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DISSOLUTION PROPERTIES OF DIRECT COMPRESSION TABLETS CONTAINING AN AGGLOMERATED CELLULOSE POWDER

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ABSTRACT

In previous studies a novel agglomerated cellulose powder was shown to own advantageous properties for direct compression. Due to the favourable particle and powder properties this material has good binding and disintegration ability in direct compression tablets. In this study the dissolution properties of direct compression tablets containing the agglomerated cellulose powder as a filler-binder were evaluated. Especially the effect of the amount of cellulose, the porosity of tablets, the solubility of drug material and the amount and mixing method of lubricant, magnesium stearate were studied.

Tablets containing different amounts of cellulose with dicalcium phosphate as a filler and 10 wt % of water soluble sodium tolmetin as a drug were compressed at a constant pressure of 150 MPa. The breaking strength of tablets increased with increasing amounts of agglomerated cellulose powder. However, the

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dissolution of drug accelerated up to cellulose amount of 50 wt %. This was due to the ability of the agglomerated cellulose powder to enhance the water penetration into powder compact and the loosening of tablet structure, i.e. formation of cracks.

Tablets containing 20 wt % of cellulose material and 10 wt % of drug material were compressed to different porosities. Tablet porosity had no effect on dissolution of poorly water soluble tolfenamic acid. Also the dissolution of water soluble sodium tolmetin was only slightly affected by the porosity of tablets. This supports the suggested disintegrant mechanism of the agglomerated cellulose powder. The expansion of cellulose agglomerates, which have been deformed, under compression, is widely responsible for the disintegration of the tablets.

An increase in the amount as well as in the mixing intensity of magnesium stearate decreased the dissolution of sodium tolmetin from tablets containing 20 wt % of agglomerated cellulose. However, the intrinsic wetting and dissolution phenomens were practically unchanged when the amount of magnesium stearate was below 2 wt %. Thus, the retardation of drug dissolution was acceptable at low lubricant concentrations.

The properties of tablets containing the agglomerated cellulose were compared to those containing microcrystalline cellulose. In all cases tablets containing the agglomerated cellulose powder liberated drug clearly faster and more properly than corresponding microcrystalline cellulose tablets.

INTRODUCTION

Dense compacts formed during tabletting should allow a fast dissolution of drug material. From uncoated tablets the dissolution of drug is often the rate deciding factor defining the transportation of drug into blood circulation. In tablet dosage form dissolution of active component is affected by many different factors. Besides drug and excipient properties also formulation factors, tabletting process and tabletting circumstances are of most importance.

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A filler–binder is often the major component of tablet mass. Thus its properties, such as hydrophilicity, tendency to form strong interparticle bonds and sensitivity to hydrophopic lubricants, could affect significantly water penetration into tablets, disintegration of tablets and drug dissolution. Cellulose powders are widely used as filler–binders and also as disintegrants (1,2,3). Recently Pesonen et al. (4) introduced a novel cellulose material for direct compression. This agglomerated cellulose powder consists mainly of large and roughly spherical cellulose agglomerates. These are very porous resulting in a specific surface area fifty times greater than that of microcrystalline cellulose (5). The agglomerated cellulose powder was also shown to undergo deformation mainly by plastic flow (6). Besides owning good tabletting properties, the agglomerated cellulose powder acts clearly more effectively as a disintegrant than microcrystalline cellulose (7). The disintegrant properties of this material were related to its ability to accelerate water penetration into tablets causing a pronounced effect of water due to a great amount of hydrogen bonds susceptible to being broken by water and the expansion or swelling of deformed cellulose agglomerates (7).

The aim of the present paper was to study the drug dissolution from direct compression dicalcium phosphate tablets containing the agglomerated cellulose powder. The effects of the amount of cellulose powder, the porosity of tablets, the solubility of drug and the amount and the mixing intensity of magnesium stearate on drug release were studied. A widely used excipient, microcrystalline cellulose, was used as a reference material.

MATERIALS AND METHODS

Materials

The cellulose powders studied were an agglomerated cellulose powder (ACP) and a microcrystalline cellulose powder (Emcocel®), which were both supplied by Cultor Ltd (formely Finnish Sugar Ltd), Kantvik, Finland. Sodium tolmetin (Orion Pharmaceutica, Farmos, Finland), which is water soluble, was used as a

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TABLE 1.
Compositions of tablet masses.

Material (%)	Lot A The effect of the amount of cellulose	Lot B The effect of tablet porosity and drug solubility	Lot C The effect of magnesium stearate
ACP/Emcocel	10 20 30 50 70	20 20	20 20 20 20
Emcompress	80 70 60 40 20	70 70	70 70 70 70
Sod. tolmetin	10 10 10 10 10	-- 10	10 10 10 10
Tolfen. acid	-- -- -- -- --	10 --	-- -- -- -
Magn.stear.	½ ½ ½ ½ ½	½ ½	½ 1 2 5

drug material. A poorly water soluble tolfenamic acid (Leiras Pharmaceuticals, Finland) was used to study the effect of the solubility of drug on dissolution profile. Dicalcium phosphate dihydrate (Emcompress®, Edward Mendell Co, Redhill, UK), used as a tablet base material, was previously shown to have no own disintegrant effect (7). Magnesium stearate (Ph. Eur.) was used as a lubricant.

Methods

Flat faced direct compression tablets, 500 mg in weight and 13 mm in diameter, were compressed using an instrumented Korsch EK-O single punch tablet machine (4,7). Tablet formulations used are shown in Table 1. Cellulose, Emcompress and drug material were, firstly, mixed for ten minutes in a Turbula 2P mixer and after the addition of magnesium stearate mixing was continued for five minutes. Magnesium stearate of 1 wt % (lot C) was mixed into tablet mass by two different methods; firstly, with Turbula as described above and, secondly, manually with spatula for one minute. Tablets of lot A were compressed at a constant compressional pressure of 150 MPa. Tablets of lot B were compressed using different compressional pressures between 75 and 225 MPa. Tablets of lot C were compressed to a constant breaking strength of 5.6 kp.

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Porosity of tablets was calculated from the dimensions and the weight of the tablets and the apparent particle density of the tablet mass (4). Breaking strength was measured with Schleuniger 2E apparatus and disintegration time was determined using Ph. Eur. method with discs.

Water penetration rate into tablets was studied with a modified Enslin apparatus as previously described (7). The instant water penetration rate was calculated as a zero order slope with the method of least squares using from four to twelve measurement points. The number of points included in calculations was selected so that the coefficient of correlation was better than 0.99. The maximum water uptake was determined at the end point of penetration curve where tablet was totally wetted.

The data from dissolution experiments was treated according to the first order dissolution rate. The coefficient of correlation for the rate constant of different tablet formulations varied between 0.83 and 0.99. The lowest coefficient of correlations were observed with very fastly dissolving ACP tablets. Thus the amount of drug dissolved during six minutes (for poorly soluble tolfenamic acid thirty minutes) was found to be a suitable parameter to describe and compare the dissolution properties of various tablet formulations. Dissolution of slowly disintegrating tablets of lot A was studied according to the method described in the official USP monograph for sodium tolmetin tablets. Thus the paddle method with stirring rate of 50 rpm and 900 ml of phosphate buffer of pH 4.5 were used. Variations between replicates of fastly disintegrating and dissolving ACP tablets in lots B and C were very wide when the official paddle method was used. The paddle method requires that the position of a tablet is every time exactly the same on the bottom of the dissolution vessel. In the case of fastly disintegrating water insoluble tablet matrix even small differences led to an unacceptable great variation (standard deviation of about 20 per cent) in dissolution results. For this reason the basket method with stirring rate of 75 rpm was used for tablets of lots B and C. The basket method was also used for tablets, which contained a poorly water soluble tolfenamic acid as a drug material. The stirring rate and dissoluti-

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on medium for tolfenamic acid tablets were 150 rpm and 900 ml of phosphate buffer of pH 7.4, respectively. The dissolved sodium tolmetin and tolfenamic acid were measured spectrophotometrically (Hitachi 220, Japan) at 320 nm and 289 nm, respectively.

RESULTS AND DISCUSSION

The Effect of The Amount of Cellulose on Drug Dissolution

The excellent binding properties of microcrystalline cellulose continuously increased the strength of Emcompress tablets resulting in a longer disintegration as the amount of cellulose increased (Table 2). At the amounts of 10 and especially 20 wt % the ability of microcrystalline cellulose to accelerate water penetration into the tablets was able to overcome the binding effect of this material. Tablets with greater amounts of microcrystalline cellulose were too intact for fast water penetration. The increasing amounts of microcrystalline cellulose in Emcompress tablets accelerated the dissolution of water soluble tolmetin only up to cellulose amount of 20 wt %. Dissolution of tolmetin correlated well with the rate of instant water penetration into tablets containing microcrystalline cellulose.

An increase in the amount of the agglomerated cellulose powder, ACP increased both strength and disintegration time of tablets (Table 2). On the contrary to microcrystalline cellulose tablets, the dissolution of tolmetin from ACP tablets was accelerated by increasing the amount of cellulose up to 50 wt %. Only with the very intact tablets containing 70 wt % of ACP a clear decrease in drug dissolution was seen. All the ACP tablets, except those containing 70 wt % of ACP, liberated tolmetin faster than all the microcrystalline cellulose tablets. Also on the contrary to microcrystalline cellulose tablets no correlation between dissolution of tolmetin and instant water penetration rate was seen.

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TABLE 2.

The properties of tablets containing different amounts of cellulose and dicalcium phosphate, 10 wt % of sodium tolmetin and 0.5 wt % of magnesium stearate. The values in parenthesis represent the standard error of the mean.

Amount of cellulose (%)	Breaking strength (kp)	Disintegration time (sec)	Instant water penetration rate (µl/sec)	Total water uptake (µl)	Dissolution during 6 min (%)
0	5.0 (0.1)	402 (10)	0.6 (0.1>)	51 (½>)	11 (½>)
ACP					
10	6.6 (0.3)	25 (1)	5.6 (0.1)	210 (4)	39 (2)
20	8.8 (0.3)	30 (2)	7.6 (0.1)	319 (4)	48 (2)
30	11.8 (0.1)	47 (2)	6.4 (0.2)	404 (3)	49 (4)
50	>20	177 (9)	3.1 (0.1)	600*	54 (2)
70	>20	578 (12)	0.6 (0.1>)	389**	13 (1)
Emcocel					
10	6.4 (0.1)	46 (1)	2.4 (0.1)	128 (1)	18 (1)
20	8.2 (0.3)	56 (2)	2.7 (0.1)	200 (½>)	24 (2)
30	11.2 (0.1)	85 (6)	2.0 (0.1)	242 (1)	22 (1)
50	17.0 (0.1)	195 (6)	1.1 (0.1)	335 (4)	16 (1)
70	>20	393 (38)	0.7 (0.1>)	385 (3)	10 (½>)

*Exceeded capacity of capillary pipet
**Not saturated during 600 seconds

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The disintegrant action of ACP is related to its ability to accelerate water penetration into tablets but also to expansion of deformed ACP agglomerates inside tablets (7). Part of the penetrating water goes inside the porous ACP agglomerates causing them to swell or expand and thus cracks are created in tablet structure (7). The extent of this process is related to total water uptake (Table 2). Thus total water uptake is more important than instant water penetration rate in dissolution process of tolmetin from ACP tablets.

Disintegration of a tablet is usually a prerequisite for fast dissolution of drug. The observed dissolution rate of tolmetin from ACP tablets did, however, not correlate with the disintegration time of these tablets (Table 2). The visual examination of tablets during disintegration test revealed that ACP tablets were broken down into slowly disintegrating fragments, which were able to liberate tolmetin but not to pass the screen of Ph. Eur. disintegration testing apparatus. Thus in this kind of case the Ph. Eur. disintegration test does not properly predict the dissolution properties of tablets.

The Effect of Tablet Porosity on Drug Dissolution

An increased porosity of tablets containing microcrystalline cellulose increased instant water penetration rate and decreased disintegration time of these tablets (Table 3). This was due to the looser structure of tablets as the compressional pressure was decreased. In agreement with the previous results of Khan and Rhodes (8) the dissolution of water soluble drug, tolmetin was accelerated progressively with increasing porosity of tablets.

The dissolution of tolmetin from ACP tablets was also dependent on the porosity of tablets. The dissolution of tolmetin was, however, clearly faster from ACP tablets than from microcrystalline cellulose tablets (Table 3). Even the densest ACP tablets liberated tolmetin faster than the loosest microcrystalline cellulose tablets.

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TABLE 3.

The properties of tablets compressed to different porosities. Tablets contained 20 wt % of cellulose, 70 wt % of dicalcium phosphate, 10 wt % of sodium tolmetin and 0.5 wt % of magnesium stearate. The values in parenthesis represent the standard error of the mean.

Porosity of tablet (%)	Breaking strength (kp)	Disintegration time (sec)	Instant water penetration rate (µl/ml)	Total water uptake (µl)	Dissolution during 6 min (%)
ACP					
16	13.0 (0.1)	52 (2)	5.8 (0.2)	339 (2)	59 (1)
19	10.7 (0.3)	17 (1)	9.1 (0.2)	351 (6)	76 (2)
21	7.3 (0.1)	16 (½>)	12.5 (0.2)	320 (5)	82 (1)
26	5.0 (0.1)	9 (1)	13.2 (0.4)	308 (4)	90 (1)
Emcocel					
15	14.2 (0.3)	107 (3)	1.6 (0.1)	183 (1)	16 (1)
18	10.0 (0.2)	46 (1)	3.4 (0.1)	203 (1)	27 (1)
21	8.1 (0.1)	28 (1)	5.2 (0.2)	212 (½>)	35 (1)
26	5.0 (0.1)	13 (½>)	8.2 (0.2)	226 (1)	54 (2)

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TABLE 4.

The properties of tablets compressed to different porosities. Tablets contained 20 wt % of cellulose, 70 wt % of dicalcium phosphate, 10 w % of tolfenamic acid and 0.5 wt % magnesium stearate. The values in parenthesis represent the standard error of the mean.

Porosity of tablet (%)	Breaking strength (kp)	Disintegration time (sec)	Dissolution during 30 min (%)
ACP			
20	10.4 (0.5)	26 (1)	13.1 (0.6)
22	7.1 (0.1)	20 (1)	11.7 (0.4)
26	4.9 (0.2)	17 (½>)	12.5 (1.0)
Emcocel			
19	8.8 (0.3)	91 (5)	3.2 (0.1)
22	7.3 (0.1)	82 (2)	3.6 (0.2)
26	4.7 (0.1)	43 (1)	3.6 (0.5)

In our previous study (7) the porosity of ACP–Emcompress tablets, without a drug, had no distinct effect on water penetration into tablets. This was shown to be due to a creation of cracks in tablet structure. In the present study tablet porosity and amount of ACP were greater and also a soluble drug material was present. Because of looser compacts water was able to penetrate more easily into tablets through capillaries. Thus, besides the creation of cracks also the presence of large capillaries was important for the instant water penetration. On the contrary to microcrystalline cellulose tablets, the total water uptake of ACP tablets showed, in agreement with the previous study (7) no distinct trend with tablet porosity (Table 3). Thus the densest tablets took even more water than the looser ones. This pointed out that the expansion or swelling of deformed agglomerates, causing formation of cracks, occured during water penetration basically similarly as in the previous study. The relative effect of tablet porosity on tolmetin dissolution was smaller for ACP tablets than for microcrystalline cellulose tablets. Thus even in rather loose ACP tablets with water soluble materials the formation of cracks plays an important role making the dissolution process less dependent on the initial tablet structure.

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The dissolution of poorly soluble tolfenamic acid was clearly faster from tablets containing ACP than from those containing microcrystalline cellulose. Tablet porosity had, on the contrary to tablets containing tolmetin, no effect on the dissolution of tolfenamic acid from ACP tablets and only a trivial effect on the dissolution from microcrystalline cellulose tablets. The disintegration time, however, increased for both cellulose materials with decreased porosity (Table 4). This result agrees with the previous results of Chilamkurti et al. (9) that dissolution of a poorly water soluble drug was independent on disintegration time of water insoluble tablet matrix.

The Effect of Magnesium Stearate on Drug Dissolution

Ganderton (10) and Van Kamp et al. (11) have shown that increasing amounts of magnesium stearate prevented water penetration into tablets. Khan et al. (12), on the other hand, suggested that magnesium stearate would not decrease water penetration into microcrystalline cellulose tablets and that bonding strength and porosity were dominant factors affecting disintegration of these tablets. The results of Lerk et al. (13) for microcrystalline cellulose tablets contradicted with those of Khan et al. (12). Also our results disagreed with the results of Khan et al. (12). In the present study an increase in the amount of magnesium stearate resulted in longer disintegration time, slower water penetration and slower tolmetin dissolution for both cellulose materials (Table 5). However, the intrinsic wetting and dissolution phenomens were, according to the shapes of penetration and dissolution curves (Fig. 1 and 2), unchanged when the amount of magnesium stearate was below 2 wt %. When tablets contained at least 2 wt % of magnesium stearate both penetration and dissolution processes were deteriorated and the shape of these curves changed. Thus it is well possible to add the commonly used amounts of hydrofobic lubricant in ACP tablets without harmfully affecting the dissolution properties of tablets.

Disintegration time was shorter and water penetration and tolmetin dissolution were faster for tablets containing ACP than for those containing microcrystalline

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TABLE 5.

The properties of tablets containing different amounts or differently mixed magnesium stearate. Tablets contained 20 wt % of cellulose, 70 wt % of dicalcium phosphate and 10 wt % of sodium tolmetin. The values in parenthesis represents the standard error of the mean.

Amount of magnesium stearate (%)	Breaking strength (kp)	Disintegration time (sec)	Instant water penetration rate (µl/sec)	Total water uptake (µl)	Dissolution during 6 min (%)
ACP					
1/2	5.5 (0.1)	11 (½>)	14.6 (0.3)	332 (4)	89 (1)
1	5.4 (0.1)	12 (½>)	12.1 (0.2)	323 (4)	81 (1)
1*	5.6 (0.1)	12 (1)	12.7 (0.1)	327 (5)	87 (1)
2	5.9 (0.1)	26 (1)	9.0 (0.2)	324 (4)	63 (1)
5	5.4 (0.1)	311 (7)	3.7 (0.2)	281 (6)	49 (1)
Emcocel					
1/2	5.4 (0.1)	14 (1)	7.5 (0.2)	220 (½>)	48 (1)
1	5.4 (0.1)	20 (1)	5.5 (0.2)	212 (2)	38 (1)
1*	5.8 (0.1)	17 (1)	6.2 (0.2)	214 (2)	41 (2)
2	5.9 (0.1)	48 (2)	3.7 (0.1)	194 (3)	29 (1)
5	5.7 (0.1)	75 (4)	1.1 (0.1>)	143 (1)	15 (1)

*Mixed manually with spatula

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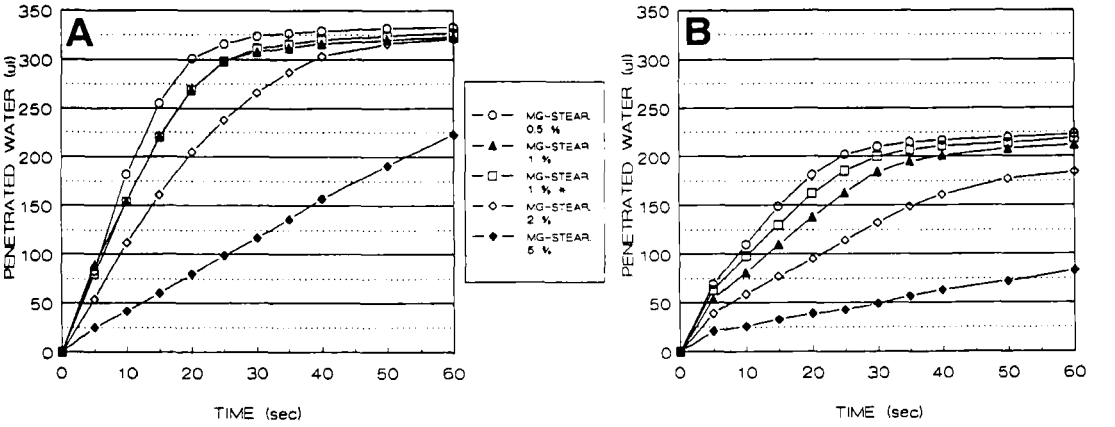

FIGURE 1. Water penetration into tablets containing different amounts or differently mixed magbesium stearate. Tablets containing 20 wt % of cellulose, 70 wt % dicalcium phosphate and 10 wt % of sodium tolmetin. ACP tablets on the left (1A) and Emcocel tablets on the right (1B). The standard error of the means fall within symbols. * = mixed manually with spatula.

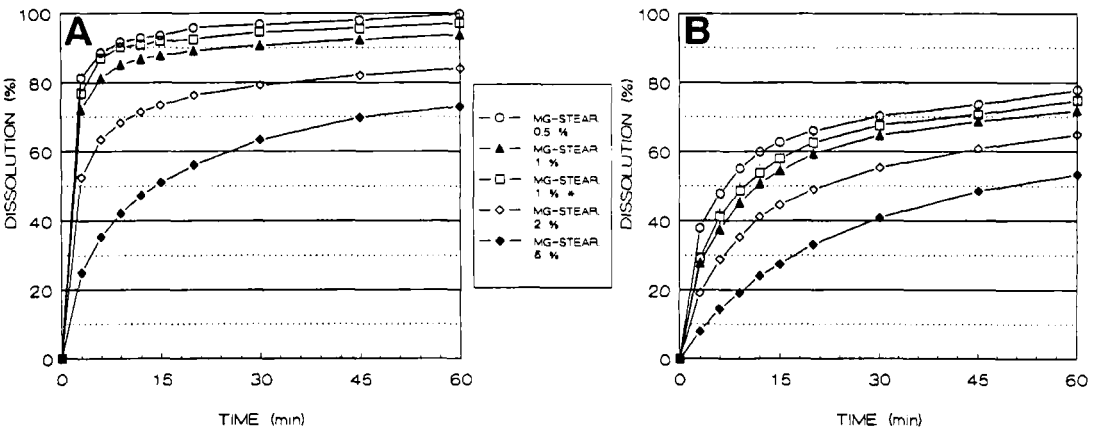

FIGURE 2. Dissolution of sodium tolmetin from tablets containing different amounts or differently mixed magnesium stearate. Tablets containing 20 wt % of cellulose, 70 wt % dicalcium phosphate and 10 wt % of sodium tolmetin. ACP tablets on the left (2A) and Emcocel tablets on the right (2B). The standard error of the means fall within symbols. * = mixed manually with spatula.

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cellulose (Table 5). However, when the amount of magnesium stearate was increased the occuring relative decreases in penetration and dissolution rates were quite similar for both celluloses. Van der Watt (14) studied interactions between magnesium stearate and various size fractions of microcrystalline cellulose powder during mixing process. The formation of magnesium stearate film around microcrystalline cellulose was more pronounced for larger cellulose particles. On the basis of the larger particle size of ACP compared to that of microcrystalline cellulose (4) it could be assumed that water penetration and drug dissolution were slower for ACP tablets. However, the specific surface area of rough and porous agglomerates of ACP is 50 times greater than that of smoother microcrystalline cellulose particles (4). Thus the capacity of ACP agglomerates to survive from coverage of magnesium stearate was better than that of microcrystalline cellulose. ACP agglomerates also underwent partial fragmentation during compression (6) thus creating new clean surfaces without magnesium stearate.

Contradicting results concerning the effect of mixing time of magnesium stearate on disintegration of tablets have been published (12,15). Supporting the findings of Bolhuis et al. (15) a prolonged mixing resulted in an increase in disintegration time and decrease in water penetration and dissolution (Table 5). The differences between differently mixed tablet masses were, however, nearly similar and not very dramatic for both cellulose materials.

CONCLUSIONS

According to the results of this study the agglomerated cellulose powder is an advantageous direct compression filler–binder to be used in tablets containing either water soluble or poorly water soluble drug material. Independently on the amount of cellulose in tablet, the porosity of tablet, the solubility of drug material and the amount and the mixing intensity of hydrophobic lubricant added into tablet mass, tablets with the agglomerated cellulose powder liberated drug material faster than corresponding tablets with microcrystalline cellulose.

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