11.81	9.31	9.57
F_D (kN)	3.06	3,13	1.65	1.18
R	0.737	0.728	0.853	0.893
$W_{FR}{}^5$ (J)	1.93	1.45	0.74	0.63
FRR[6]	15.4	12.3	7.9	6.6
μ_2	1.42	1.37	0.86	0.61
$F_{L_O}{}^7$ (N)	259	205	37	0
F_E (N)	312	260	121	56
Mechanical strength of tablets (unlubricated die)				
Porosity (%)	17.2	20.3	13.8	9.6
$F_x{}^8$ (N)	331	220	152	365
$W_f{}^9$ (mJ)	34.0	21.6	10.8	80.1
$\sigma_x{}^{10}$ (MPa)	5.1	3.2	2.3	5.5
σy^{11} (MPa)	14.5	11.2	8.3	19.9
$\sigma_z{}^{12}$ (MPa)	2.3	1.5	0.3	1.6
H (MPa)	26.2	24.6	16.6	25.3
$IR_1{}^{13}$	2.84	3.52	3.56	3.41
$IR_2{}^{14}$	0.44	0.46	0.12	0.28
Friability (%)	2.5	2.9	10.2	4.2

[1]For many symbols, see Table 8; [2]Ratio of the radial to axial stress at maximum pressure; [3]Residual die wall pressure; [4]Elastic recovery according to Eq 10; [5]Work of friction according to Järvinen and Juslin (113); [6] Friction ratio = W_{FR} / W_U x 100; [7] Residual force on the lower punch immediately before ejection; [8] Diametral crushing force;[9] Work of failure calculated by integrating the force-displacement diagram during the diametral test; [10] Radial tensile strength; [11]Bending strength; [12]Axial tensile strength; [13]Isotropy ratio 1 = σ_y / σ_x; [14] Isotropy ratio 2 = σ_z/σ_x.

mentioned that the claim of a high residual die wall pressure as an indicator of strong compacts being formed, is not valid here.

The four MCC products demonstrate different frictional properties, especially at compression. Avicel PH-101, for instance, generates much more friction than Unimac MG-100 (higher F_D, W_{FR}, FFR, μ_2 and F_{Lo} values, lower lubrication ratio R). The ejection force is increased but remains very low. From that study, no general conclusion can be drawn, maybe because the products differ considerably in their moisture content.

Effect of moisture content

In the previous example, MCC powders were used as received from the manufacturers but it has been already been seen that some basic mechanical properties of MCCs are moisture dependent (see Fig. 1 for instance). The effect of moisture content on the strength of tablets has already been reported long time ago in the literature (5, 76, 97-99, 108, 114-116). Moisture content may affect the strength of the tablets during their manufacture, but also during storage if the tablets are placed in a different environment. Only the first case will be discussed here. Figure 4 illustrates the effect of water content on various parameters of Avicel PH-101 compressed at 10 kN.

Elastic recovery (Eq. 10) and the plastic compression term (Eq. 14) slightly decrease with moisture content. The tensile strength of the formed compacts follows the same trend while for the ejection force, the decrease is much more pronounced because here water acts as a lubricant by forming a film on the surface of the particles. Malamataris et al. (99) also observed a decrease in compact tensile strength but no data were available for MCC containing less than about 2.5% water.

Slightly different, and maybe more logical results were found by Wenzel and Kala (108) for Avicel PH-101 and various Heweten types (VEB Freigurger Zellstoff- und Papierfabrik Weissenborn, Freiberg, Germany) (Fig. 5).

When considering the Avicel PH-101 (Fig. 5, left) and Heweten 40 (Fig. 5, right) profiles, a molecular explanation can be given. Up to about 3% moisture (based on the penetrable amorphous portion only) water is tightly bound as one molecule of water per anhydroglucose unit. Water becomes part of the material, decreases the interparticulate distance (117, 118) and increases the particle

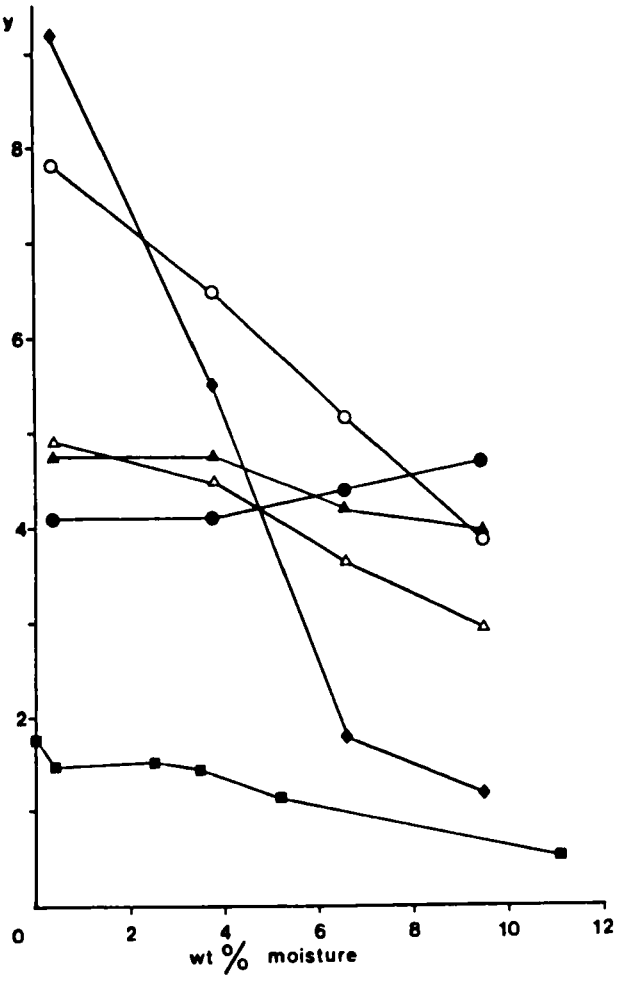

FIGURE 4

Change in mechanical properties of Avicel PH-101 with increased moisture content (adapted from (98)).

Key : ◆, ejection force (y x 10 kN); ○, yield pressure (y x 10 MPa); △, plastic compression (y %); ▲, elastic recovery (y %); ●, packing fraction (y / 10); ■, tablet tensile strength (y x 10 MPa).

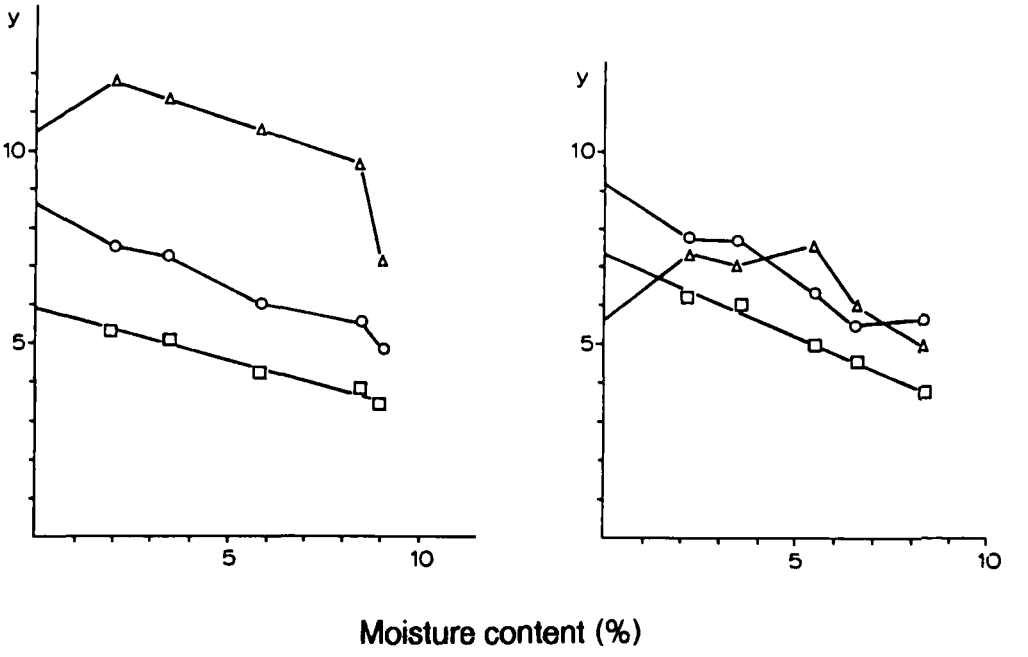

FIGURE 5

Change in mechanical properties of Avicel PH-101 (left) and Heweten 40 with increased moisture (108).

Key : △ , diametral crushing force (y x 10 N); ○ , maximum compressional force (y x 1 kN); □ , work of formation (y x 1 J).

attraction and hence the compact strength. Above 3%, water is less tightly bound and reduces the intermolecular attraction and thus the compact strength.

Wenzel and Kala (108) observed the same pattern for Heweten type 10 but not for type 12. These discrepancies can probably be explained by differences in the crystallinity of the various products and / or in the force of compression used . A maximum in tensile strength of Avicel PH-101 compacts at an intermediate water content has also been observed by Hüttenrauch and Jacob (119) and also by Ragnarsson and Sjögren (97) who investigated the effect of both the water content and the die wall prelubrication on the compaction variables (Table 11).

The sample with a normal water content (4.9 %) produced a much higher tablet strength than both the samples with a low moisture (1.1 %) and a high moisture (8.2 %). The sample with low water content is less deformable (high

TABLE 11

The Effect of Water Content of Avicel PH-101 and Die Wall Lubrication on Compaction Variables and Tablet Diametral Crushing Force (97).

Moisture content	1.1 %		4.9 %		8.2 %	
Die wall lubrication[1]	UL	L	UL	L	UL	L
F_U[2] (MPa)	146	142	141	140	148	148
W_{AN}[3] (J)	9.16	9.52	8.35	8.20	5.99	5.88
ER (%)	10.0	8.0	6.0	6.5	7.5	7.8
P_y (MPa)	104	100	74	72	59	58
μ_1[4]	1.23	0.22	1.79	0.22	0.94	0.13
F_x[5](N)	264	263	360	370	276	269

[1] UL = unlubricated die; L = prelubricated die; [2] Upper punch force; [3] W_{AN} = apparent net work (upper punch work less frictional work and expansion work); [4] Friction coefficient at maximum pressure; [5] Diametral crushing force.

W_{AN} and P_y values). Due to the external and internal lubrication by water, the moist sample is much more compressible but for the reasons already discussed loosely bound water decreases the interparticle attraction and thus reduces tablet strength. Owing to these combined effects, an intermediate moisture content is definitively preferable. Die wall lubrication does not have much influence, compared to moisture content.

Effect of lubricants

The strength lowering effect of lubricants, especially of hydrophobic lubricants, on MCC tablets has been reported many times (12, 66, 76, 86, 120-125). As an example, Fig. 6 shows the effect of the concentration of magnesium stearate and stearic acid on the radial and axial tensile strengths of Avicel PH-102 in comparison with various other DC excipients. Data for dicalcium phosphate with stearic acid are not presented because in neither case were the two tensile strengths markedly affected by the presence of the lubricant. The same holds true

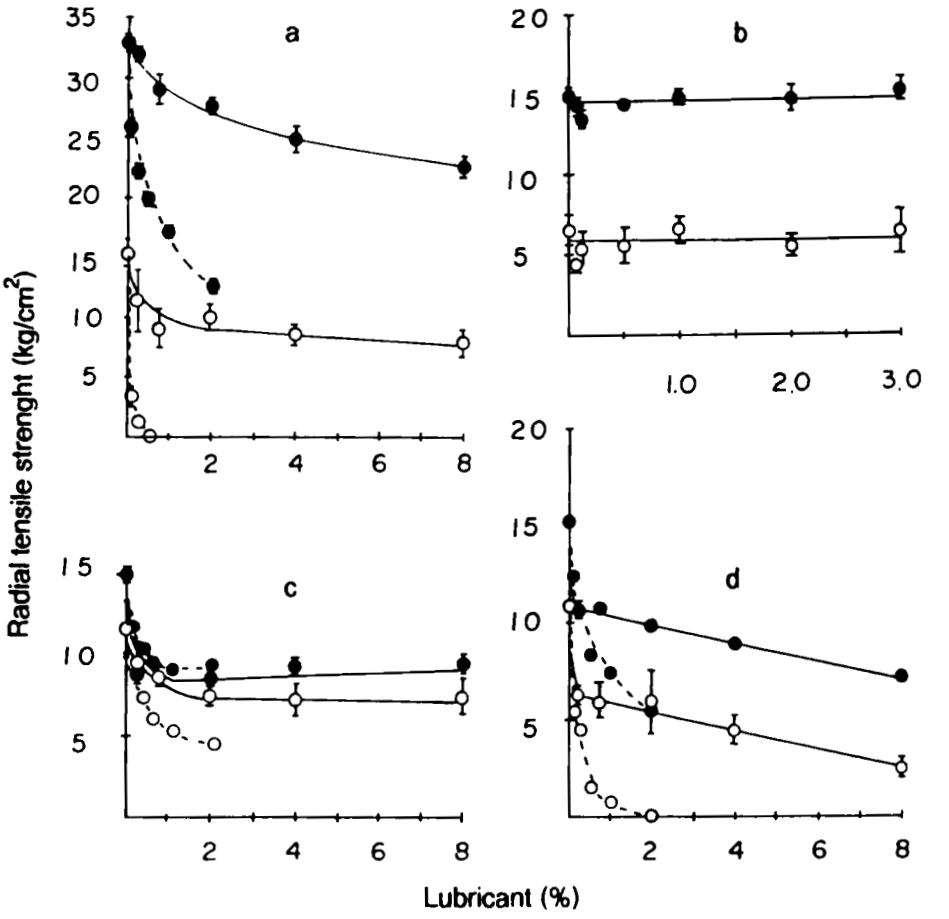

FIGURE 6

Effect of stearic acid (—) and magnesium stearate (---) on the radial (●) and axial (○) tensile strengths of tablets prepared with (a) MCC, (b) dicalcium phosphate dihydrate, (c) anhydrous lactose and (d) aspirin (121).

when adding magnesium stearate (Fig. 6b). In contrast, the two tensile strengths of anhydrous lactose, also a brittle material, were significantly affected by both lubricants, especially by magnesium stearate (Fig. 6c). As expected, the plastic MCC (Fig. 6a) and aspirin (Fig. 6d) gave much weaker tablets.

The effect of the lubricant is not necessarily the same on the radial strength, σ_x, as on the axial strength, σ_z, and may depend on the concentration used with the result that the isotropy ratio IR_2 ($= \sigma_z / \sigma_x$) varies (Table 12).

TABLE 12
Influence of Type and Concentration of Lubricant on the Isotropy Ratio IR_2 of Tablets (117).

Lubricant	Dicalcium phosphate dihydrate				Anhydrous lactose				MCC			
Concentration %	0	0.5	1.0	2.0	0	0.5	1.0	2.0	0	0.5	1.0	2.0
Mg stearate	0.44	0.39	0.44	0.38	0.78	0.62	0.59	0.47	0.47	0.10	-	-
Stearic acid	0.44	-	0.47	0.44	0.78	-	-	0.87	0.47	-	-	0.36
Lubritab[1]	0.44	0.46	0.50	0.50	0.78	0.94	1.02	0.89	0.47	0.34	0.34	0.34
Talc	0.44	0.51	0.52	0.53	0.78	1.06	0.93	0.88	0.47	0.34	0.34	0.36
PEG 4000	0.44	0.58	0.54	0.57	0.78	1.03	1.15	1.11	0.47	0.25	0.22	0.23

[1] Hydrogenated vegetable oil.

The addition of a lubricant does not affect the mechanical isotropy of dicalcium phosphate tablets, whereas opposite trends are observed for anhydrous lactose. With magnesium stearate, the compact is weakened in the axial plane, but is strengthened with other lubricants, and being mechanically isotropic, capping will not occur. In the case of MCC with magnesium stearate, the low value of IR_2 reflects a very weak bonding in the axial direction and indicates that capping is a potential problem. With other lubricants capping is less probable.

It has been suggested in the literature (126) that the susceptibility of a material to magnesium stearate reflects its propensity to fragmentation, a tablet of a material which is plastically deformed, like MCC, giving a lower strength reduction ratio, defined as the ratio of the tensile strength of a compact prepared with the lubricant to that of a compact of pure material. In fact, it has been demonstrated that in addition to the mechanism of consolidation other factors play a role in the effect of magnesium stearate, such as particle size (surface area), particle texture, flowability, mixing time and compaction pressure, by influencing the formation of the lubricant film around the particles (124, 125). The effect of particle size and indirectly that of flowability have been shown by many workers. Vromans et al. (125) have compared the strength reduction ratio of different samples of materials of varying particle size, calculated from their outer surface area measured by permeametry (Table 13).

TABLE 13

Compared Strength Reduction Ratios of Different Preparation of Dicalcium Phosphate Dihydrate, Lactose Microcrystalline Cellulose and Powder CelluloseVarying in their Specific Surface Area, S_W, after Addition of 1 % Magnesium Stearate (125).

Material	S_W (m^2/g)	Crushing force, unlubricated (kg)[3]	Strength reduction ratio
Dicalcium phosphate dihydrate[1]			
Sample 1	0.36	4.5	0.93
Sample 2	0.09	9.0	0.89
Sample 3	0.03	4.2	0.90
Anhydrous lactose[1]			
Sample 1 (32-63 μm)	0.131	18.3	0.67
Sample 2 (250-315 μm)	0.023	14.7	0.31
Lactose monohydrate[1]			
Sample 1 (32-63 μm)	0.117	8.0	0.61
Sample 2 (250-315 μm)	0.021	4.9	0.29
Microcrystalline cellulose			
Avicel PH-105	0.55	21.1	0.77
Avicel PH-101	0.24	16.9	0.17
Avicel PH-102	0.20	15.7	0.07
Budex 2001[2]	0.32	15.0	0.43
Budex 2002[2]	0.19	11.0	0.09
Powdered cellulose			
Elcema P 050	0.51	13.3	0.81
Elcema P 100	0.26	14.4	0.41
Elcema F 150	0.22	13.8	0.05
Elcema G 250	0.10	10.7	0.08

[1] Samples were obtained by sieving; [2] Chemische Fabrik Budenheim, Germany; [3] Different compaction pressures were used for the different materials.

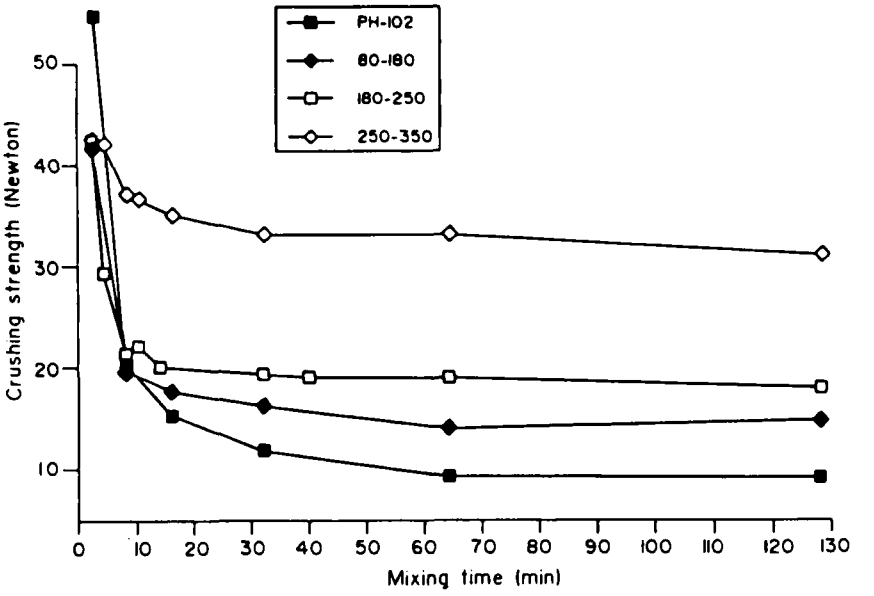

FIGURE 7
Diametral crushing force vs mixing time for sieved fractions of Avicel PH-102 containing 1 % magnesium stearate. Unsieved Avicel PH-102 is indicated with PH-102 (124).

Cleary, fine materials with poor flowability are less susceptible to magnesium stearate due to the incompleteness of the surface film formed. The poor mixing is also a probable reason for the small influence observed for dicalcium phosphate dihydrate containing with magnesium stearate. In fact, if this material is properly coated to 2 % by a solution of a lubricant such as hexanoic acid, strength reduction ratios of 0.31, 0.25 and 0.39 are obtained for the three size fractions, respectively.

The effect of particle size and accessorily that of the mixing time on the tablet crushing strength have been shown by van der Watt (124) who fractionated Avicel PH-102 before admixing with 1 % magnesium stearate (Fig. 7).

Decrease in strength was more pronounced for Avicel PH-102 than for the sieved fractions but these were all in the upper particle size range of the original product. Here, finer size fractions were found more sensitive to the presence of lubricant and mixing time.

Different materials do not have the same sensitivity to mixing time with a lubricant so that comparing blends mixed for the same time may be misleading. In other words, the value of the strength reduction ratio may vary with the mixing time. This is of course not valid for substantially insensitive materials like dicalcium phosphate dihydrate or lactose, but is relevant for instance for celluloses. Vromans et al. (125) obtained in their experimental conditions (load, blender, mixing time, 1 % magnesium stearate) a similar value for Avicel PH-102 and Elcema G 250 (see Table 13). In fact, as these two materials do not have the same sensitivity to mixing time, their observation is valid only for the conditions they used (Fig. 8).

When choosing a special type of MCC or a substitute, it is worthwhile to compare their sensitivity to a lubricant. Thus we calculated the strength reduction ratio of 9 materials of type 1 MCC (claimed to be similar to Avicel PH-101) and 7 MCCs of type 2 similar to Avicel PH-102. The characteristics of the unlubricated powders (in four cases they were second batches of the same brand) are listed in Table 14.

Figure 9 combines the values of diametral crushing force for both lubricated (0.5 % magnesium stearate) and unlubricated MCC compacts, listed by decreasing order of strength reduction ratio.

Big differences are observed, even between batches of the same brand. Generally coarser materials (type 2) seem more sensitive to lubricant. Apart from particle size, other explanations for the big differences observed may lie in the surface texture or the moisture content.

The combined effects of lubricant and moisture content on the compressibility (yield pressure) and compactibility (tensile strength) of Avicel PH-101 have been investigated by Fassihi (116) (Fig. 10)

When comparing only the tensile strength values (the height of the bars) of compacts of pure Avicel and those of Avicel added with magnesium stearate, a considerable influence of the moisture content was observed. Strain rate sensitivity values were approximately 0.43 at the low moisture content (1.5%), 0.86 at the optimum moisture content of 5% and 0.75 at the high moisture content (8%). Note also that the deleterious effect of magnesium stearate nearly disappeared when colloidal silica was added to the binary mixes, a fact confirmed by the findings of Staniforth and Ahmed (123), but already observed long time ago by Lerk et al. (127) for pregelatinized starch and sodium chloride compacts.

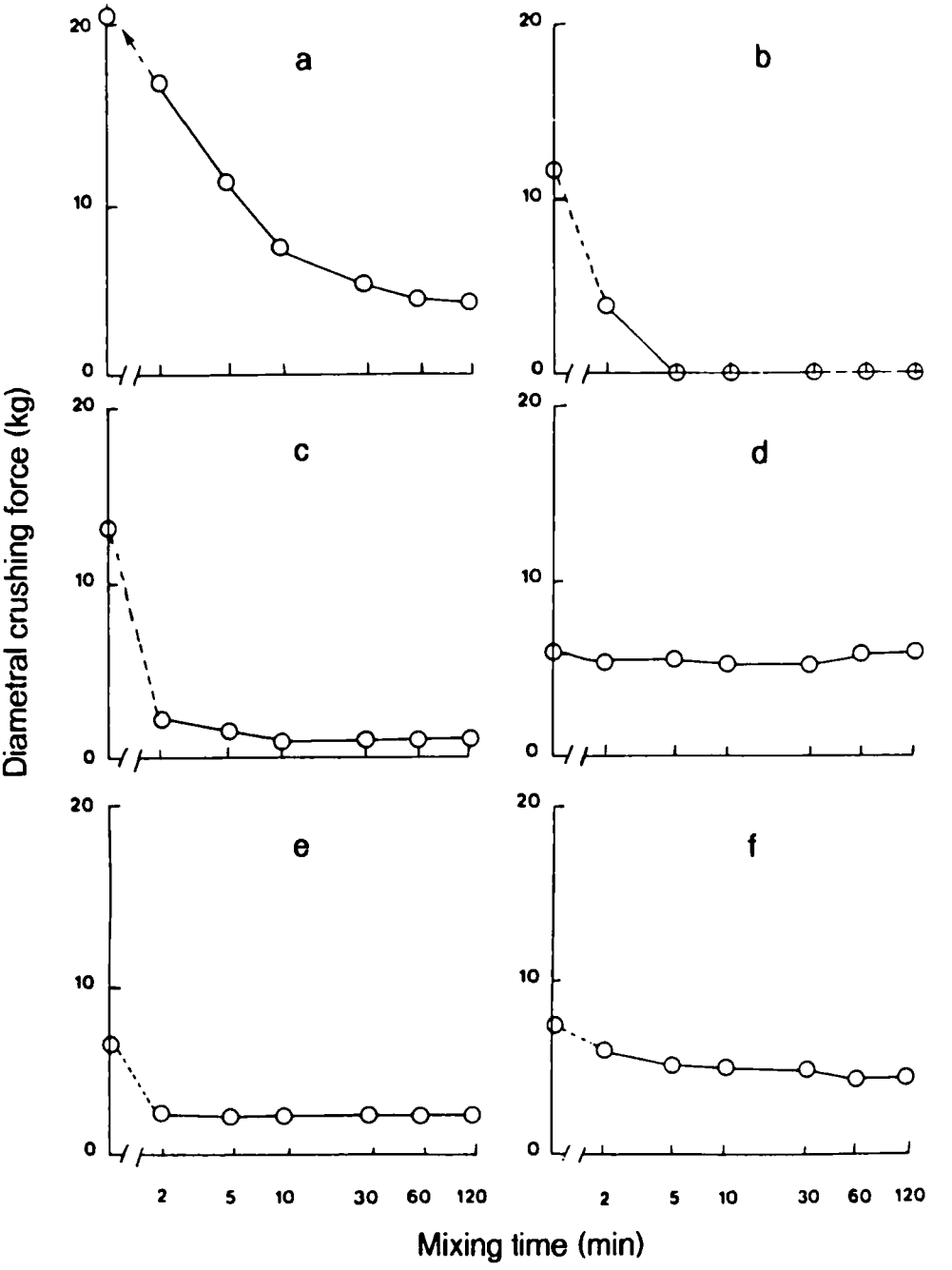

FIGURE 8
Diametral crushing force vs mixing time for (a) Avicel PH-102, (b) Starch 1500 (c) Elcema G 250, (d) Emcompress, (e) lactose monohydrate, and (f) anhydrous lactose (120).

TABLE 14
Characteristics of Unlubricated MCC Powders (86)

Material	Moisture content (%)	True density (g/cm^3)	d_{gw}[1] (μm)	σ_g[2]	d_{vs}[3] (μm)
Avicel PH-101, batch 1	4.7	1.532	40	1.74	34
Emcocel 50M	5.0	1.543	43	1.94	35
Avicel PH-101, batch 2	4.6	1.553	46	1.82	39
Sanaq 101 L[4]	4.4	1.542	40	2.29	28
Unimac MG-100	3.7	1.547	39	1.99	31
MCC type 101, batch 2	3.8	1.555	42	2.95	23
Medicel 101[5]	5.1	1.541	49	2.20	36
MCC type 101, batch 1	5.0	1.537	47	2.62	30
Ex Cel[6]	4.5	1.537	40	4.10	15
Avicel PH-102, batch 1	4.9	1.564	73	2.25	53
Avicel PH-102, batch 2	5.1	1.537	82	2.65	51
Emcocel 90M	4.6	1.557	77	2.41	52
Medicel 102[5]	5.1	1.542	64	2.48	42
MCC type 102, batch 2	5.0	1.535	79	2.94	44
MCC type 102, batch 1	5.1	1.536	75	2.95	42
Unimac MG-200	3.8	1.541	105	3.69	45

[1] Weight geometric mean diameter; [2] Geometric standard deviation; [3] Volume-surface mean diameter; [4] Wei Ming Pharm., Taipei, Taiwan (Pharma Trans Sanaq, Basle, Switzerland); [5] Cargile, Taipei, Taiwan (G. Walther, Zürich, Switzerland); [6] Cellulose Products of India, Ahmedabad, India, (Sitco, Highland Park, USA). The other manufacturers are mentioned in Table 5.

The concomitant effect of both the mixing time with the lubricant and of the moisture content is further illustrated for a formulation containing MCC (Avicel PH-102) 97%, potassium phenethicillin 2% and magnesium stearate 1% (Fig. 11).

MCC having a 4.8% water content gave stronger tablets with higher disintegration times than MCC with a 2% water content. The mechanical strength decreased with increasing mixing time. Surprisingly, the same was observed for

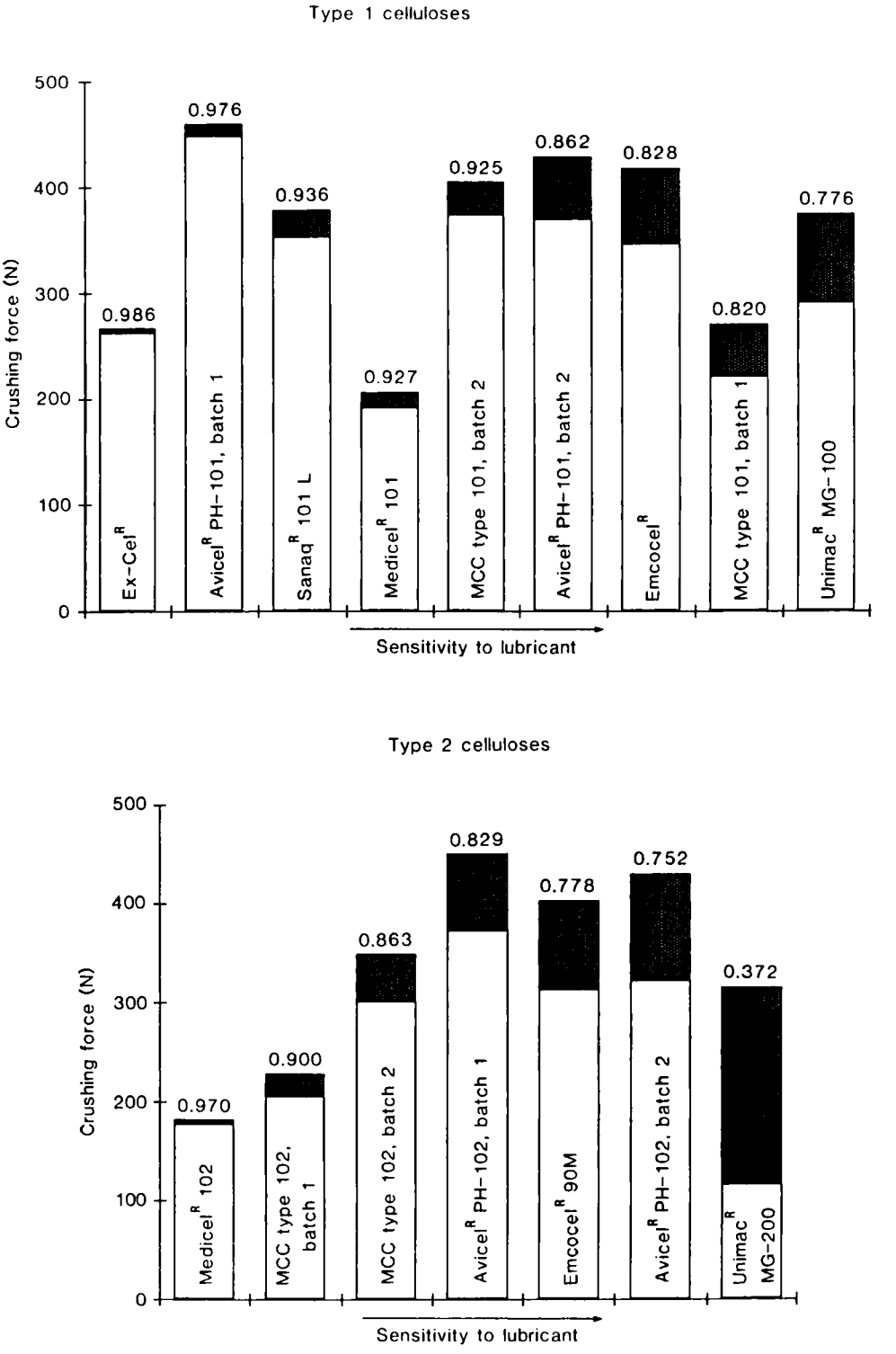

FIGURE 9

Crushing strength values for unlubricated compacts (shaded plus unshaded areas) and lubricated compacts (unshaded areas only) prepared at 100 MPa. Figures are for strength reduction ratios (86).

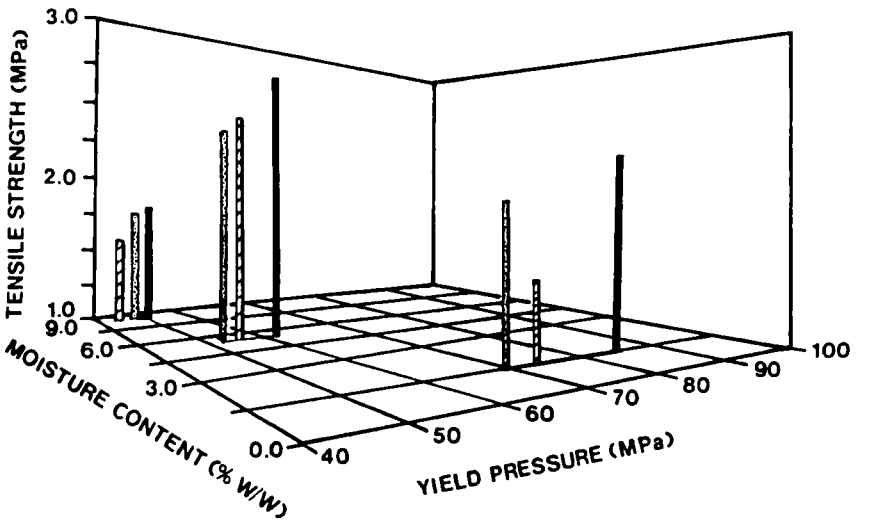

FIGURE 10

Interrelationships between yield pressure, moisture content and tensile strength of compacts prepared from (■) Avicel PH-101 alone, (▨) Avicel PH-101 + 0.5% magnesium stearate, and (▩) Avicel PH-101 + 0.5 magnesium stearate + 2% colloidal silica (116).

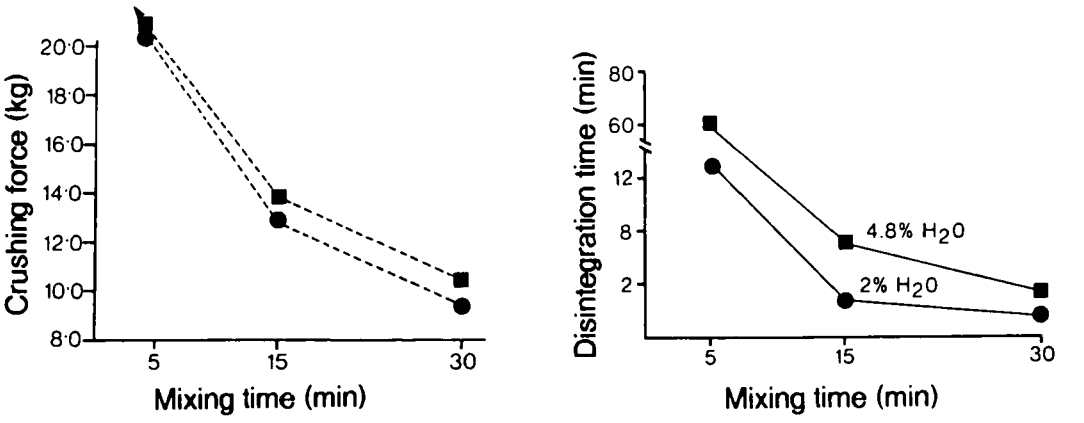

FIGURE 11

Effect of mixing time on the crushing force (left) and disintegration time (right) of 2% phenethicillin tablets prepared with MCC containing (■) 4.8% or (●) 2% moisture and lubricated with 1% magnesium stearate (128).

the disintegration time, suggesting that bonding strength and porosity of the tablets were the dominant factors affecting disintegration, and not the hydrophobic lubricant film as such.

Effect of added diluents or active ingredients

Up to this point, the properties of pure MCC products or lubricated were reviewed, but any MCC represents rarely more than approximately 60% of direct compression formulations. If the drug is highly dosed and is a poorly compactible substance - say paracetamol or ascorbic acid - MCC will be used alone owing to its outstanding properties as a dry binder and the drug content will generally not exceed 40-50 %. If the drug is of satisfactory compactibility - say hydrochlorothiazide or aspirin - or more frequently if its content is low in the formulation (e.g. prednisone), MCC will be used at a level of 20 to 40 % in mixture with another diluent or filler such as lactose or dicalcium phosphate dihydrate. This is generally done to reduce the cost of the final tablets and improve the flow properties of the formulation.

The two situations do not differ in substance : in both cases the problem is to find out the minimum concentration of MCC necessary to achieve good compactibility of the blend. In the first case, the drug is a component of a binary system whereas in the second case the diluent is a component of a ternary system which reduces to a binary system when the drug content is low. For reasons of convenience and because it is the usual practice in the literature, we will examine the two situations separately. We will give the results obtained using the various approaches described previously and will examine whether factors such as the lubricant and the moisture noted for pure MCC still have an influence on blends with MCC. When available, comparative data for different MCC products will also be presented. The incidence of adding a high proportion of drug on the mechanical strength of MCC tablets is our main interest but some attention will also be paid to disintegration.

MCC-drug systems

Interesting basic data are available for the MCC-paracetamol system (19,47,76,78,129-135). Thus, the effect of the relative proportion of the two

TABLE 15

Plasto-elasticity Ratio, Net Bonding Energy, % Energy Ratio of Avicel PH-101 - Paracetamol Mixtures, and Radial Tensile Strength and Friability of Corresponding Tablets Compressed at 7 kN (adapted from (78))

Mass fraction of MCC	ER/PC ratio	Net bonding energy[1] (J/g)	% Energy ratio[2]	σ_x[3] (MPa)	Friability (%)
0	1.92	9.1	18.2	Capping	Capping
0.15	1.44	11.4	12.5	0.59	4.05
0.30	1.28	14.0	11.3	1.36	1.63
0.50	1.11	16.6	9.4	2.62	0.64
0.75	0.85	20.4	7.4	5.25	0.40
1.0	0.30	29.2	6.4	6.54	0

[1] (1st compression energy - relaxation energy) - mean recompression energy;[2] (Mean recompression energy-relaxation energy)/net bonding energy; [3] Radial tensile strength.

ingredients on the plastic compression PC (Eq. 14), the elastic recovery ER (Eq. 15), the plasto-elasticity ratio (Eq. 16) and the radial tensile strength of the tablets were investigated (47,76,78). Malamataris et al. (47) studied the effect of the mixture composition and of the particle size, and they found that satisfactory tablets were obtained when the ratio ER/PC < 9. In particular, capping was observed when a coarse fraction of paracetamol was used. Bangudu and Pilpel (76) noted a minimum in ER/PC value and a maximum in tablet tensile strength for a given moisture content. Yu et al. (78) determined in addition to the previous parameters some terms of compression work, among which what the authors called the energy of bonding and the energy ratio. Table 15 lists values for the compression terms, and for the mechanical strength of the formed tablets (radial tensile strength and friability) as a function of the mass fraction of MCC.

In the conditions used, capping occured when the ER/PC ratio and the % energy ratio were greater than 1.5 and 15%, respectively, i.e. when the mass fraction of Avicel PH-101 was less than 0.15. Based on the radial tensile strength and the friability data, a proportion of MCC of 50% would be optimal according to the above authors, but mention should be made that a loading period of 60 s was used.

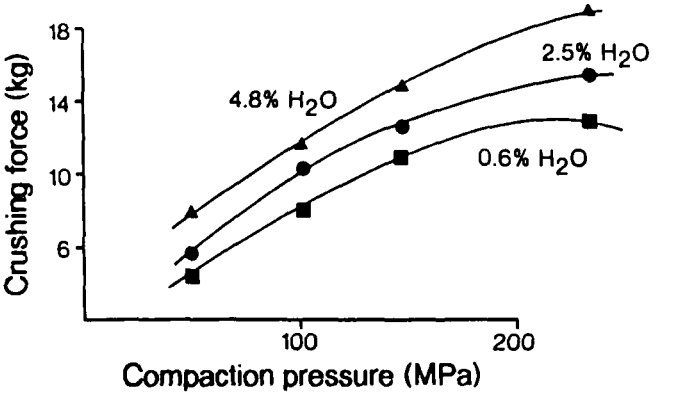

FIGURE 12
Diametral crushing force vs compaction pressure for paracetamol tablets containing MCC, at various moisture levels (129).

A more realistic case has been addressed by Khan et al. (129) who investigated the effect of both moisture content and compaction pressure on the characteristics of tablets made of 49.5% Avicel PH-102, 49.5% paracetamol and 1% magnesium stearate (Fig. 12). The crushing strength progressively increased with higher compaction pressures, following the general pattern for pure MCC or formulations of MCC containing low doses of active substances. Thus, when admixed with an equal portion of paracetamol, MCC retained its original compression properties.

In contrast, a formulation containing 30% Avicel PH-102, 68% potassium phenethicillin and 2% magnesium stearate showed either a maximum or a plateau of mechanical strength suggesting some capping or laminating tendency of the tablets (128). For this drug, the critical content is thus less than 68%. Disintegration of the tablets was very rapid for all preparations except for paracetamol tablets compressed at higher pressures. For both formulations compactibility decreased progressively with decreasing moisture content. The same observation was made by Ritter and Sucker (136) for MCC formulations containing other active ingredients. A precise specification for the water content is therefore necessary, in particular if MCC is partially dried because used with moisture sensitive drugs.

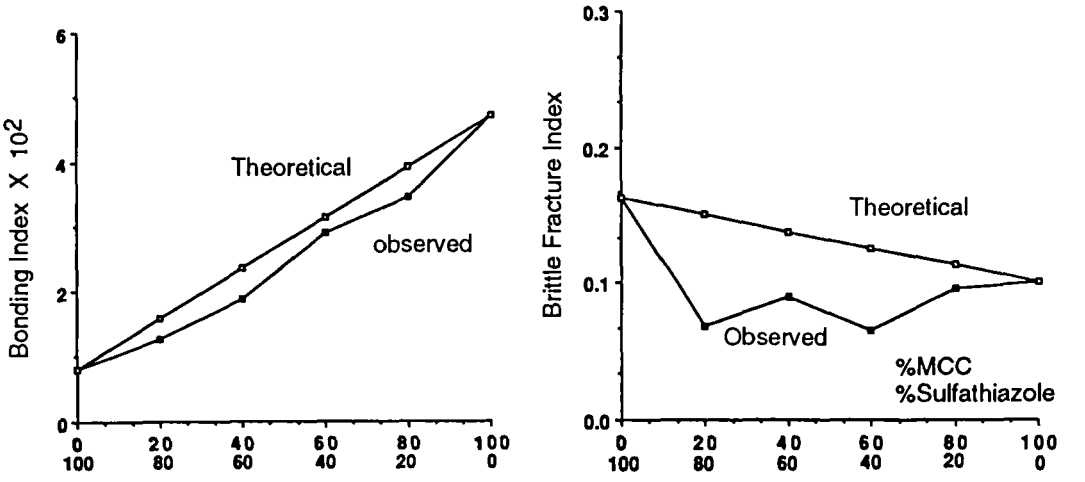

FIGURE 13
Change in bonding index (left) and brittle fracture index (right) of compacts, prepared at a solid fraction of 0.81 as a function of mixture composition (66).

Also concerning paracetamol, it is noteworthy that Lamberson and Raynor (19) were able to prepare acceptable tablets containing 61.9% of the drug with Avicel PH-101 or Avicel PH-102 but that they used a granular quality of paracetamol which probably exhibited some compactibility. In fact, Parvez (133) also succeeded in producing acceptable tablets with a high proportion of granular paracetamol (65%) but this time Avicel PH-102 proved to be much poorer.

Other basic studies were published concerning blends with other drugs. Thus, Bolhuis et al. (137) investigated the effect of particle size of aspirin on the characteristics of Avicel PH-101 based tablets. At a compression force of 20 kN, strong tablets could be prepared containing approximately 85% of drug, whether crystalline or powdered.

Humbert-Droz et al. (58) reported on hydrochlorothiazide formulations based on dicalcium phosphate dihydrate (DCP) or Avicel PH-101. The yield stress of the DCP mixtures changed appreciably when the proportion of drug was more than 50%, but the diametral crushing force of the resulting tablets did not vary because both DCP and hydrochlorothiazide have identical compactibilities. In contrast, formulations containing MCC had all similar P_y values, both components being plastically deforming materials, but the crushing force

TABLE 16

Characteristic Properties of Sulfathiazole Tablets Prepared with two Different MCC Products (139)

MCC product	Compaction force (kN)	Porosity (%)	Crushing force (kg)	Friability (%)	C.U.[1] (CV%)	Disintegration time (s)	Dissol. $t_{50\%}$ (min)[2]
Avicel PH-101	10	18.2	6.2	1.7	0.7	59	40
Heweten 40	10	16.9	3.6	2.4	1.0	45	9
Avicel PH-101	20	12.5	10.9	1.1	0.5	116	> 60
Heweten 40	20	14.0	7.3	1.7	1.3	77	23

[1] Content uniformity expressed as coefficient of variation; [2] Time for 50% of the drug to dissolve.

increased with increasing proportions of MCC and the critical drug content was probably above 75%.

A basic investigation of the MCC-sodium sulfathiazole system was made by Williams and McGinity (66) who mesured both Hiestand's bonding and brittle fracture indices (Fig. 13).

As expected, the bonding index increased with increasing Avicel PH-101 percentage but a negative interaction was observed when compared to the theoretical values assuming an additive behavior of the BI values of the two ingredients. This was even more pronounced for the brittle fracture index which was lower at some intermediate proportions than that of the pure materials. Tensile strength values were given by the authors but were those of the square compacts used to determine the Hiestand's tableting indices. It is therefore difficult to draw a definite conclusion on what would be the mechanical strength of conventional tablets. Note that Chowan and Yang (138) also found deviations from linear additive behaviors when investigating other MCC-based systems.

Sulfathiazole-based tablets containing two different MCC grades were compared by Kedvessy et al. (139). The formulation contained 250 mg sulfathiazole, 70 mg Avicel PH-101 or Heweten 40, 10 mg talc, 7 mg colloidal silica and 3 mg magnesium stearate. Table 16 lists the characteristic properties of the two sulfathiazole-containing tablet batches prepared at 10 and 20 kN.

The dry binding properties of Avicel PH-101 (at about 0.2 mass fraction) were superior to those of Heweten 40 (see crushing force and friability values) at both compaction forces. The content uniformity was better too but not the dissolution efficiency for which Heweten proved to be a much better promoter.

The tableting properties of Avicel PH-101 and PH-102 were compared for granular paracetamol formulations (see above), but also for ascorbic formulations. With 60% of fine crystals, tablets based on Avicel PH-101 and PH-102 were equivalent but of low mechanical strength (19). With finely granular ascorbic acid, higher dilution ratios were obtained with Avicel PH-101 (70%), an experimental powdered cellulose (60%) and again Avicel PH-102 failed to produce acceptable tablets (132). Emcocel 50M and Emcocel 90M were also evaluated in comparison with the standard Avicel PH-101 as dry binders for highly dosed formulations (112). Tablets of aspirin (30 and 70%), phenobarbital (30%) and a spray-dried plant extract (36%) gave tablets of good quality in terms of weight variation, mechanical strength, as well as disintegration and dissolution characteristics.

MCC-filler systems

In the case of formulations with a low drug content, MCC, if used, is admixed with a cheap filler or diluent, most of the time lactose or dicalcium phosphate. We will thus first discuss basic data concerning binary MCC-filler systems and then examine the implications of the presence of a drug. Some twenty years ago, two different research groups published simultanously the tableting characteristics of mixes of lactose or dicalcium phosphate dihydrate with dry binders or disintegrants among which MCC.

Delattre and Jaminet (16,17) studied the effect of various agents, incorporated at 20%, on the compactibility of lactose monohydrate and dicalcium phosphate dihydrate (Emcompress special). Avicel PH-101 or PH-102 appeared to have the best binding capacities for both fillers. Dicalcium phosphate-based tablets were generally stronger than lactose-based tablets, at all compaction forces used. Tablets of lactose alone or added with MCC disintegrated very rapidely (less than 2 min for 20% Avicel PH-101), whereas tablets with dicalcium phosphate alone or with Avicel PH-101 (or PH-102) did not disintegrate within 30 min unless the

proportion of MCC was at least 15% and the compaction force not more than 1000 kg.

Lerk et al. (13) found somewhat similar results with Emcompress special and lactose monohydrate added with various dry binding-disintegrating agents in different proportions. They also gave data for mixes of Avicel with dextrates, dextrose monohydrate and anhydrous lactose and the results confirmed that combinations of dicalcium phosphate dihydrate or lactose with MCC result in blends with an excellent overall performance for direct compression.

The dicalcium phosphate dihydrate - Avicel PH-102 system was later extensively studied by Wells and Langridge (131). The strongest tablets in terms of tensile strength and friability were obtained for the 90:10 ratio. Additionally, the reworking potential of a mixture composed of 2 parts of MCC and 1 part of dicalcium phosphate was examined. The mixture was compressed, the tablets were milled and retableted. The reworking potential was poor, both the tensile strength and the friability being impaired.

The compressibility and compactibility of the Avicel PH-102 - lactose system have been investigated by Jetzer (140). Experimentally determined values for compactibility, H_0, and compression susceptibility, γ (Eq. 2), showed some deviation from the theoretical profiles calculated using Leuenberger's equations for binary systems (141).

A positive interaction has been recently observed by Garr and Rubinstein (142) for the dicalcium phosphate-Emcocel 90M system. In addition to the effect of the compaction speed they noted a maximum in radial tensile strength for a proportion of 75% MCC and 25% dicalcium phosphate dihydrate.

It is also worthwhile to mention the work of Duberg and Nyström (134) dealing notably with the effect of the proportion of Avicel PH-105 on the radial and axial tensile strenghs as well as on the isotropy ratio IR_2 (see Tables 10 and 12) of tablets based on lactose monohydrate, dicalcium phosphate dihydrate, sodium chloride, sodium bicarbonate, paracetamol and aspirin. Very variable tendencies were observed according to the densification and bonding properties of the materials mixed with MCC.

The tableting characteristics of MCC-filler mixtures containing a drug in a low or medium dose have been investigated extensively (112,130,131,143-146). In a general evaluation of tablet lubricants in direct compression, Bolhuis et al. (130) studied the effect of the type of lubricant and mixing time on various

TABLE 17
Effect of Mixing with Lubricant on Ejection Force, Diametral Crushing Force, Friability and Disintegration Time, respectively, of Prednisone Tablets Compressed at 20 kN (130).

Lubricant	Mixing time (min)	Ejection force (N)	Crushing force (kg)	Friability (5)	Disintegration time (s)
-	-	1750	9.5	< 0.1	8
Boeson[1] VP 1%	5	190	8.7	< 0.1	20
	15	190	8.4	< 0.1	16
Sterotex[2] 1%	5	250	8.1	0.2	14
	15	300	7.4	< 0.1	13
Magnesium stearate	5	180	5.6	0.1	12
	15	150	4.7	0.5	20

[1] Mixture of hydrogenated beef tallow and hydrogenated soya oil; [2]Hydrogenated cotton seed oil.

characteristics of prednisone tablets. These contained 2% of active ingredient, 0.5 or 1% lubricant, plus lactose monohydrate and Avicel PH-102 in a ratio of about 3:1 (Table 17).

Even in presence of a high proportion of the brittle lactose monohydrate, magnesium stearate drastically diminished the mechanical strength of the tablets. The effect was more pronounced with a 15 min mixing time. Hydrogenated oil additives were as much as effective lubricants as magnesium stearate but had nearly no effect on the crushing strength and friability of the tablets. Disintegration was very rapid for all tablet batches.

Wells and Langridge (131) incorporated extra fine paracetamol powder in an Avicel PH-102-dicalcium phosphate dihydrate matrix. 5 % sodium starch glycolate and 0.5 % magnesium stearate were present. Interestingly, the tensile strength of the tablets reached a maximum for a given MCC-filler ratio, which was dependent on the drug concentration (Fig. 14). The inclusion of an increasing level of drug and / or the addition of a disintegrant increased the proportion of dicalcium phosphate required for optimum compression. A critical drug content of 30% was found for this system.

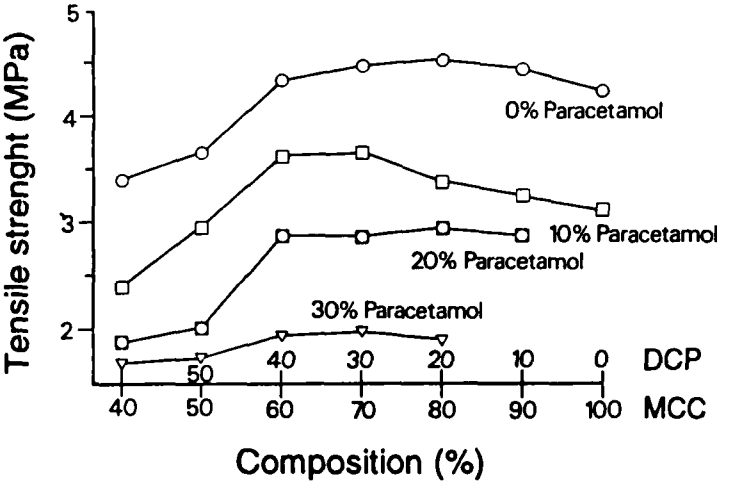

FIGURE 14
Tensile strength of tablets prepared with MCC and dicalcium phosphate dihydrate in various ratios and containing extra fine paracetamol (131).

An interesting work on the effect of drug solubility on the disintegration time of MCC-filler tablets is that of Chilamkurti et al. (145). A different picture was obtained when hydrochlorothiazide or amitryptiline hydrochloride was incorporated at a level of 10% in a dicalcium phosphate dihydrate-Avicel PH-101 matrix (Fig. 15).

Adding 10% hydrochlorothiazide to the matrix did not change the tablet crushing strength, especially when the formulation contained more than 50% dicalcium phosphate. With 10% amitryptiline hydrochloride, a significant decrease in strength was observed at any matrix composition. For all three cases, tablet crushing strength increased as expected with the increasing proportion of MCC.

Disintegration varied markedly with the drug incorporated. The disintegration time of formulations containing the relatively water-insoluble drug hydrochlorothiazide did not change significantly from that of the placebo formulations. In contrast, with the formulations containing the water-soluble drug amitryptiline hydrochloride, the disintegration time increased drastically when the MCC concentration was decreased beyond 75%. Moreover, dissolution rate was independent of disintegration time for hydrochlorothiazide formulations, whereas

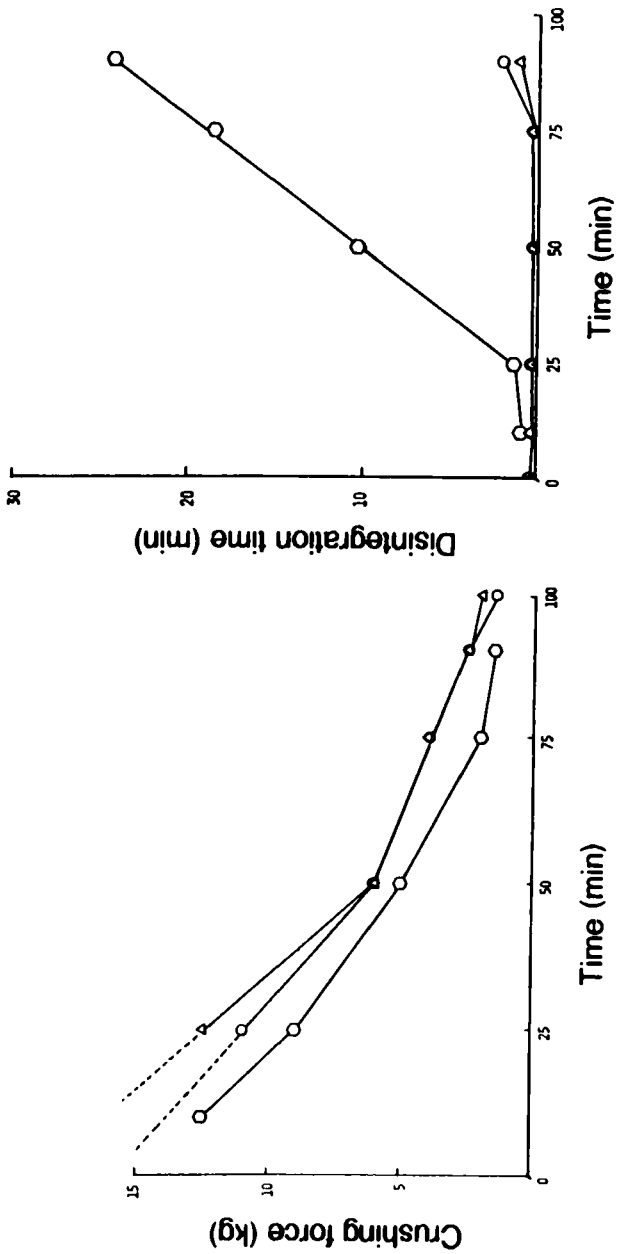

FIGURE 15
Effect of matrix composition on the diametral crushing force (left) and disintegration time (right) of tablets containing (△) no drug, (○) 10% hydrochlorothiazide or (○) amitryphiline hydrochloride compressed at 8.9 kN (145).

for amitryptiline hydrochloride formulations, dissolution rates tended to follow disintegration pattern. The dissolution rate decreased significantly when the concentration of MCC was decreased beyond 25% for the hydrochlorothiazide tablets and beyond 75% for the amitryptiline hydrochloride tablets. Note that when the concentration of the water-soluble drug was increased beyond 15%, MCC was capable of acting as a disintegrant at a 10% level, so that the disintegration time decreased with a concomitant increase in dissolution rate.

Similar results were obtained by Plaizier-Vercammen et al. (112) who compared three MCC brands in tablets containing 60% aspirin and a 3:1 filler-MCC matrix. Tablets did not disintegrate within 15 min when dicalcium phosphate was used, whereas disintegration was quite rapid in the presence of lactose. When a disintegrant was added, dicalcium phosphate dihydrate based tablets disintegrated in few minutes, but disintegration times became longer for lactose based tablets.

As a conclusion, formulations based on MCC can be reasonably well predicted in terms of mechanical strength of resultant tablets whereas the disintegration and drug dissolution pattern may vary considerably and must be given adequate attention when formulating.

FLOW PROPERTIES OF MCC POWDERS AND WEIGHT VARIATION OF TABLETS

MCC products are known to exhibit poor flow properties, which can lead to excessive tablet weight variation. Except the new Avicel PH-200, none of the MCC products are free flowing powders. Direct measurement of flow rates is therefore not possible unless vibratory hopper techniques are used. Indirect methods include the determination of the blocking aperture size, the Hausner ratio or the Carr index. Values obtained using these techniques are poorly reproducible and can be compared only if determined by the same authors. A more trustworthy method for evaluating the flow characteristics of cohesive powders is to use shear cells. Table 18 compares the flow characteristics of the pioneer Avicel PH-101 with those of other common diluents for direct compression and gives corresponding coefficients of weight variation for tablets lubricated with 1% magnesium stearate and produced either on a Manesty SP1 single punch machine (8 and 10 mm punches) or a Manesty Betapress rotary machine (5 mm punches). Data are listed by increasing tablet weight variation.

TABLE 18

Comparative Flow Properties of Common DC Diluents, and Weight Variation of Tablets Prepared on a Single Punch Machine and a Rotary Machine (147)

Material	Flow properties								Weight variation (%)[9]		
	Angle of repose	Flow rates (ml/s)		H[6]	T[7] (kN/m^2)	C[8] (kN/m^2)	FF[8]	1/FF[8]	Excentric		Rotary
		20 mm[4]	Manesty[5]						8 mm	10 mm	5 mm
Emcompress	49	59.6	34.4	1.23	0.13	0.16	14.8	0.067	0.53	0.62	0.66
Emdex[1]	53	63.7	46.6	1.09	0.18	0.20	9.7	0.103	0.71	0.70	-
Dipac[2]	54	92.0	37.8	1.19	0.14	0.21	11.7	0.085	0.82	0.87	0.81
Lactose spray-dried	65	14.1	no flow	1.28	0.10	0.31	6.8	0.147	1.37	1.71	1.05
Starch 1500[3]	70	no flow	no flow	1.32	0.18	0.51	4.8	0.211	1.58	-	1.69
Avicel PH-101	70	no flow	no flow	1.45	0.55	0.69	3.8	0.263	3.59	5.66	1.78

[1] Dextrates formerly named Celutab (E. Mendell); [2] Compressible sucrose (Amstar); [3] Formerly named Sta-Rx 1500;
[4] 20 mm orifice; [5] Hopper of a Manesty SP1 machine; [6] Hausner ratio calculated from the compressibility K, using: H = 100/(100-K);
[7] Tensile strength obtained using a Warren-Spring tester; [8] Cohesiveness, flow factor and reciprocal of flow factor determined using a Jenike shear cell; [9] powders were added with 1% magnesium stearate.

Avicel PH-101 exhibited the worse flow properties by all techniques and produced tablets with the highest weight variation. Some relationship seems to exist here between weight variation and flow properties as determined by simple methods but this may be fortuitous when considering the poor reproductibility of the flow data (especially the angle of repose values). The best correlation for weight variation was obtained with the cohesiveness, C, of the powders, but the flow factor, FF, and its reciprocal are also good predictors.

Comparable weight variation data can be found in the literature concerning Emcompress, Emdex, Starch 1500 and Avicel PH-101. The authors (107, 122) found the highest variability with the MCC products but noted lower coefficients of variation with Emdex than with Emcompress. In this cases, the tablets contained 0.5% magnesium stearate.

The following values of cohesiveness, C, and flow factor, FF, were measured by Marshall (147) for the various Avicel-PH grades :

Avicel PH	C (kN/m^2)	FF
102	0.113	9.2
101	0.112	6.9
103	0.112	5.4
105	0.320	2.8

The higher value of the flow factor certainly explains the better weight reproductibility of Avicel PH-102 over Avicel PH-101 which was observed for instance by the two above-mentioned research groups (107,122). Comparative data for the four Avicel grades will be discussed later.

Conventional MCC products, when tested pure, definitely exhibit with together powdered celluloses the poorest flow characteristics of all well known DC excipients. We will examine first the incidence of this undesirable properly on weight variation of pure MCC tablets and then give some data concerning systems in which MCC was admixed with drugs or other diluents.

It has been suggested that adding some lubricant to MCC powders would increase their flowability and therefore reduce the weight variation of the resulting tablets (19,149). Table 19 shows the effect obtained when adding magnesium stearate to Avicel PH-101 and Avicel PH-102 powders.

TABLE 19

Effect of Adding Magnesium Stearate at Various Concentrations on the Flow Characteristics of Avicel PH-101 and Avicel PH-102 and on the Weigh Variation of Corresponding Tablets (19)

	Avicel PH-101				Avicel PH-102			
Magnesium stearate (%)	0	0.25	0.5	1.0	0	0.25	0.5	1.0
Flow rate[1] (g/min)	50	70	75	80	55	60	60	60
Flow variation (%)	5.5	13.5	12.0	17.5	1.1	1.0	1.3	2.2
Hausner ratio	1.35	1.40	1.32	1.29	1.33	1.23	1.26	1.24
Coefficient of weight variation (%)	1.25	0.98	0.49	0.98	0.76	0.43	0.57	0.75

[1] Vibratory hopper, 1 cm diameter orifice.

Although more pronounced for Avicel PH-101 , the improvement in the flow properties is actually very small : none of the powders become free flowing. Flow variation even worsens with increasing lubricant concentration.In contrast, adding magnesium stearate is useful for improving the reproducibility of tablet weight and for instance a concentration of 0.5 % was shown to be optimal for Avicel PH-101. The coefficients of weight variation were generally quite acceptable, when using a Stokes RB2 rotary press and 7/16 in punches.

The lesser variation in weight when using Avicel PH-102 instead of Avicel PH-101 is well documented but we were also interested in comparing their performance to that of the new products launched recently on the market. The 16 MCC products described in Table 14 were lubricated with 0.5% magnesium stearate and compressed at 100 MPa into 8-mm diameter tablets of a target weight of 160 mg and a diametral crushing force of 70 N. Tablets were prepared using a high speed rotary machine equipped with a force-feed delivery and a compaction force monitor (Manesty Unipress, 1400 tablets/min). Table 20 presents the general characteristics of the tablets, listed by decreasing compactibility (MCC products of type 1 at the top and type 2 at the bottom).

Big differences in compactibility were observed, but generally type 1 materials were more compactible. Some interbatch variability was also noticeable but which

TABLE 20

General Characteristics of Tablets Prepared at 100 MPa on a Rotary Press from16 MCC Products Lubricated with 0.5% Magnesium Stearate (86)

Material	Compaction force (kN)	Crushing force (N)	Friability (%)	Disintegration time (min) with disks	Disintegration time (min) without disks
Avicel PH-101, batch 1	15.0	74	0	1.5	3.5
Emcocel 50M	21.0	72	0	1.5	3.5
Avicel PH-101, batch 2	21.3	57	0.14	1	1.5
Sanaq 101 L	22.5	63	0.32	2	20
Unimac MG-100	24.5	56	0.09	2	10
MCC type 101, batch 2	26.5	66	0.01	2	> 240
Medicel 101	30.0	67	0.11	18	63
MCC type 101, batch 1	34.0	64	0.05	1	8.5
Ex-Cel	- [1]	47	0.11	2	7
Avicel PH-102,batch 1	18.5	74	0.03	1.5	2.5
Avicel PH-102, batch 2	18.8	72	0.05	1	4.5
Emcocel 90M	21.5	71	0.09	2	3
Medicel 102	28.0	52	0.24	11	43
MCC type 102, batch 2	31.5	69	0.03	1	6.5
MCC type 102, batch 1	35.5	66	0.12	0.5	5
Unimac MG-200	38.5	60	0.10	0.5	1

[1] Due to the low packing density of this material the target weight and crushing force could not be achieved for technical reasons.

was lesser for type 2 products. Because of the variable strength reduction effect of the lubricant, the compactibility sequence was of course different from that of the unlubricated samples (Fig. 9). However, our results were in agreement with those found by others in similar conditions :

- Pesonen and Paronen (91): Avicel PH-101 = Emcocel 50M
- Whiteman and Yarwood (109): Emcocel 50M > Avicel PH-101 > Unimac MG-100
  and Avicel PH-102 > Unimac MG-200
- Plaizier-Vercammen et al. (112): Avicel PH-101 = Emcocel 50M = Emcocel 90M

Note that 1 or 2% magnesium stearate was added in the latter case. Additionally, two materials of type 1 add very poor disintegrating properties.

TABLE 21
Flow Characteristics of MCC Products and Coefficients of Weight Variation, Thickness and Mechanical Strength of the corresponding Tablets (86)

Material	Flow rate (g/s)[1]	Hausner ratio	Weight C.V. (%)	Thickness C.V. (%)	Crushing force C.V. (%)
Avicel PH-101, batch 2	-	1.20	0.76	0.55	4.8
MCC type 101, batch 1	-	1.18	0.87	0.38	5.2
Emcocel 50M	-	1.25	0.96	0.58	7.7
MCC type 101, batch 2	-	1.21	1.05	0.47	4.6
Unimac MG-100	-	1.23	1.20	0.23	11.5
Sanaq 101 L	-	1.25	1.31	0.51	12.2
Medicel 101	-	1.22	1.52	0.30	8.4
Avicel PH-101, batch 1	-	1-28	1-90	0.32	9.3
Ex-Cel	-	1.23	4.49	0.46	17.8
Emcocel 90M	10.8	1.14	0.39	0.33	4.7
MCC type 102, batch 1	14.3	1.18	0.62	0.58	4.7
Avicel PH-102, batch 1	9.1	1.18	0.63	0.14	6.2
Unimac MG-200	12.0	1.22	0.67	0.12	6.7
Avicel PH-102, batch 2	9.6	1.15	0.70	0.32	4.4
MCC type 102, batch 2	14.8	1.17	0.85	0.42	3.7
Medicel 102	7.0	1.20	2.36	0.77	11.6

[1] Vibratory hopper; no flow was possible with type 1 materials.

Table 21 examines the same tablet batches in terms of variability of properties together with the corresponding flow characteristics of the lubricated powders. Products were listed this time by increasing weight variation.

Except for one product, tablets prepared from type 2 MCCs showed less variability than type 1 tablets. Weight reproducibility was thus excellent (< 1.0%) for six type 2 materials in the conditions used. Three samples of type 1 MCC had a similar rating. The variability was acceptable for five other samples and very poor for Ex-Cel.

No actual correlation could be seen between weight variation and flow characteristics as assessed by the flow rate through a vibratory hopper and the Hausner ratio. The sequence of coefficients of weight variation did not either parallel that of the thickness or of the crushing force.

Again, looking at comparable studies, the following orders were observed for the coefficient of weight variation :

- Personen and Paronen (91): Avicel PH-101 < Emcocel 50M;
- Whiteman and Yarwood (109): Avicel PH-101 < Emcocel 50M < Unimac MG-100
  and Avicel PH-102 < Unimac MG-200;
- Plaizier-Vercammen et al. (112): Emcocel 90M < Emcocel 50M < Avicel PH-101.

The last-mentioned authors have however shown that weight reproductibility among brands varies differently according to the percentage of magnesium stearate and mixing time with the lubricant. Thus ratings have to be taken with caution. The values of the coefficient of weight variation are also very dependent on the tableting machine and the operating conditions. Khan et al. (129) found also a high dependency of tablet weight uniformity on the moisture content of MCC, when testing a formulation containing Avicel PH-102 97%, potassium phenethicillin 2% and magnesium stearate 1%. The coefficient of weight variation increased in the following order of the moisture content :

$$4.8\% < 2.3\% < 0.9\% < 7.3\% < 0.6\%$$

Conventional Avicel grades and the new generic products have poor flow properties and recently the FMC Corporation has introduced a new grade of Avicel called Avicel PH-200. In connection with its declared average particle size aggregates are larger and more rounded than those of Avicel PH-102. The new product is claimed to have the same compactibility as that of grade PH-102, and to improve tablet weight reproductibility. For example, data given by the manufacturer (150) show that the coefficients of weight variation were 1.96% for Avicel PH-102 and 0.89% for Avicel PH-200 when using a low speed Stokes B-2 machine. C.V. values were 9.04 and 4.25% respectively, when using a high speed Manesty Express, also with a gravity feeder. We have performed a similar study to compare Avicel PH-200 wich conventional Avicel PH grades, and also to evaluate another new grade Avicel PH-112, with a reduced moisture content but a particle size similar to that of Avicel PH-102. The tableting conditions were those described earlier (86), except that unlubricated powders were used. The full results are being published elsewhere (151) and Table 22 compares the coefficient of weight variation obtained in the two cases.

TABLE 22
Coefficients of Weight Variation of Various Avicel PH Grades, Lubricated with 0.5% Magnesium Stearate and Non-Lubricated.

Material	0.5% magnesium stearate (ref. 86)	no lubricant (ref. 150)
Avicel PH-105	-	3.37
Avicel PH-103	-	3.58
Avicel PH-101	0.76, 1.90[1]	1.68
Avicel PH-102	0.63, 0.70[1]	0.88
Avicel PH-112	-	0.83
Avicel PH-200	-	0.56

[1] Two different batches were used.

Avicel PH-200 gave better tablet weight reproductibility than the PH-102 grade, and the low-moisture Avicel PH-112 was slightly better than the standard Avicel PH-102, in accordance with other data (152). However it seems that Avicel PH-200 is more lubricant-sensitive than Avicel PH-102 (150), Avicel PH-112 being worse than the PH 102 grade (152). Because of its low water content, Avicel PH-112 is also less compactible than PH 102 (152). As a matter of fact, Avicel PH-200 will probably remedy the main drawback attributed to all the MCC materials currently on the market, i.e. the tablet weight variations they may cause. However, in some cases the dilution potential may not be as good as that of Avicel PH-102 (ascorbic tablets proved to be weaker with Avicel PH-200 (151)) because its coarser particles may not provide comparable contact area for bonding. Also the content uniformity will not be systematically better with Avicel PH-200 because of risks of segregation, although preliminary results have shown lower variability of drug content in paracetamol tablets (151). In fact, each case has probably to be studied as its own.

To improve flow properties, MCC materials, in addition to lubricants, are frequently admixed with other DC diluents. This is also necessary for reasons of cost, when the active ingredient represents only a minor proportion of the tablet. Interesting but contradictory papers have been published on the dicalcium phosphate dihydrate-MCC binary system. Lerk et al. (13) studied the effect of the

TABLE 23

Coefficient of Variation of Upper Punch Force, F_U, and Tablet Characteristics as Function of MCC (Avicel PH-101 or 102) Concentration in Dicalcium Phosphate Dihydrate Added with 0.5% Magnesium Stearate (13)

% MC in system	F_U C.V. (%)		Crushing force (kg)		Disintegration time (min)	
	PH-101	PH-102	PH-101	PH-102	PH-101	PH-102
0	1		6.5		>>10	
2.5	1	1	6.5	7	> 10	3.3
5	1	1	6.5	7	5.8	1.8
10	1.5	1.5	7.5	8	2.5	< 1
20	1.5	1.5	9	9.5	1	< 1
40	4	2.5	14	13.5	< 1	< 1
100	> 10	4	>> 16	>> 16	4.2	4.2

concentration of Avicel PH-101 or Avicel PH-102 added to Emcompress special on the coefficient of variation of the upper punch force during tableting and on various properties of the corresponding tablets prepared on a single punch machine (Table 23).

The variability in upper punch force recorded during tableting increased dramatically when the proportion of MCC reached 40%. At that time, the mechanical strength of the tablets increased as well, showing that the characteristics of the MCC became predominant in the system. No significant differences were seen between Avicel PH-101 and Avicel PH-102. Only tablets made of pure dicalcium phosphate did not disintegrate adequately.

Chilamkurti et al. (145) made a similar study with Emcompress and Avicel PH-101, but here the coefficient of weight variation was determined in addition to other parameters. Samples of 300 mg, lubricated with 0.5% magnesium stearate, were tableted on a single punch machine at a compression force of 8.9 kN. (Table 24). Crushing forces are found in Fig. 15. Similar conclusion can be drawn from

TABLE 24
Coefficient of Variation of Upper Punch Force and Coefficient of Tablet Weight Variation of the Dicalcium Phosphate-Dihydrate-MCC System Added with 0.5% Magnesium Stearate (145)

% MCC in system	Upper punch force variation (%)	Weight variation (%)
0	1.54	0.34
10	1.46	0.32
25	1.34	0.31
50	2.21	0.61
75	1.94	0.50
90	3.39	0.74
100	4.68	1.19

this work : above approximately 75% MCC, weight variation becomes relatively high, and so does the variability of the upper punch force recorded during tableting.

The result of Wells and Langridge (131) led to a different conclusion. Tablet weight variation was maximum at intermediate proportions of Avicel PH-102 and dicalcium phosphate dihydrate and was the lowest for pure MCC. Incidentally, Marshall (148) noted in shear cell measurements that MCC (Avicel PH-101) exhibited some glidant properties for SD lactose at concentrations below 4%.

Similarly to MCC which generally alters the variability of tablet weight of filler-MCC systems, it is known that a drug may affect the coefficient of weight variation when incorporated into pure MCC material or a filler-MCC matrix. For instance, the C.V. for lubricated phenethicillin formulations containing Avicel PH-102 with 4.8% moisture increased from 0.55% (average values obtained at four compaction pressures) to 1.22% when the drug content was increased from 2% to 68% (129).

Another important question is whether the differences observed with pure MCC are still valid here. Data of Plaizier-Vercammen et al. (112) are interesting in this respect, since they compared three MCC grades, namely Avicel PH-101, Emcocel 50M and Emcocel 90M. Aspirin was incorporated into pure MCC

TABLE 25

Effect of Added Active Ingredients on the Relative Performance of Three Different MCC Grades, Alone or Admixed with Filler[1] (112)

MCC (%)	Filler (%)	Drug (%)	Crushing force (kg)	Weight variation (%)
Avicel PH-101 (100%)	-	-	5.6	1.7
Emcocel 50M (100%)	-	-	6.2	1.0
Emcocel 90M (100%)	-	-	6.0	0.9
Avicel PH-101 (70%)	-	Aspirin (30%)	10.7[2]	3.7
Emcocel 50M (70%)	-	Aspirin (30%)	14.7[2]	2.3
Emcocel 90M (70%)	-	Aspirin (30%)	12.7[2]	1.3
Avicel PH-101 (30%)	-	Aspirin (70%)	16.3[2]	2.7
Emcocel 50M (30%)	-	Aspirin (70%)	14.5[2]	1.8
Emcocel 90M (30%)	-	Aspirin (70%	15.7[2]	1.4
Avicel PH-101 (10%)	Emcompress (30%)	Aspirin (60%)	4.5	1.0
Emcocel 50M (10%)	Emcompress (30%)	Aspirin (60%)	4.2	0.6
Emcocel 90M (10%)	Emcompress (30%)	Aspirin (60%)	4.7	0.6
Avicel PH-101 (10%)	Lactose (30%)	Aspirin (60%)	8.2	0.5
Emcocel 90M (10%)	Lactose (30%)	Aspirin (60%)	5.8	1.3

[1] 1% magnesium stearate was included in all formulations but was not taken into account when calculating percentages of components; [2] Tablets were prepared at 3 kN.

powders or blends with fillers (dicalcium phosphate or lactose). Tableting of the formulations lubricated with 1% magnesium stearate was performed on a single punch machine (12 mm) at 5 different compaction forces. Table 25 gives the results obtained with a compaction force of 2 kN and a mixing time with lubricant of 1 min.

When 30% aspirin was added to the MCCs, the order of mechanical strength was the same as that of the pure dry binders. When 70% of drug was incorporated, the sequence changed. This was also true when fillers were present. It is however hazardous to draw definite conlusions because all three MCC materials had similar compactibilities.

Concerning the tablet weight variation, the sequence of the formulations containing 30 and 70% aspirin was the same as that of pure MCCs. This was also true for the dicalcium phosphate dihydrate matrix systems but not when MCCs were mixed with lactose.

Again, differences are small and it would be interesting to make similar investigations using MCC materials of very different properties.

AGING OF MCC TABLETS

The physical stability of tablets, with regards to changes in dimensions, weight, mechanical strength, disintegration time and dissolution rate, is of great concern and in this respect MCC tablets, made of a polymeric material, could have an unexpected behavior. We will consider successively the evolution of the characteristics of the tablets (mainly of the mechanical strength) in the short term (say hours) and the long term aging in normal and extreme conditions.

Short term aging

It has been observed by many authors that several minutes or hours are necessary for the tablets after preparation to reach equilibrium. Most of the data available deal with sodium choride tablets for which an increase in strength has been always noted during the first few hours, even when stored in normal conditions. To the author's knowledge, the only data available on MCC are those of Karehill and Nyström (153) who did not record within two days any significant change in strength for Avicel PH-101 tablets, both unlubricated and lubricated (Fig. 16). By comparison an increase was observed for sodium choride, sodium bicarbonate and pregelatinized starch tablets.

In this experiment, powders were conditioned at 20°C and 40% relative humidity before compaction and the tablets, once prepared, were maintained under the same conditions. We performed a similar study, but powders (Avicel PH-101, Emcompress, pregelatinized starch, spray-dried lactose and sodium

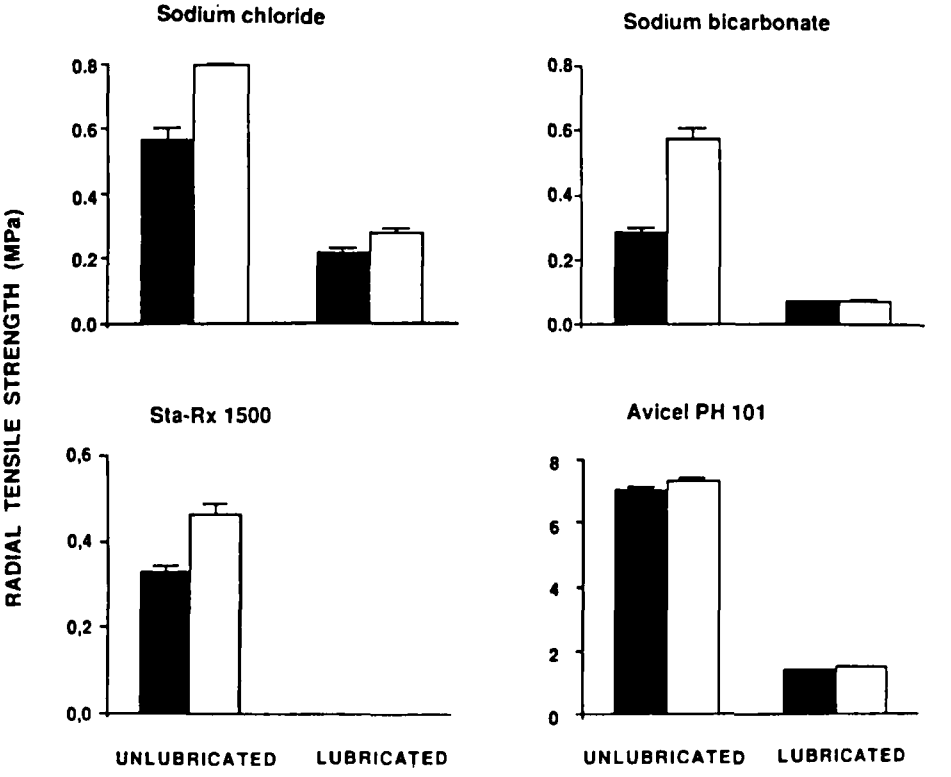

FIGURE 16
Radial tensile strength of unlubricated and lubricated tablets measured directly after compaction (closed columns) and after two day storage (open columns) (153).

chloride) were used as received and stored in closed containers. The tablet diametral crushing force was determined immediately after preparation and after 24 hrs. A 19% decrease in strength was noted after 24 hrs, similar to what had been observed for pregelatinized starch and spray dried lactose. The decrease was stronger for dicalcium phosphate (30%) whereas an increase in strength was confirmed for sodium chloride compacts (154). Interestingly, when the freshly prepared tablets were tumbled for a while (for instance in a friabilator), they exhibited approximately the same changes as the stored tablets, without any significant weight loss. This accelerated aging test is claimed to be useful for adjusting the tableting machine setting.

TABLE 26
Changes in Avicel PH-101 Tablet Characteristics After a Four Week Storage in Various Conditions (from Enezian (7,10))

Conditions	Weight	Strength	Thickness
Ambient conditions	Unsignificant	Unsignificant	Unsignificant
Elevated temperature (60°C)	2,1-3.1% decrease	Almost unsignificant	± 0.2%
Elevated relative humidity (75%, 25°C)	4.2-4.5% increase	33-50% decrease	5-8% increase

Long term aging and storage-induced change

Weeks or months after preparation characteristics of MCC tablets evolve differently according to the environmental conditions. These changes observed when the tablets are placed under different conditions of relative humidity or temperature may be desirable or unwelcome. Earlier work by Reier and Shangraw (5) was summarized by Enezian (7,10) and conclusions are presented in Table 26.

The major observation is the tendency of the tablets to soften and swell at high humidites, but initial characteristics can be restored by removal of the humid conditions. Elevated temperature did not affect hardness. The trend was the same for the different formulations. Similar observations were made by many authors on pure MCC tablets (114,115,122,129,155,156). Decrease in tablet strength was generally attributed to breakage of hydrogen bonds created at the compression stage.

Bolhuis et al. (122) showed that among the common DC diluents tested, MCC was the most moisture sensitive, at both 50 and 85% relative humidities. The decrease in crushing strength of MCC tablets was directly related to the amount of water sorption (114,129). In particular, Nyqvist and Nicklasson (114) demonstrated from desorption experiments that the changes in physical properties of Avicel PH-102 were irreversible. Disintegration time was also related to the

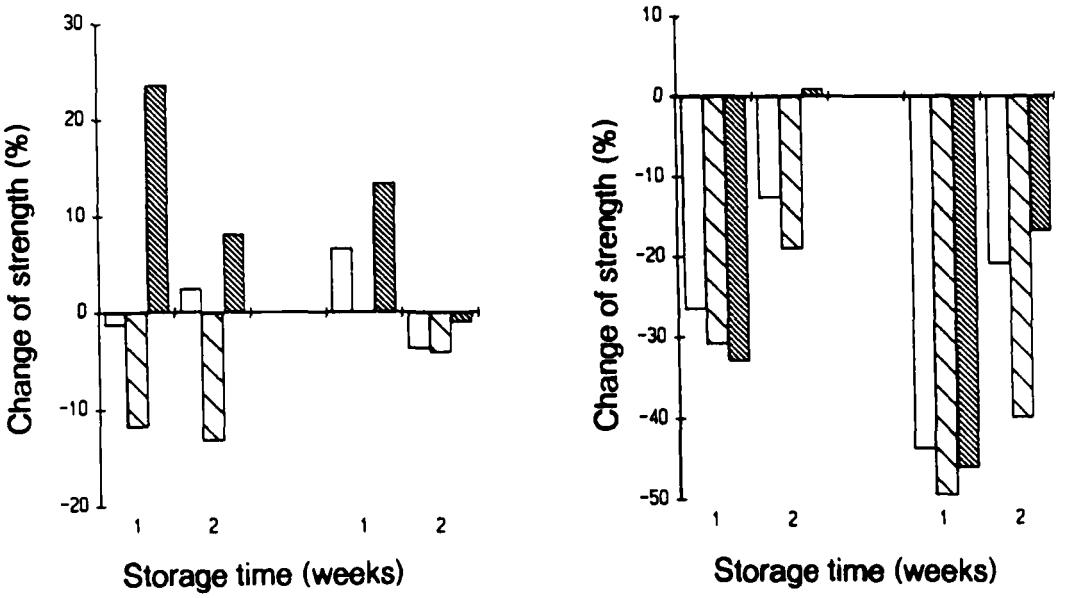

FIGURE 17

Change of diametral crushing force for the tablets after: (left) one week at 0% RH and 60°C (1), and after another week at 30% RH and room temperature (2); (right) one week at 80% RH and room temperature (1), and after another week at 30% RH and room temperature (2). On the left of both graphs, plain cellulose tablets and on the right tablets containing a mixture of 40% w/w MCC and 60% w/w ascorbic acid (156).

Key: ☐ , Avicel PH-101; ▨ , Emcocel 50M; ▩ , experimental cellulose.

water content, tablets stored at high relative humidities disintegrating more rapidly. Dissolution or crystallisation of added substance were also found to affect the physical properties of the tablets.

Personen et al. (155) examined the physical aging of plain MCC tablets and tablets containing MCC and ascorbic acid. Three MCC brands were compared, namely Avicel PH-101, Emcocel 50M and an experimental cellulose of claimed superior binding capacity (84,91). The tablets were stored for one week at 0% relative humidity and 60°C or at 80% relative humidity and room temperature, and then for another week at 30% relative humidity and room temperature (Fig. 17).

During normal storage, the strength of plain Avicel and experimental cellulose tablets increased slightly whereas that of Emcocel decreased. Under dry

conditions, the behavior of the three tablets was clearly different : a very small reversible decrease for Avicel, a permanent decrease for Emcocel and a nearly permanent increase for the experimental product. In very moist conditions, the strength of all the plain MCC tablets decreased markedly, in a nearly permanent way, except for the experimental product.

The strength of all the tablets containing ascorbic acid decreased markedly under normal room conditions. Under extreme conditions, a similar trend was observed, but after a first storage in very moist conditions, tablet strength increased more, possibly due to the recrystallisation of partially dissolved ascorbic acid and then to the formation of solid bridges between particles.

An increase induced by a partial moisture loss has been show by Chowhan and Palagyi (157) for MCC tablets containing a water-soluble drug, but in that case tablets were prepared by wet granulation. Moisture loss was also shown to shorten the disintegration time of the MCC tablets (129,157), in contrast to Nyqvist's findings (114).

The physical stability of tablets containing prednisone or phenobarbital and based on lactose and Avicel PH-102 was examined (143). The tablet mechanical strength decreased after eight week storage at 20°C and 85% relative humidity. No significant change was observed at 50% relative humidity. With a high dosage of aspirin (about 85%) both increase and decrease in tensile strength were noted, depending on the formulation (137).

MCC tablets undergo expansion after compression, because of viscoelastic strain relief, but dimensional changes may be more considerable during a coating process as shown recently in a simulation study (158). The tablets were first stored under ambient conditions and then exposed to a higher temperature (30°C or 40°C) simulating a coating run. They were finally allowed to re-equilibrate at room temperature (Fig. 18.)

At the end of the viscoelastic recovery (72 hrs), the maximum axial expansion was the largest for the Avicel PH-101 tablets. On exposure to a heating/coating cycle, all the tablets, except those of Emcompress, underwent considerable contraction and then an expansion that could result in coating defects.

Generally speaking, moisture mediated changes for MCC tablets are an important problem although conflicting results have been reported. Changes in dimensions, mechanical strength, disintegration time and possibly dissolution rate

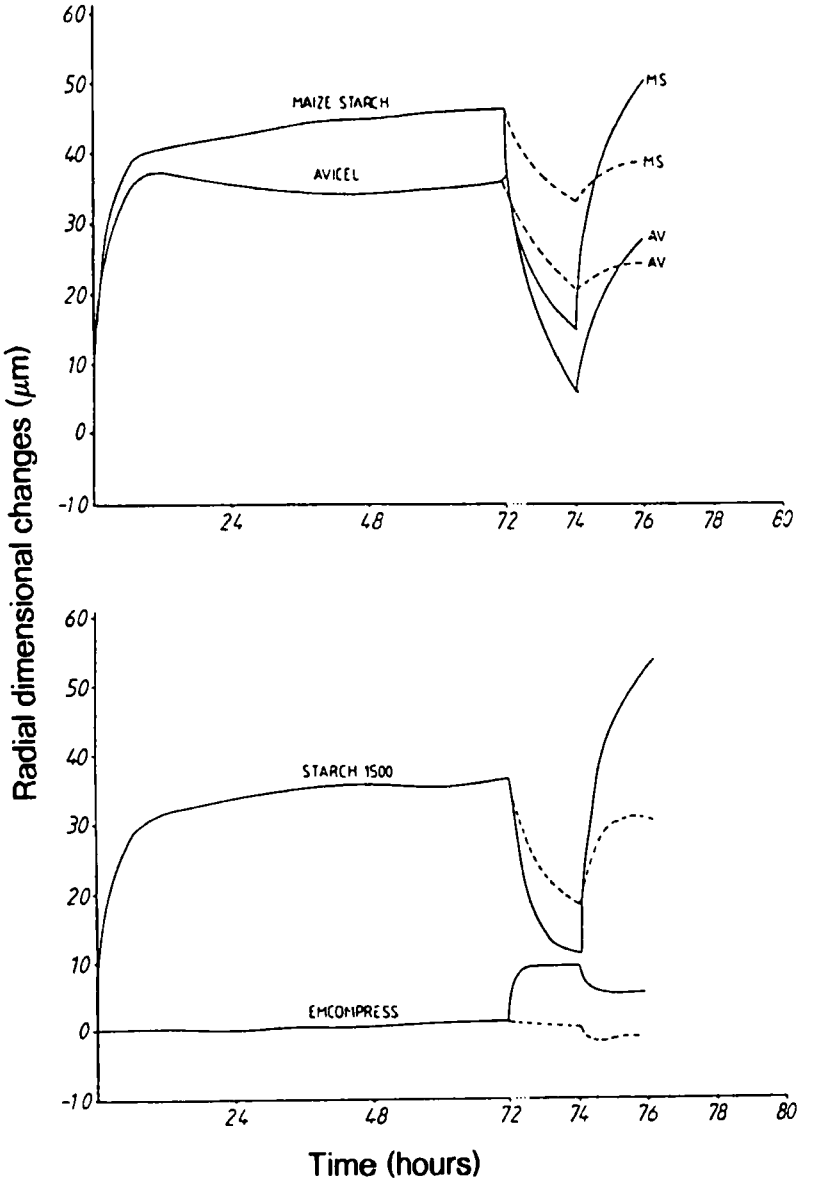

FIGURE 18
Dimensional change of tablets during simulated storage and coating temperature cycles of 30°C (---) and 40°C (—) (158).

of MCC based tablets should be prevented by a careful control of environmental conditions and adequate packaging.

CONCLUSION

MCC is by far the best dry binder to date to be used in direct compression formulation. Its outstanding compactibility is not fully understood and may simply result from a good balance between high plasticity, viscoelasticity and low brittleness, but also from particle interlocking. Nevertheless, MCC suffers some drawbacks. Its sensitivity to lubricants and moisture may be remedied by adequate formulation, processing and packaging. Although pure MCC causes neither jamming on compression nor high ejection forces, it must be admixed with lubricants when used with other components and when high speed tableting is needed. Also, the disintegrating properties of MCC are not very consistent and highly depend on the formulation. Use of disintegrants is therefore advised. But above all, the conventional MCC products and the generic materials generally exhibit poor flow properties and in this respect there is place for improvement. Finally, when confronted to the numerous MCCs now on the market, the formulator should be aware that big differences exist among products, even if all of them comply with compendium specifications.

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