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Influence of the granulating method on bulk properties and tablettability of a high dosage drug

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Summary

Tocainide hydrochloride, a high dosage drug, was granulated by spraying in a fluid bed granulator or by wet massing in a planetary mixer. The influence of the granulation method and the amount of binder, 0–3.4% methylcellulose (MC), on granulate properties and tablet strength was investigated. Tablets were prepared by using an instrumented tablet machine. Fluid bed granulation with sufficient amounts of MC gave a granulate with a narrow particle size distribution and good flowability. The best flow properties were obtained by prolonged spraying with dilute binder solutions. Wet massing produced a denser granulate with poorer flow properties and was very little affected by the amount of MC. Fluid bed granulates gave considerably stronger tablets than traditional granulates. High MC-concentrations and long spraying time improved the bonding properties. The tablet strength correlated well with the work required for compression, indicating that improved bonding properties were mainly caused by changed deformation behaviour during compaction.

Introduction

The formulation of high dosage drugs into tablets is often a difficult task because most active substances have poor tabletting properties and the room for excipients is limited. The most common way to improve the properties of the substance is to granulate with a suitable binder. Obviously the choice of the binder and its concentration affects the properties of the granulate and the tablets but also the method of granulation may be of importance. A spray-drying technique with hydrolyzed gelatin as a binder gave, for example, better bonding properties to paracetamol than did precompression or wet massing (Seager et al., 1979; Rue et al.,

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1980). The higher concentration of binder at the granulate surface was suggested as the explanation for this effect. Fluid bed granulation can be expected to give quite different distribution of the binder in the granules than granulation by wet massing and may therefore utilize the added binder more efficiently. Little information is available on the effect of fluid bed granulation in this respect and it was therefore of interest to compare this technique with wet massing in the formulation of a high dosage drug, tocainide hydrochloride. The substance is light and fluffy and binds poorly to tablets. The dose is 0.6 g, 2 or 3 times daily, and it is consequently desirable to use only small amounts of excipients in the tablets. Methylcellulose was chosen as a binder since pilot studies indicated that it was efficient in low concentrations. The particle size and flow properties of the granulates were evaluated and the compaction properties were studied in an instrumented tablet press.

Materials and methods

Materials

Tocainide hydrochloride (Astra Pharmaceuticals, Södertälje, Sweden) is a crystalline freely water-soluble powder. The crystals are needle or platelet shaped (Fig. 1)

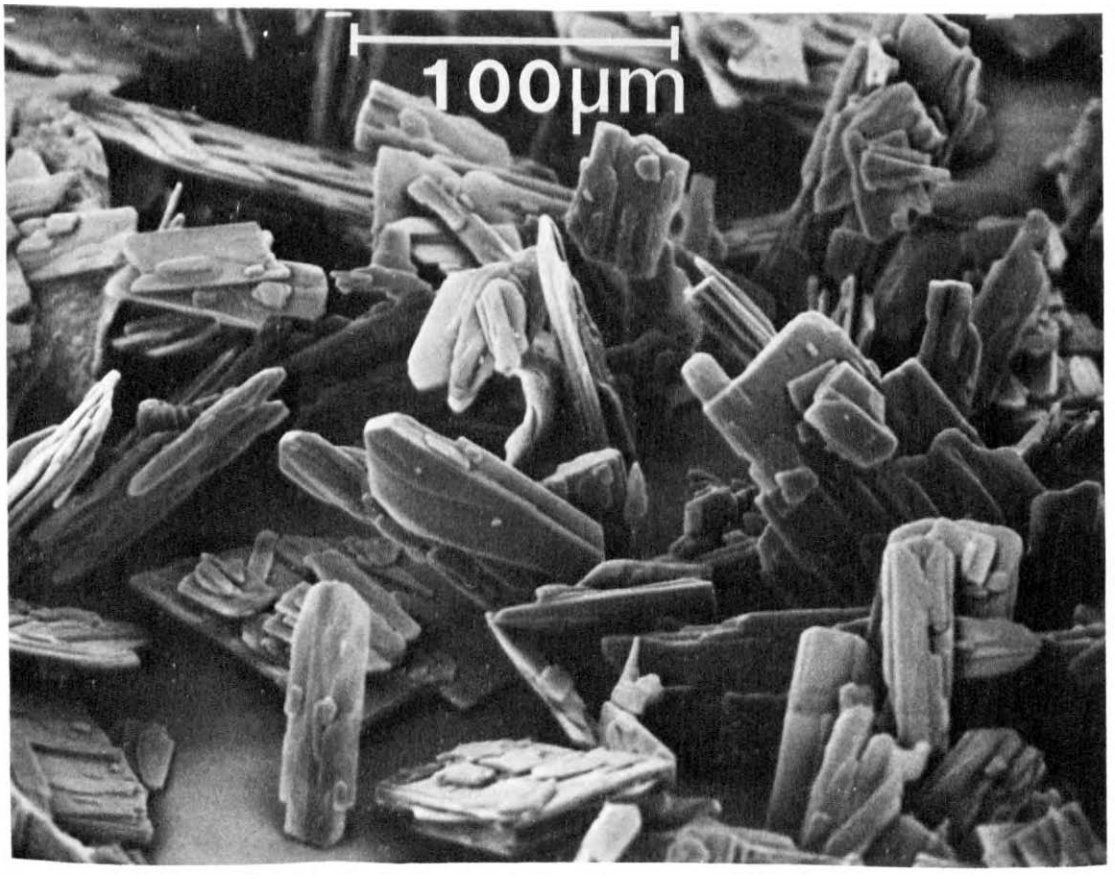

Fig. 1. Tocainide hydrochloride substance.

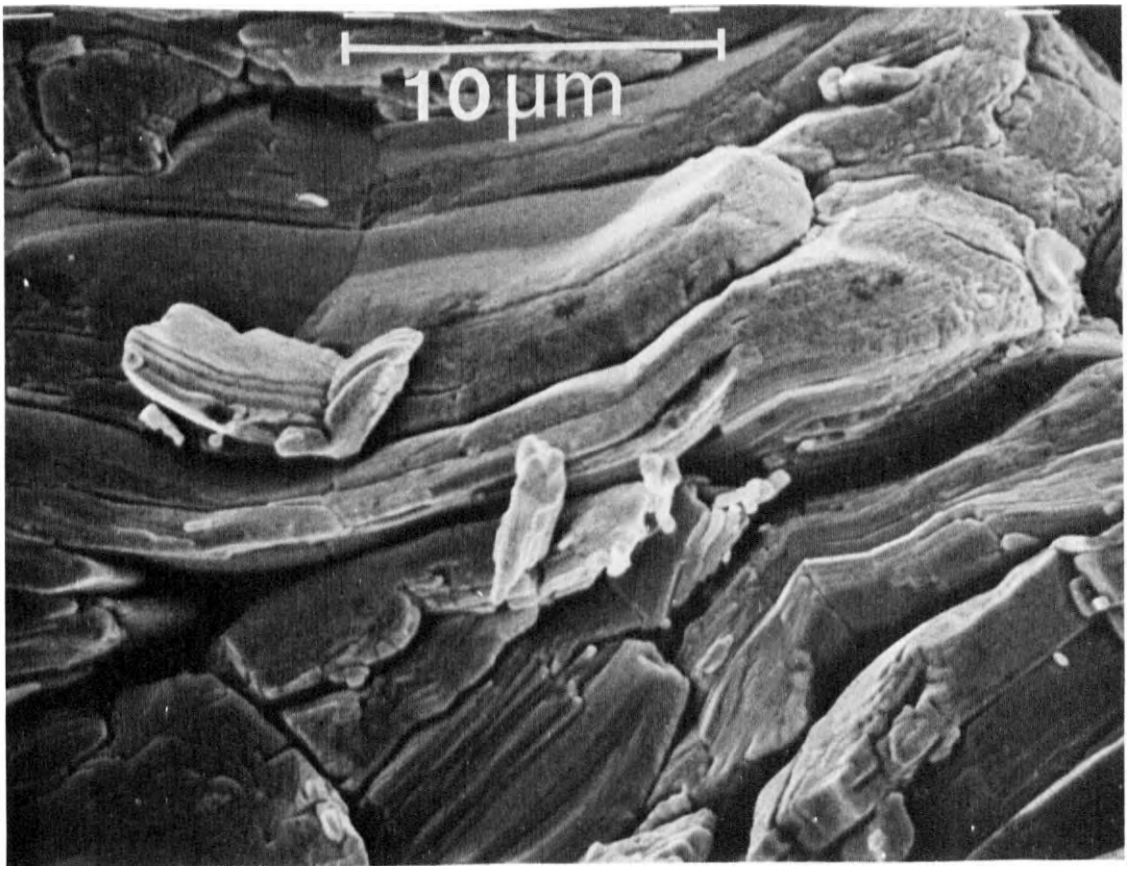

Fig. 2. Cross-section of a tocainide hydrochloride tablet compressed at 150 MPa.

and 98% passes 32 µm in an Alpine air-jet siever. They can deform plastically during compaction (Fig. 2) but the compacts are weak and prone to capping.

Methylcellulose (Methocel A15 15 cps premium, Colorcon, England).

Magnesium stearate USP (Unilever Emery, The Netherlands).

Methods

The amount of the materials used to prepare the various granules and the concentrations of binder in the granulation liquids is summarized in Table 1.

Tocainide hydrochloride was granulated by wet massing in a planetary mixer (Kenwood domestic mixer) or by spraying in a fluid bed granulator (Glatt WSG 5). The pure drug or mixtures of drug and methylcellulose (MC) were wet massed with water or aqueous MC solutions. The amount of water was kept constant. The mixtures were massed intensively for 7 min and were passed through a 4.0 mm screen and dried on trays at 60°C for 24 h. The dried masses were milled through a 1.6 mm screen in an Erweka oscillating granulator. The fluid bed granulator was equipped with a standard spray nozzle, no. 12, and the solutions were applied at a rate of 90 g/min with 0.15 MPa atomizer pressure. The net application rate was approximately 66 g/min due to two breaks per minute when the filters were shaken for 3–4 s. The temperature of the inlet air was 80°C and its water content was 10–11

TABLE I

AMOUNT OF MATERIALS AND THE CONCENTRATION OF METHYLCELLULOSE (MC) SOLUTIONS USED IN THE PREPARATION OF THE GRANULATES

Granulate	Tocainide-HCl (kg)	Water (kg)	MC conc. in the granulate (%)	MC conc. in the granulation liquid (%)
Wet mass				
T	0.6	0.11	0	0
W_1	0.6	0.11	0.87	0
W_2	0.6	0.11	0.87	5
W_3	0.6	0.11	1.72	0
W_4	0.6	0.11	1.72	10
W_5	0.6	0.11	3.38	0
Fluid bed				
F_1	2.5	1.73	0.87	1.25
F_2	2.5	3.46	1.72	1.25
F_3	2.5	1.71	1.72	2.5
F_4	2.5	6.91	3.38	1.25
F_5	2.5	3.41	3.38	2.5
F_6	2.5	1.66	3.38	5

g/kg of dry air. The granulates were dried to an outlet temperature of 60°C.

All granulates had a moisture content below 0.6% measured with an Ultra X moisture test balance at 110°C for 15 min. Magnesium stearate, 0.75%, was admixed for 2 min at 78 rpm in a planetary mixer (Björn Varimixer Type R30). A spinning riffler (Retsch Laboratory Sample Divider Type PR) was used to obtain samples of suitable size for evaluation. Duplicate samples were used in all tests if not stated otherwise, and the mean was calculated. Loose bulk density was measured by gently pouring 50 g granulate through a funnel into a 250 cm^3 graduated glass cylinder. The granulate volume was read to the nearest ml. Angle of repose was measured according to Dahlinder et al. (1982) by 5 individual measurements per sample. Particle size analysis was carried out with an Allen Bradley Sonic Sifter (model PF). Cumulative undersize percentages were plotted on a logarithmic probability grid and the geometric mean diameter and standard deviation were calculated.

Tablets were compressed in a reciprocating tablet machine with flat 1.13 cm circular punches. The machine was equipped as described by Hölzer and Sjögren (1979) with piezoelectric load washers on the upper and lower punches. Inductive displacement transducers were used to measure punch movement and tablet height during compression.

The tablet weight was calculated from the density of each granulate (Beckman Air Comparison Pycnometer 930) to provide tablets of 2.5 mm height at zero porosity. The materials were filled by hand into the die and compressed at 3 different upper punch pressures, 75, 150 and 330 MPa, respectively, with a machine speed corresponding to 30 tablets per minute. The tablets were stored for 24 h at 30% RH,

before diametral crushing strength and work of failure was measured. The crushing was done between two metal plattens operating at a constant rate of 0.6 mm/min in an apparatus recording both the force and the work of crushing. Tablet disintegration was tested on 5 tablets according to USP XX without discs.

Microphotos were taken with a Jeol JSM-T20 scanning electron microscope. The samples were gold-coated by an ion sputtering technique.

Results and discussion

Granulate properties

The two methods of granulation gave very different results (Table 2). Wet massing gave denser granulates with broader particle size distributions than fluid bed granulation and the binder had little effect on the granulate properties. Solutions of MC gave slightly coarser granules than water but the angle of repose was not improved. As the drug is very soluble in water it readily forms crust granulates when massed with water. Milling of these hard and brittle granulates resulted in a broad size distribution.

During fluid bed granulation granules are formed by small particles adhering to each other with the aid of solution droplets from the spray gun. Very little of the drug or the solid binder will dissolve during this process due to the rapid drying. The best agglomeration is consequently obtained when the binder is dissolved in the granulation liquid. Preliminary trials showed that it was not possible to get a proper

TABLE 2

GRANULATE EVALUATION

Granulate [a]	Loose bulk density ($g \cdot cm^{-3}$)	Angle of repose (deg.)	Geometric mean diameter (μm)	Standard deviation	Percent passing through 63 μm
T	0.38	50.5	310	3.24	3.9
W_1	0.37	48.3	324	3.71	4.6
W_2	0.38	49.1	480	4.60	6.7
W_3	0.39	49.3	315	3.98	6.9
W_4	0.40	52.1	525	5.75	9.6
W_5	0.39	54.7	310	5.13	15.7
F_1	0.26	54.0	115	1.70	16.3
F_2	0.26	47.0	165	1.68	5.2
F_3	0.26	51.3	125	1.74	12.4
F_4	0.25	42.6	330	1.39	0.7
F_5	0.28	43.5	280	1.48	1.5
F_6	0.30	45.2	270	1.47	3.9

[a] See Table 1.

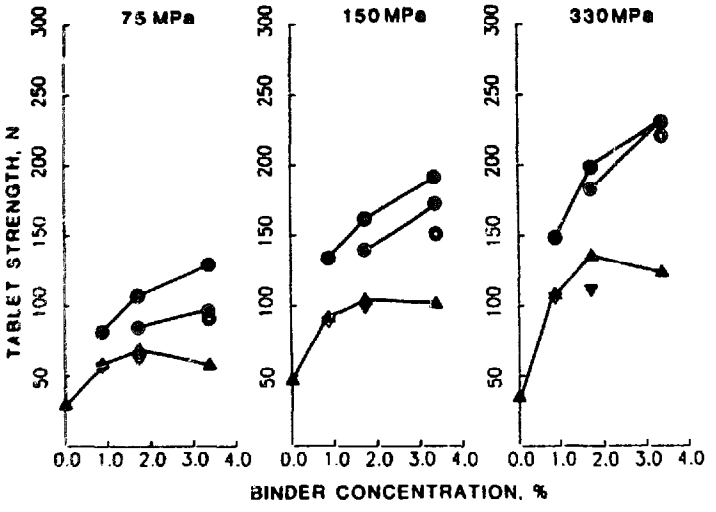

Fig. 3. Tablet strength vs binder concentration for tablets compressed at 3 pressure levels. Fluid bed granulates: ❶, 1.25%; ●, 2.5%; and ❍, 5% MC-solutions. Wet massed granulates: ▽, 5%; ▼, 10% MC-solutions; ▲, water (MC added as a dry powder).

granulation when using pure water as granulating liquid. The most concentrated solution, i.e. 5%, gave the fastest agglomeration which would be expected since the most viscous solution will form the biggest droplets (Shaefer and Wørts, 1977, 1978). About the same result was obtained in 26 min as with 4 times longer spraying time of 1.25% solution.

The diluted binder solution gave less fines, however, (Table 2) which is in agreement with the results of Ormòs et al. 1973. The angle of repose was closely correlated to the amount of fines in the granulates. The correlation coefficient was 0.996 for the fluid bed granules and 0.981 for the wet massed granules with MC.

Tablet properties

Tocainide hydrochloride granulated with water gave very weak tablets, 29–46 N, and lamination at pressures exceeding 150 MPa. Addition of MC improved the bonding properties but an increase in the amount of binder above 0.9% had little effect in wet-massed granulates (Fig. 3). Addition of the binder as a solution or as a dry powder was also of little importance. Granulates prepared by fluid bed granulation gave considerably stronger tablets and increasing amounts of binder improved the tablet strength. These results indicate that the distribution of the binder is more important than its actual concentration in the tablet. Fluid bed granulation, especially when using long spraying times, can be expected to give a layer of binder around each granule and this would promote good bonding as shown by Rue et al. (1980) and Nyström et al. (1982).

Since no disintegrant was present, the tablets mainly dissolved from the surface during the disintegration test. The disintegration times were relatively short and independent of compaction pressure but increased to some extent with the amount of binder (Table 3). Evaluation of the tablet toughness as the work of crushing

TABLE 3

TABLET PROPERTIES

Granulate [a]	Disintegration time (min) [b]			Work of failure (Nmm) [c]			Tablet expansion (mm) [d]		
	Tabletting pressure (MPa)			Tabletting pressure (MPa)			Tabletting pressure (MPa)		
	75	150	330	75	150	330	75	150	330
T	2.5	2.5	2.5	1.3	1.7	0.9	0.22	0.27	0.28
W_1	3.7	3.6	3.4	2.7	4.1	4.3	0.21	0.20	0.22
W_2	3.8	3.7	3.6	2.9	4.2	5.0	0.20	0.25	0.24
W_3	4.3	4.0	3.9	3.0	5.1	7.2	0.19	0.20	0.20
W_4	4.3	4.0	4.0	3.4	5.1	6.7	0.21	0.21	0.25
W_5	4.8	4.5	4.8	3.1	5.0	6.4	0.22	0.24	0.22
F_1	3.7	3.6	3.4	5.2	7.7	6.9	0.20	0.24	0.22
F_2	4.2	4.3	4.2	6.3	12.1	14.8	0.17	0.21	0.25
F_3	4.2	4.1	4.1	4.8	8.2	11.8	0.21	0.23	0.21
F_4	5.1	4.8	5.5	8.8	12.9	15.7	0.20	0.24	0.22
F_5	5.5	5.3	4.9	5.7	11.2	14.0	0.21	0.21	0.24
F_6	5.3	5.3	5.0	5.8	11.4	15.5	0.22	0.24	0.25

[a] See Table 1. [b] Maximum values of 5 tablets. [c] Mean of 5 tablets. [d] Mean of 10 tablets.

(Table 3) gave approximately the same picture as the measurement of the tablet strength. This indicates that the granulation method did not affect the plastic/elastic properties of the tablets to any great extent, in contrast to the previously mentioned spray drying technique (Rue et al., 1980). The granulation appears to influence the

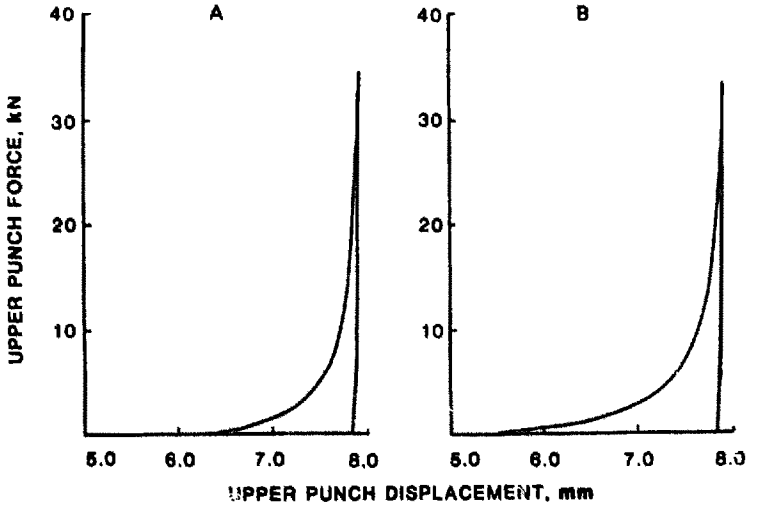

Fig. 4. Upper punch force vs upper punch displacement for tocainide hydrochloride containing 3.4% MC. A: granulate W_5 (see Table 1). B: granulate F_4 (see Table 1).

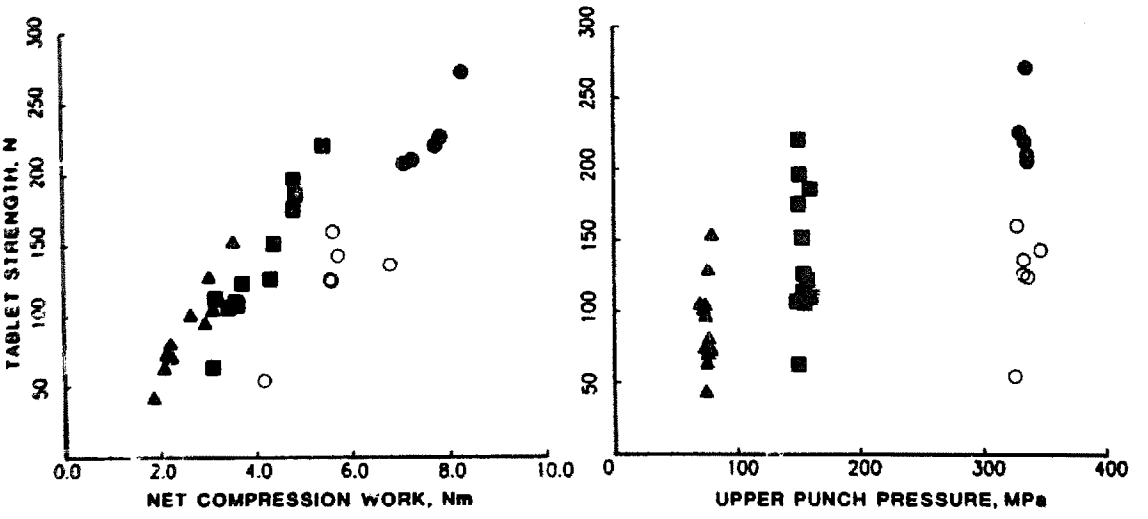

Fig. 5. Tablet strength vs net compression work and upper punch pressure respectively for tablets compressed at an upper punch pressure of: ▲, 75 MPa; ■, 150 MPa; ●, 330 MPa; and ○, 330 MPa and showing evidence of capping.

deformation resistance of the granules during the compression, however, as can be seen from plots of upper punch force vs upper punch displacement (Fig. 4). The work performed by the upper punch, i.e. the integral of the force–displacement curve up to the maximum pressure, equals the work for rearrangement of particles, elastic/plastic deformation, fragmentation, formation of bonds and overcoming friction. The tablet strength correlated fairly well with the net compression work, see Fig. 5, ($r = 0.940$ if the tablets with sign of capping were excluded). The correlation included all granulates and all compaction pressure levels. The net compression work was calculated from the gross input by subtracting frictional work (Järvinen and Juslin, 1974) and work of expansion. The latter was estimated from the decompression curve (Fig. 4). The strength of the bonds formed during the consolidation was obviously much better correlated to the net energy input than to the maximum compaction pressure (Fig. 5).

The granulates with the best bonding ability, e.g. F4, gave measurable resistance in the powder bed much earlier in the compression cycle (i.e. at higher porosities) than poorly bonding granulates. This difference may to some extent depend on the bulk densities but not entirely. The better granulates were subjected to measurable compaction forces for longer periods during the compression cycle than the poorer granulates. The time required to increase the upper punch force from 100 to 7300 N was, for example, 145 and 150 ms for the fluid bed granulates F1 och F4, and 120 and 135 ms for the wet-massed granulates T and W5. The longer exposure to shear forces will probably enhance plastic flow-crushing of the material and thus facilitate formation of strong bonds. The elastic expansion of the tablets from the minimum volume during compaction to the final volume after ejection was similar for all formulations containing MC (Table 3), as was the work of expansion. Thus we could

not demonstrate any effects of the granulation technique on the elastic behaviour. It is probable, however, that the ability of the compact to relieve stresses during decompression without breakage of particle bonds is affected by the binder distribution.

It can be concluded that small amounts of MC improve the tablet strength considerably for tocainide hydrochloride. The distribution of the binder in the granulate may be at least as important as the concentration since fluid bed granulation gave much stronger tablets than wet massing. When granulating by the former technique, concentrated binder solutions will give the fastest agglomeration but longer spraying with diluted binder solution improved the bonding properties as well as the flowability of the granulate. The tablet strength was well correlated to the net compression work which indicates that the MC addition mainly improved the deformation behaviour of the granulate during compaction. The elastic expansion was not significantly affected. Since fluid bed granulation seems to give a much more efficient binder distribution it should be considered a technique of special interest in the formulation of tablets of high dosage drugs.

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