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Research paper

Evaluation of Vitacel M80K as a new direct compressible vehicle

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Abstract

Vitacel M80K, a cellulose powder coated with 2% colloidal silica, is a recently developed direct compressible vehicle (DCV). The aim of this study is to investigate the performance of M80K, in comparison with: a laboratory prepared vehicle (ELC^+) consisting of a mixture of Elcema P050 (ELC) and 2% Aerosil, and a microcrystalline cellulose (MCC), Avicel PH 101 (Avicel). Bulk density, flow and surface characteristics of the DCVs were determined. Tablets were prepared by direct compression using various drugs; ascorbic acid (fine and coarse crystals), cimetidine, and paracetamol. Tablets prepared with M80K showed less weight variation than those prepared with Avicel. Ascorbic acid-Avicel tablets were slightly harder than those with M80K. However, in the presence of either cimetidine or paracetamol, M80K resulted in the production of tablets with maximum hardness. In most cases, except with paracetamol, M80K produced tablets with slightly higher friability in comparison to Avicel, while ELC^+ showed maximum friability. M80K-paracetamol tablets showed the minimum friability values and highest hardness sensitivity towards increase of the applied compression force between 5 and 35 kN. M80K-containing formulations showed better hardness tolerance upon the addition of magnesium stearate. Disintegration times for most tablets were relatively short (<5 min).

Keywords: Direct compression; Microcrystalline cellulose; Vitacel M80K; Silicon dioxide; Elcema P050; Avicel PH 101; Ascorbic acid; Cimetidine; Paracetamol; Tablets

1. Introduction

Direct compression is a continuously growing field in tablet manufacture. Many direct compressible vehicles (DCVs) have been introduced and still many others are under development for better performance and/or lower costs. Microcrystalline cellulose (MCC) possesses almost ideal properties as it is highly compressible with maximum dilution potential, self lubricating glidant, disintegrant, and inert [1,2]. Therefore, MCC has been used successfully for direct compression with many drugs, including critical examples like pancreatin [3], hydrochlorothiazide [4] and paracetamol [5]. It was suggested by many authors that MCC be used in a concentration above 25% to prevent capping and lamination in paracetamol tablets [6]. However, the most obvious drawback for MCC is its relatively high cost and poor fluidity in comparison with many DCVs e.g. calcium phosphate- and sugar-based products [1,2]. Nürnberg and Wunderlich have reported lately [7] on the improvement of tabletting properties of low dose tablets by the application of some investigational silicon dioxide-coated cellulose products. Moreover, Vitacel M80K is a recently presented [8] DCV as an inexpensive alternative to MCC. M80K is prepared from microfine cellulose powder, after being coated evenly, by purely mechanical means, with 2% colloidal silica to improve its flow properties.

It is worth mentioning that, during tablet preparation, mixing of drugs, even in low concentration, with the DCVs could result in many changes of tablet properties. Formulation of timolol maleate, amitriptyline hydrochloride, indomethacin or hydrochlorothiazide (5% each) tablets with different excipients, resulted in variation of tablet char-

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acteristics in comparison with the respective placebo tablets [9]. Therefore, for better evaluation of the efficiency of DCVs it is important to test them in formulations with drugs. Of special interest are drugs with inherent difficulties in tablet manufacture e.g. high dose level, bad compressibility, poor flowability, as well as inadequate drug stability. Senjkovic et al. [10] studied the formulation of paracetamol (40% of tablet weight) tablets by direct compression with different excipients. In addition, many authors [11,12] studied the plasto-elastic behaviour of paracetamol-MCC mixtures and pointed out the optimum concentration of MCC as ranging between 25 and 50%. Further, Choulis [13] evaluated seven commercial tablet preparations of cimetidine. The results pointed out that only one preparation complied with the dissolution requirements, suggesting the presence of formulation problems. Moreover, ascorbic acid tablets demonstrated substantial changes in physical and chemical stability upon storage [14].

In this report, the performance of M80K was evaluated as DCV in comparison to Avicel PH 101 (Avicel) and an excipient (ELC^+) prepared by simple mixing of microfine cellulose, Elcema P050 (ELC), with 2% Aerosil. The study involved the preparation of tablets, under different compression forces, using drugs usually prescribed in large doses and posing variable difficulties in tabletting. Cimetidine, paracetamol, and two grades of ascorbic acid (fine and coarse crystals) were investigated in combination with each of the DCVs.

2. Experimental

2.1. Materials

Supplies of Vitacel M80K were obtained from J. Rettenmaier and Söhne GmbH (D-Ellwangen-Holzmühle), Avicel PH 101 (FMC, Lehmann and Voss and Co., D-Hamburg), Elcema P050 and Aerosil 200 (Degussa AG, D-Frankfurt), magnesium stearate (Otto Bärlocher GmbH, D-München), corn starch (DAB 10), fine ascorbic acid crystals (500074, E. Merck, D-Darmstadt) and coarser investigational ascorbic acid crystals, paracetamol and cimetidine (Höchst AG, D-Frankfurt). All other chemicals were of analytical reagent grades.

2.2. Methods

2.2.1. Materials characterization

The DCVs were subjected to particle size analysis by a Laser diffraction spectrometer (Helos, Sympatec GmbH, D-Clausthal-Zellerfeld) which enables measurement of particle sizes between 0.18 and 875 μm. The registration and evaluation of the data was done by a Hewlett-Packard, Vectra ES/12 computer supplied with a Sympatec Helos software. The dry dispersion method (Rodos) was adopted for studying particle size distribution.

The surface properties of the DCVs were studied by scanning electron-microscopy using a DSM 940A apparatus (Carl-Zeiss, D-Oberkochen).

In addition, the flow characteristics of the DCVs were determined by the angle of repose method [15], using a constant height of 2 cm.

The bulk densities of the DCVs were also determined by transfer of an aliquot from each powder into a 100 cm^3 cylinder, followed by weighing each powder quantity. The cylinder was dropped onto a wood surface three times from a height of 2.54 cm at 2-s intervals to determine the bulk volume [16]. The median diameters for the tested drugs were determined by sieving and the values are indicated below.

2.2.2. Preparation of the tablets

Tablets containing fine (56 μm) and coarse (200 μm) ascorbic acid, cimetidine (71 μm), and paracetamol (93 μm) were prepared under two compression force levels each. The detailed compositions of the different formulations are summarized in Table 1. The constituents (except magnesium stearate) of each formulation were appropriately sieved and mixed in a turbula mixer for 10 min. Finally, magnesium stearate was added to the blend and hand-mixed before compression. All batches were prepared on an instrumented rotary tablet press (Pharma 106, Korsch, D-Berlin) operated at 20 rpm. and using 11 mm flat punches with bevelled edges. A force-feeder was necessary for the preparation of the tablets, except those containing coarse ascorbic acid crystals, to maintain homogeneous flow of the formulations. The compressional forces were continuously registered and stored during the course of preparation using a Turbo-Pascal program (Messfex, Dr. Herzog, D-Tübingen). Ascorbic acid tablets, weighing 396–437 mg, were compressed at 8 and 12 kN, while cimetidine (316–351 mg) and paracetamol (317–346 mg) tablets were compressed at 10 and 20 kN. Additional batches of paracetamol tablets were prepared according to the above formula (Table 1), but without magnesium stearate, to study the effect of compression force (5–35 kN) on hardness and friability of the tablets.

2.2.3. Evaluation of the tablets

The following physical properties of the prepared tablets

Table 1

Composition of the different tablet formulations

Ingredients	Composition			
Drug (parts)	Ascorbic acid (coarse) 60	Ascorbic acid (fine) 60	Cimetidine 200	Paracetamol 200
Excipient (parts)	40	40	100	100
Starch (parts)	5	10	30	30
Magnesium stearate (%)	0.2	0.2	0.6	0.6

were evaluated shortly after manufacture. Weight variation of each batch was determined by weighing ten tablets individually, and their mean and standard deviation were determined simultaneously using an analytical balance (Type AE 200, Mettler GmbH, D-Gießen).

The hardness of ten tablets, mean and standard deviation were determined and registered using a tablet hardness tester (Model 2E, Dr. Schleuninger, CH-Solothurn).

Twenty tablets from each batch were subjected to friability test for 5 min at 25 rpm, employing a Type PTF1 friabilator (Pharma test Apparatebau GmbH, D-Hamburg). The tablets were weighed before and after the test to calculate percentage friability.

The disintegration times for six tablets from each batch were determined in water at 37°C using a disintegrator Type PTZ1 (Pharma Test Apparatebau GmbH, D-Hamburg).

3. Results and discussion

3.1. Characterization of the powders

3.1.1. Particle size analysis

The different DCVs exhibited similar particle size distribution profiles as indicated by their frequency distribution plots and cumulative under-size distributions (Fig. 1). The mean particle size of M80K, Avicel and Elcema were as follows; 51.8, 57.4 and 37.3 μm, respectively. Furthermore, the estimated specific surface area for the three DCVs were found to be 0.232, 0.185 and 0.297 m^2/cm^3, respectively. It could be concluded from the above results that there was great similarity between M80K and Avicel, both being relatively coarser than ELC.

Kanerva et al. [17] pointed out that acicular shaped particles are difficult to compare by employing different techniques and, therefore, it is necessary to calibrate the light scattering device before measuring non-ideal particles. Accordingly, in the present study comparison of the different DCVs were carried out by the same technique after proper calibration to allow reliable comparison.

The wide variation in the particle size of the chosen drugs would give better conclusions about the usefulness of each DCV.

3.1.2. Surface properties of the DCVs

Electron photomicrographs for M80K and ELC$^+$ are presented in Fig. 2. Both excipients exhibited similar general appearance at lower magnification. At higher magnification, M80K particles exhibited a homogeneously coated surface with the finely divided colloidal silica. This observation was confirmed by a search for silicon along a detector line superimposed on electron photomicrograph of M80K, indicating that silicic acid is evenly distributed over the cellulose particles [8]. In contrast, ELC$^+$ surface appeared to be coated with discontinuous lesions of aerosil particles having different sizes and shapes (Fig. 2). These results could explain the improved flow characteristics of M80K in comparison with ELC$^+$ or ELC, as will be discussed later.

Avicel is known to have irregular particles, similar to M80K and ELC, but shows somewhat rounded and shiny crystalline areas associated with irregular cavities [1].

3.1.3. Flow properties of the DCVs

The flow characteristics of the DCVs, as determined by

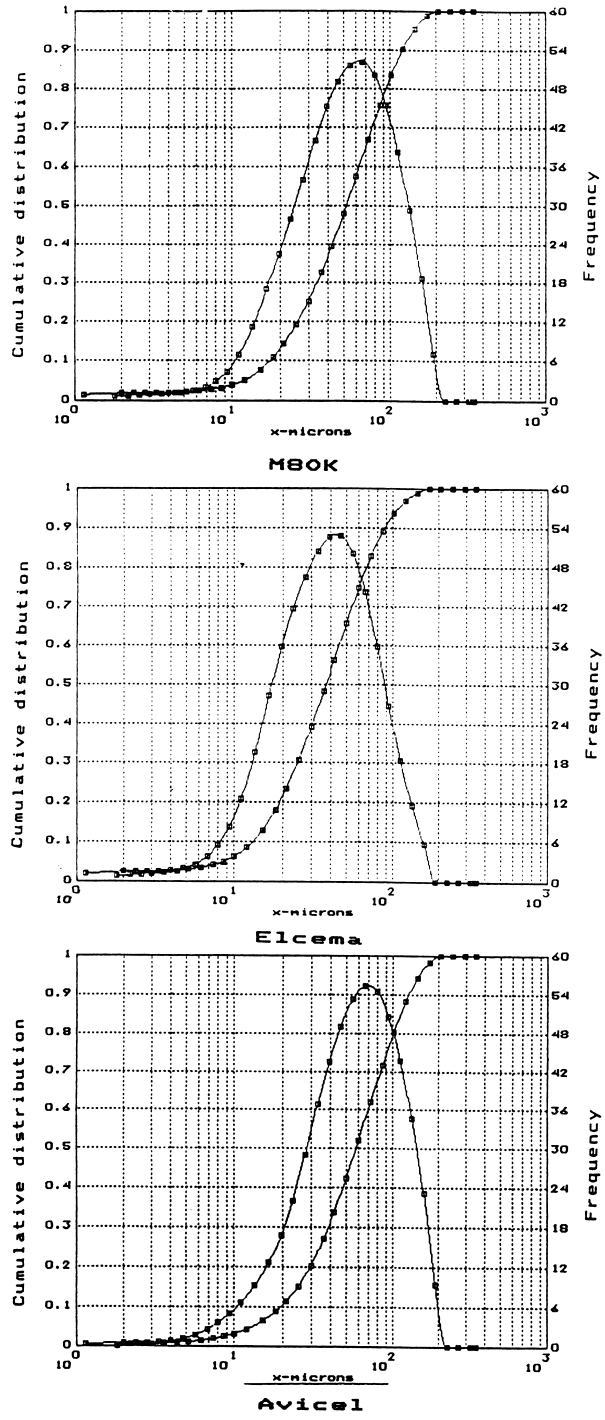

Fig. 1. Particle size distributions of the direct compressible vehicles studied.

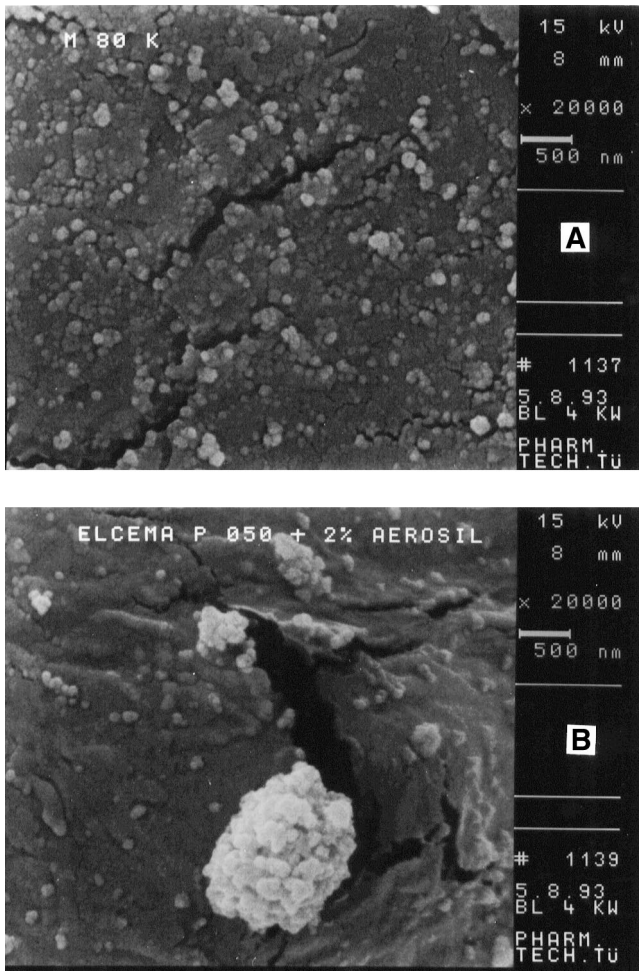

Fig. 2. Electronphotomicrographs of the direct compressible vehicles; Vitacel M80K (A) and Elcema mixture with 2% colloidal silica (B).

their repose angle, are summarized in Table 2. It is obvious from these results that Avicel and M80K exhibited smaller angles of repose (38° and 40.5°) in comparison to ELC (52.8°). For most pharmaceutical powders the angle of repose ranges from 25° to 40° [1]. Simple mixing of ELC with Aerosil improved the flow properties of cellulose fibers as indicated by a decrease of repose angle from 52.8° to 50.5°, yet it was still higher than M80K and Avicel. The similarity in flow properties for M80K and Avicel could be explained by their closely related particle size distributions (Fig. 1) and the relatively better surface properties (Fig. 2).

Table 2

Angle of repose and bulk density of the different excipients

Parameter	M80K	Avicel	Elcema (ELC)	Elcema + 2% Aerosil (ELC^+)
Bulk density (g/cm^3)	0.28	0.35	0.25	0.27
Angle of repose (°)	40.6	38.0	52.8	50.6

The estimated bulk densities for the different DCVs are tabulated in Table 2. The bulk densities for M80K, ELC and ELC^+ were quite similar and ranged from 0.25 to 0.28 g/cm^3), which are relatively smaller than Avicel (0.35 g/cm^3). The higher density of Avicel is due to its crystalline nature [1], which would contribute to its relatively better flow. However, the relatively lower density of M80K could improve its dilution potential.

3.2. Evaluation of the tablets

3.2.1. Ascorbic acid tablets

The results of physical examination of the tablets are summarized in Tables 3 and 4. Tablets containing the finer crystals together with either M80K or ELC^+ exhibited similar weight variations, while those containing Avicel showed higher variations; as indicated from the calculated percentage relative standard deviation (RSD). This result points out the usefulness of M80K in the formulation of fine drug particles usually associated with poor flow characteristics e.g. paracetamol and cimetidine. All tablets prepared from the coarser ascorbic acid grade, with each DCV, exhibited satisfactory values for RSD (<3%); Table 4. The improved RSD values for the last tablets in comparison with those prepared from the finer grade could be attributed to the better flow of the coarser grade that contained blends during preparation of the tablets. Formulation of the tablets containing the coarse grade ascorbic acid with Avicel revealed the best weight uniformity which may be explained by the minimum angle of repose exhibited by Avicel in comparison with the other DCVs (Table 2).

Table 3

Physical characteristics of Vit. C (Merck, fine) tablets

Excipient	Compression force (kN)	Hardness (N) (%-rel. SD)	Weight (mg) (%-rel. SD)	Disintegration time (min)	Friability (%)
M 80 K	8	83.7 (18.8)	396 (3.83)	2	0.25
	12	153.4 (14.4)	398 (2.68)	4	0.0
Elcema P050 + 2% Aerosil	8	66.6 (21.5)	429 (2.67)	1	0.439
	12	109.9 (26.5)	432 (3.14)	1.5	0.07
Avicel PH 101	8	102.3 (12.2)	414 (4.57)	0.5	0.17
	12	147.6 (9.61)	413 (5.90)	0.5	0.074

Table 4

Physical characteristics of Vit. C (coarse) tablets

Excipient	Compression force (kN)	Hardness (N) (%-rel SD)	Weight (mg) (%-rel. SD)	Disintegration time (min)	Friability (%)
M80 K	8	64.0 (12.19)	402 (2.19)	9.4	1.035
	12	106.5 (9.67)	397 (1.66)	15.4	0.051
Elcema + 2% Aerosil 200	8	34.6 (28.2)	415 (2.79)	0.5	5.65
	12	55.6 (31.7)	400 (2.89)	0.5	1.35
Avicel PH101	8	82.6 (9.0)	437 (1.12)	0.5	0.45
	12	118.4 (4.9)	436 (1.26)	0.5	0.0

Regarding tablet hardness, both M80K- and Avicel- containing tablets showed high and comparable values. In contrast, ELC^+ produced tablets that had lower corresponding hardness values. In general, tablets containing the finer ascorbic acid exhibited hardness values that were relatively higher than those containing the coarser grade. The effect of drugs on various tablet parameters will be considered under Section 3.2.4.

The determined percentage friability for the finer ascorbic acid tablets was less than the corresponding tablets containing the coarser crystals. This difference was more obvious at the lower force of compression (8 kN). The percentage friability values remained, however, within satisfactory ranges for Avicel and M80K, but rather high for ELC^+ tablets; 0.45, 1.03 and 5.6%, respectively. These findings point out the superior compressibility of both Avicel and M80K.

All tablets showed good disintegration times up to 5 min. The observed relatively longer disintegration times; 9 and 15 min at 8 and 12 kN, respectively, for the coarser drug/M80K tablets may be explained by the lower disintegrant content in this formulation (Table 1). Furthermore, coating of M80K by a continuous layer of colloidal silica, rather than non-homogeneously dispersed Aerosil particles in case of laboratory coated ELC (Fig. 2), might be responsible for retardation of disintegration especially at higher compaction.

3.2.2. Cimetidine tablets

The physical characteristics of the prepared tablets using the three DCVs are shown in Table 5.

The weight variations observed for all batches were satisfactory and the determined RSD values were less than 3.6%. Avicel-containing tablets showed higher values relative to M80K or ELC^+ tablets.

In addition, tablets containing M80K exhibited higher hardness at each compression force (10 and 20 kN). The observed hardness values were generally less than those exhibited by ascorbic acid tablets, although higher compression forces were required for cimetidine tablets, indicating the poor compressibility of cimetidine powder.

The determined percentage friability for all tablets was generally low (<0.17%), yet those containing M80K showed the lowest values in comparison with either Avicel- or ELC^+- tablets. These results again confirm the potential application of M80K to improve the flow characteristics of tablet-blend comprising finely powdered drugs exhibiting poor fluidity.

Furthermore, the disintegration times for all batches were short and did not exceed 1.5 min in any case.

3.2.3. Paracetamol tablets

The physical properties of the tablets were determined for each batch and the data are presented in Table 6.

Regarding weight variation, the determined RSD values for all tablets were generally satisfactory, up to 5.6%. The values of RSD could be arranged in the following order; $ELC^+ < M80K < Avicel$.

The observed hardness values for the tablets prepared from M80K or ELC^+ were comparable and exceeded those recorded for those containing Avicel. This result stands in agreement with the observed improvement of mechanical properties of tablets containing specially processed cellulose products with silicon dioxide [7].

Further, the determined percentage friability values for

Table 5

Physical characteristics of cimetidine tablets

Excipient	Compression force (kN)	Hardness (N) (%-rel SD)	Weight (mg) (%-rel. SD)	Disintegration time (min)	Friability (%)
M 80 K	10	105.2 (17.9)	323 (2.91)	<0.5	0.093
	20	138.6 (10.7)	316 (1.92)	<1.5	0.063
Elcema P050 + 2% Aerosil 200	10	86.6 (8.1)	342 (235)	<0.5	0.147
	20	127 (6.7)	351 (1.22)	<0.5	0.085
AVICEL PH 101	10	92.5 (24.3)	341 (3.46)	<0.5	0.176
	20	121.1 (12.46)	346 (3.62)	<0.5	0.115

Table 6

Physical characteristics of paracetamol tablets

Excipient	Compression force (kN)	Hardness (N) (%-rel SD)	Weight (mg) (%-rel. SD)	Disintegration time (min)	Friability (%)
M 80 K	10	78.2 (16.4)	319 (2.16)	<1.0	1.141
	20	134.2 (7.7)	317 (3.73)	<2.5	0.269
Elcema P050 + 2% Aerosil 200	10	83.1 (5.6)	346 (2.0)	<0.5	0.234
	20	132.5 (7.0)	346 (1.85)	<0.5	0.230
AVICEL PH 101	10	66.06 (26.9)	319 (4.29)	<0.5	0.720
	20	99.1 (28.2)	328 (5.66)	<0.5	0.151

all batches were generally minimal (up to 0.27%), except in M80K containing tablets compressed at 10 kN where the friability amounted to 1.14%.

In addition, all paracetamol tablet formulations showed rapid disintegration (less than 2.5 min).

3.2.4. Influence of the different drugs on performance of DCVs

The data in Tables 3–6 point out that formulation of drugs having larger particles (e.g. coarse ascorbic acid) with the tested DCVs did not result in appreciable differences in RSD for weights of the produced tablets. On the other hand, employing fine drug particles with poor flowability (e.g. paracetamol) in combination with these DCVs resulted in tablets with higher weight variation. However, tablets containing M80K and ELC$^+$ were slightly better than those formulated with Avicel in this respect. This last effect may be explained by the coating of M80K and ELC$^+$ particles with colloidal silica; facilitating the flow of tablet blend due to decreased interparticular interaction between drugs' and the DCVs' particles. The tendency of this interaction is generally kept at a minimum in the case of coarse drug particles which are not easily interlocked with the cellulose fibers of the DCVs. The maximum RSD, nevertheless, did not exceed 5.5% in the presence of any DCV under investigation (Tables 3–6).

Furthermore, the nature of the drug in each formulation also played an important role in determining the hardness of the produced tablets. The observed hardness values for tablets containing the finer crystals of ascorbic acid were higher than the corresponding values of those containing the larger crystals (Tables 3 and 4). In the presence of fine ascorbic acid crystals, more dense packing of the tablet blend is facilitated due to reduced interparticular spaces.

On the other hand, the application of fine drug particles with poor compressibility (cimetidine and paracetamol) to the formula resulted in M80K producing tablets with the maximum hardness values followed by ELC$^+$ and Avicel. However, cimetidine tablets exhibited hardness values higher than the corresponding values of paracetamol tablets (Tables 5 and 6).

Regarding friability, ascorbic acid tablets exhibited satisfactory results (<1%), except in case of coarser crystals – ELC$^+$ tablets (5.6% at 8 kN). Furthermore, paracetamol tablets showed percentage friability values higher than the corresponding cimetidine tablets. Paracetamol tablets have been found by many authors [6,18,19] to present a capping and laminating tendency in the absence of sufficient, and good, dry binders. This fact explains the observed relatively higher friability and lower hardness values of paracetamol tablets (Tables 5 and 6).

3.2.5. Hardness- and friability- compression force profiles

The effect of increasing the applied compression force from 5 to 35 kN on the hardness and friability of paracetamol tablets formulated with the various DCVs is illustrated in Fig. 3. It is obvious from the above results that the rate of increase in tablet hardness as a function of compression force was higher for M80K and ELC$^+$ tablets than for Avicel tablets (Fig. 3). Furthermore, addition of magnesium stearate to the formulations did not affect the hardness of M80K tablets, and their hardness values remained higher

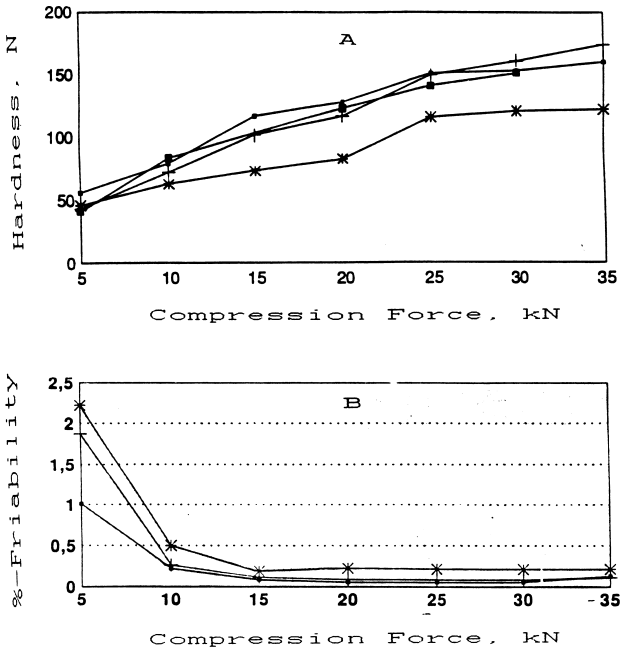

Fig. 3. Effect of applied compression force on hardness and friability of paracetamol tablets. Small closed square, M80K; +, El cema P 050; *, Avicel 101; large closed square, M80K + Mg St.

than those containing Avicel, with or without magnesium stearate.

In addition, the determined values of percentage friability for M80K tablets were found to be less than those for the corresponding tablets with Avicel. ELC$^+$ tablets exhibited intermediate percentage friability values.

4. Conclusions

1. M80K exhibits particle size distribution and flow characteristics similar to Avicel.
2. Physical mixing of microfine cellulose fibers with Aerosil in a Turbula mixer did not produce homogeneous coating of the cellulose particles with colloidal silica, as observed with M80K.
3. M80K and ELC$^+$ showed similar bulk densities which were less than the bulk density of Avicel.
4. M80K produced tablets which had less weight variation than Avicel. This effect is more obvious in drugs with bad flow properties.
5. Ascorbic acid-Avicel tablets were slightly harder than those with M80K. M80K resulted in the maximum hardness with both cimetidine and paracetamol.
6. M80K-tablets showed, in general, the lowest friability values.
7. Disintegration times for all tablets were generally short.
8. The rate of increase in hardness of paracetamol tablets as a function of the applied compression force was far higher M80K-tablets than for Avicel or ELC$^+$.
9. M80K containing formulations showed better tolerance i.e. minimal decrease in tablet hardness, upon addition of magnesium stearate.

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