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DC Calcium lactate, a new filler-binder for direct compaction of tablets

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Abstract

In this paper, a directly compressible form of calcium lactate is introduced as a filler-binder for direct compaction of tablets. Calcium lactate is one of the most important calcium sources and has, in comparison with other organic calcium salts, a good solubility and bioavailability. Two different modifications, calcium lactate trihydrate and calcium lactate pentahydrate are described in the main pharmacopoeias. This paper describes that the compaction properties of calcium lactate pentahydrate (Puracal® DC) are much better than those of the calcium lactate trihydrate (Puracal® TP). Calcium lactate pentahydrate has better compaction properties than dicalcium phosphate dihydrate, even if lubricated with magnesium stearate. Moreover, as a consequence of its crystalline structure, calcium lactate pentahydrate has a low compaction speed sensitivity. This means that, in combination with its excellent flow properties, calcium lactate pentahydrate is a suitable filler-binder in tablets prepared by high-speed compaction. In a number of formulation examples it will be illustrated that tablets containing calcium lactate pentahydrate as main or additional filler-binder have a short disintegration time and a fast drug release. Directly compressible calcium lactate can be considered as a promising excipient in both pharmaceutical tablets and tablets for the nutraceutical market.
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Keywords: Tablet; Direct compaction; Filler-binder; Calcium lactate

1. Introduction

Since the late 1960s many excipients have been introduced on the pharmaceutical market as filler-binders for tablets produced by direct compaction. The products can be classified into (derivatives of) natural products like starches, celluloses, sugars and polyalcohols and (inorganic) calcium salts. Different calcium salts have been used as filler-binders. Dicalcium phosphate dihydrate is the most common, but has a number of drawbacks in terms of compactibility and stability (Bolhuis and Chowhan, 1995). Anhydrous cal-

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cium phosphate has better stability properties, but the compactibility is not or only slightly improved if compared with the dihydrate (Carstensen and Ertell, 1990; Schmidt and Herzog, 1993). Tricalcium phosphate has indeed better binding properties than dicalcium phosphate dihydrate (Schmidt and Herzog, 1993), but also has a higher strain rate sensitivity (Patel et al., 1987). Other drawbacks of tricalcium phosphates are their high sticking tendency with dies and punches (Schmidt and Herzog, 1993) and the effect of ageing on tablet properties (Chowhan and Amaro, 1979). A general problem of tablets compressed from different calcium phosphates is their high friability (Schmidt and Herzog, 1993). Another inorganic salt for direct compaction is a specially processed grade of calcium sulphate dihydrate. It has good flow properties but a poor compactibility (Bolhuis et al., 1985).

Until now, organic calcium salts have not been described as tablet excipients. Calcium lactate is a widely used calcium source in pharmaceutical preparations and has, in comparison with other organic calcium salts, a good solubility and bioavailability (Levenson and Bockman, 1994). Two different modifications, calcium lactate trihydrate and calcium lactate pentahydrate, are described in the main pharmacopoeias.

The aim of this study was to evaluate special free flowing forms of both calcium lactate trihydrate (Puracal® TP) and calcium lactate pentahydrate (Puracal® DC) as a filler-binder for direct compaction of tablets. Moreover, they will be compared with other, commonly used filler-binders.

2. Materials and methods

Calcium lactate trihydrate (Puracal® TP) and calcium lactate pentahydrate (Puracal® DC) were obtained from Purac, Gorinchem, Netherlands. Microcrystalline cellulose (Pharmacel®102) and spray dried lactose (Pharmatose® DCL 11) were supplied by DMV, Veghel, Netherlands. Sodium starch glycolate (Primojel®) and croscarmellose sodium (Primellose®) were obtained from Avebe, Foxhol, Netherlands. The other materials used were dicalcium phosphate dihydrate (Emcompress®, Penwest Pharmaceuticals, Reigate, UK), crospovidone (Polyplasclone®XL, GAF, Frechen, Germany), theophylline monohydrate (Ph. Eur., ACF-Chemiefarma, Maarssen, Netherlands) and magnesium stearate (Ph. Eur., Centrachemie, Etten-Leur, Netherlands).

The density was determined using helium pycnometry (Quantasorb multipycnometer, Syosset, USA). The bulk density was determined by pouring about 250 g powder in a calibrated glass cylinder. The tap density was determined according to DIN 53194.

The moisture content of the calcium lactates was determined by drying at 120°C until constant weight, using a Sartorius MA 40 moisture analyser (Sartorius, Göttingen, Germany).

The particle size distribution was determined using laser diffraction (Sympatec HELOS Compact KA with 500 mm lens; Sympatec, Clausthal, Germany). The powder was dispersed with a RODOS dry powder dispenser at a pressure of 0.5 bar.

The X-ray equipment used to determine the crystallinity of calcium lactate pentahydrate was a Philips PW 1820 ω-goniometer operated in the Bragg-Brentano mode. The goniometer is adapted with a crystal monochromator so that only the Kα radiation of the used Cu tube is recorded. The calcium lactate was mixed with silicon powder that is used as an internal standard. The peak position of the silicon powder is used afterwards to correct for an error in the height adjustment of the specimens and to increase the accuracy of the experiments.

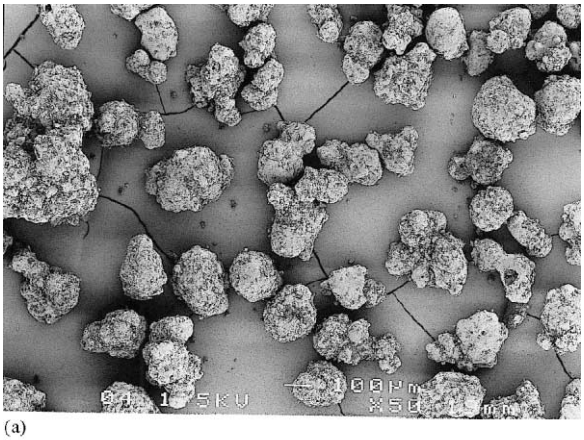
Electron micrographs were obtained using a scanning electron microscope (Jeol 6301F, Jeol Ltd, Tokyo, Japan). Prior to investigation, the sample was coated with goldpalladium, using a direct current sputter technique.

The flow properties were determined by measurement of the minimum aperture through which the material was still free flowing (funnel flow) (Klein, 1968) and by calculation of the Hausner ratio (the quotient of tap density and bulk density).

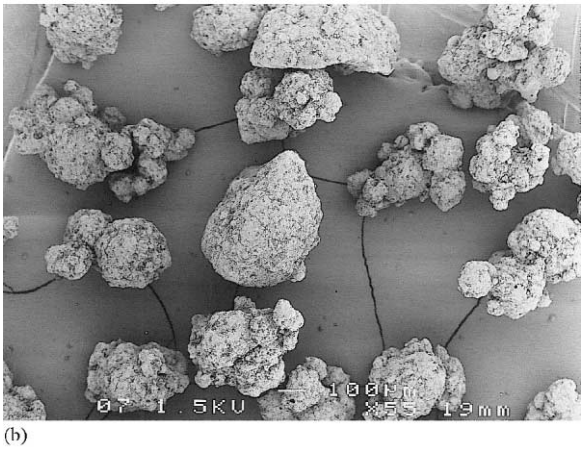
Flat-faced tablets of 500 mg and a diameter of 13 mm were compressed on a compaction simula-

tor (ESH, Brierley Hill, UK) at low speed (3 mm s^{-1}) or at high speed (300 mm s^{-1}). The compaction force varied between 8–25 kN (pressure 60–190 MPa). The upper punch displacement profiles were sine waves with different amplitudes in order to obtain the different maximum compaction pressures. The lower punch was stationary during compaction. If lubricated, the filler-binders were mixed with 0.5% magnesium stearate for 2 min in a Turbula mixer, model 2P (W.A. Bachofen, Basle, Switzerland) at 90 rpm.

Tablet formulations were prepared by mixing the excipients except magnesium stearate for 15 min in the Turbula mixer at 90 rpm. After addition of magnesium stearate, mixing was continued for 2 min.



(a)



(b)

Fig. 1. Scanning electron micrographs of (a) calcium lactate trihydrate and (b) calcium lactate pentahydrate.

Crushing strengths of the tablets were measured at least 16 h after compaction with a Schleuniger 4N strength tester (Dr. Schleuniger Productronic, Soloturn, Switzerland). The presented results are the mean of 5 tablets. Tablet friability was determined in the Roche friabilator single blade apparatus according to the Ph. Eur. The disintegration times were determined using the Ph. Eur. apparatus without disks. The presented results are the mean of 5 tablets.

The dissolution rate of theophylline monohydrate was measured in a USP XXIII paddle apparatus (Rhône-Poulenc, Paris, France) at 0.05 M phosphate buffer pH 6.8. The drug concentration was measured spectrophotometrically using an Ultrospec 4052 TDS apparatus (LKB, Zoetermeer, Netherlands) at 268 nm. All experiments were carried out in triplicate.

3. Results and discussion

3.1. Compaction properties

The two commercially available calcium lactates consist of chemically and physically stable granular powder. Table 1 shows some physical and chemical properties. In the past there was a preference in some countries to use the trihydrate grade in tablets in order to eliminate any risk of microbial deterioration of the tablets. However, when using pentahydrate with a moisture content below 27% calcium lactate pentahydrate is microbiologically stable. Although calcium lactates have binding properties of their own (Bolhuis and Chowhan, 1995), the pentahydrate form has been designed especially for direct compaction of tablets. It is a granular material, prepared by a special spray drying process. Fig. 1 shows scanning electron micrographs of both calcium lactates.

Fig. 2 shows compaction profiles of both calcium lactate trihydrate (Fig. 2(a)) and calcium lactate pentahydrate (Fig. 2(b)). For unlubricated tablets, the compaction process was performed with two different compaction velocities: 3 and 300 mm s^{-1}. Tablets lubricated with 0.5% magnesium stearate were compressed at 300 mm s^{-1}.

Table 1
Physical properties of calcium lactates

	Calcium content (%)	Moisture content (%)	Particle size (μm)			Density (kg m^{-3})	Solubility at 25°C (% m/v)
			D (*v*,0.1)	*D* (*v*,0.5)	*D* (*v*,0.9)		
Calcium lactate trihydrate	15.1	18.5	115	243	391	1516	8
Calcium lactate pentahydrate	13.8	24.9	118	227	355	1494	9

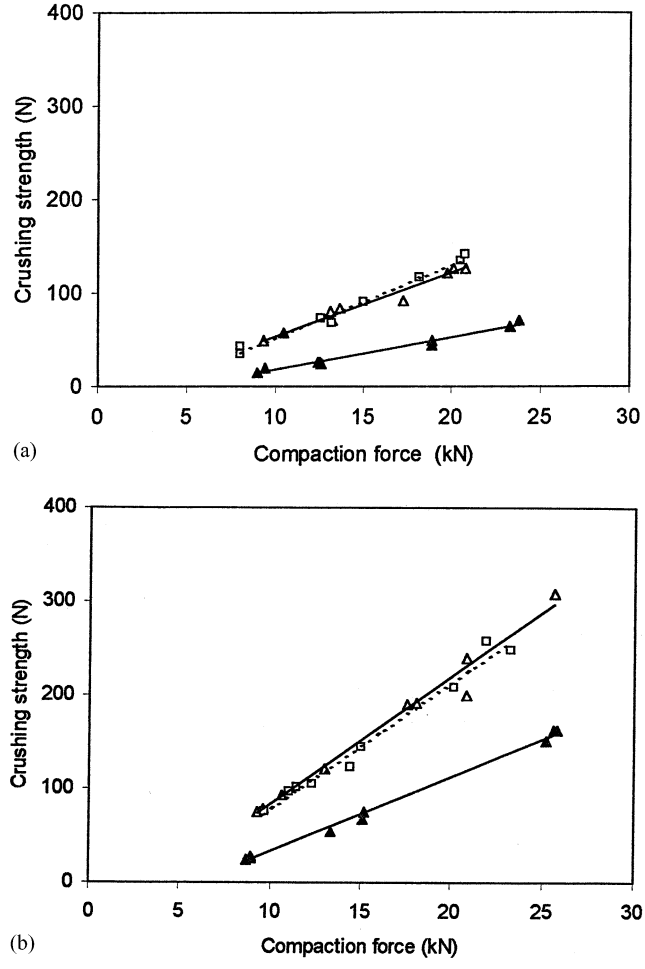


Fig. 2. (a) Compaction profiles of unlubricated calcium lactate trihydrate, compressed at (□; dotted line) 3 mm s^{-1} and (△) 300 mm s^{-1}, respectively, and (▲) calcium lactate trihydrate, lubricated with 0.5% magnesium stearate, compressed at 300 mm s^{-1}. (b) Compaction profiles of unlubricated calcium lactate pentahydrate, compressed at (□; dotted line) 3 mm s^{-1} and (△) 300 mm s^{-1}, respectively, and (▲) calcium lactate pentahydrate, lubricated with 0.5% magnesium stearate, compressed at 300 mm s^{-1}.

The highest speed can be considered as a simulation of a high-speed rotary press (Armstrong, 1990; Hokhodchi and Rubinstein, 1996). The figures show that the compaction properties of the pentahydrate are much better than those of the trihydrate but for both materials the tablet crushing strength was not affected by the speed of compaction. The Fig. 2(a) and (b) also show that the lubricant magnesium stearate decreases the tablet crushing strength for both calcium lactates.

The effect of compaction speed on crushing strength is dependent on the deformation behaviour of a material. High strain rate sensitivities have been found for ductile materials such as celluloses and starches and low strain rate sensitivities for brittle materials under which dicalcium phosphate dihydrate (Roberts and Rowe, 1985). The low compaction speed sensitivity of the calcium lactates may be caused by the fact that they are brittle, crystalline materials.

Röntgen diffraction patterns of both intact and broken particles of calcium lactate pentahydrate are presented in Fig. 3. The square root of the measured intensity is plotted as a function of the 2θ angle. The two highest diffraction peaks that are visible at $\approx 28.39°$ and 47.23 °2θ are reflec-

tions of the {1 1 1} and the {2 2 0} planes of the added silicon powder. As the penetration depth (at 70 μm depth 90% of the radiation is absorbed) is smaller than the diameter of calcium lactate particles, diffraction patterns of broken calcium lactate pentahydrate particles were measured too. The particles were carefully broken with a mortar and pestle, in order to avoid any amorphization. Fig. 3 shows that the diffraction patterns of both calcium lactate samples are identical and there are no traces of the presence of an amorphous phase (Alexander, 1969). Therefore, it seems justified to conclude that calcium lactate pentahydrate has a crystallinity index close to 100%.

The lubricant sensitivity of the calcium lactates is caused by a lubricant film, formed around the individual particles during mixing with magnesium stearate and the point of time of fragmentation of calcium lactate particles during the compression procedure. In contrast to dicalcium phosphate dihydrate, the calcium lactates are brittle materials with a low fragmentation propensity. Filler-binders with a low fragmentation propensity will initially rearrange during compression and then break. This implies that fragments originating from one particle will not be mixed with fragments of another particle and will hence not destroy the lubricant film to a large extent. As an effect, the calcium lactates have a higher lubricant sensitivity than materials with a high fragmentation propensity such as dicalcium phosphate dihydrate but a lower lubricant sensitivity than ductile materials such as celluloses or starches. (Van der Voort Maarschalk and Bolhuis, 1999).

In Fig. 4, the compaction profiles of calcium lactate pentahydrate are compared with those of another spray dried product: spray dried lactose and another calcium salt: dicalcium phosphate dihydrate, respectively. The profiles are for filler-binders, lubricated with 0.5% magnesium stearate and compressed at a speed of 300 mm s^{-1}. The figure shows that the compactibility of calcium lactate pentahydrate is almost the same as that of spray dried lactose, but much better than the compactibility of dicalcium phosphate dihydrate.

3.2. Flowability and disintegration properties

In Table 2 the bulk density, the tap density and the flow properties, expressed as flow through apertures and Hausner ratio, of the two calcium lactates are compared with those of spray dried lactose and dicalcium phosphate dihydrate. The Table shows that both calcium lactate trihydrate and calcium lactate pentahydrate have excellent flow properties, which can compete with those of excellent flowing products such as spray dried lactose and dicalcium phosphate dihydrate.

Table 3 shows the disintegration times for tablets, compressed at 20 kN with a speed of 300 mm s^{-1} from excipients lubricated with 0.5% magnesium stearate and of tablets, compressed from blends of filler-binders with 4% of a super disintegrant and 0.5% magnesium stearate. The disintegration procedure was performed without using disks. The disintegration of tablets compressed from the calcium lactates and spray dried lactose without a disintegrant is in fact deter-

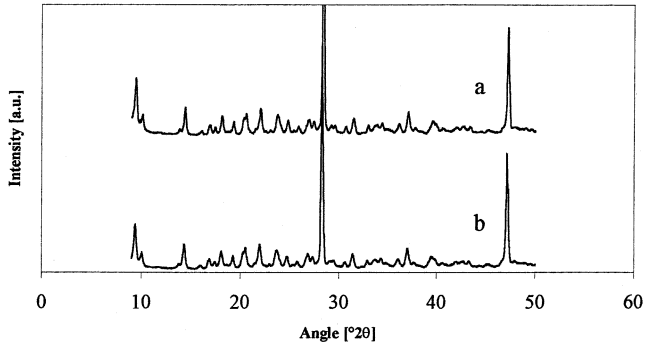


Fig. 3. Diffraction pattern of (a) intact and (b) broken particles of calcium lactate pentahydrate.

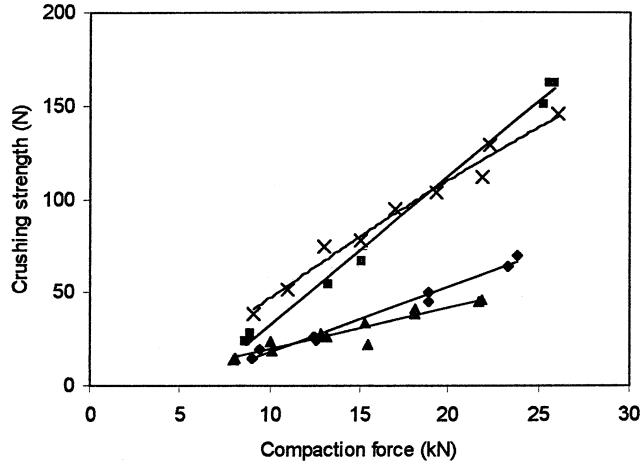


Fig. 4. Compaction profiles of different filler-binders, lubricated with 0.5% magnesium stearate and compressed at 300 mm s^{-1}. (■) calcium lactate pentahydrate, (◆) calcium lactate trihydrate, (x) spray dried lactose and (▲) dicalcium phosphate dihydrate.

Table 2
Flow properties of filler-binders

Filler-binder	Bulk density (kg m^{-3})	Tap density (kg m^{-3})	Flow through aperture (mm)	Hausner ratio
Calcium lactate trihydrate	680	788	2.5	1.16
Calcium lactate pentahydrate	559	668	2.5	1.20
Dicalcium phosphate dihydrate	956	1119	2.5	1.17
Spray dried lactose	626	729	2.5	1.16

Table 3
Disintegration time of tablets compressed from calcium lactate pentahydrate and calcium lactate pentahydrate, mixed with 4% disintegrant (All tablets were lubricated with 0.5% magnesium stearate)

Filler-binder	No disintegrant	4% sodium starch glycolate	4% croscarmellose sodium	4% crospovidone
Calcium lactate trihydrate	454 ± 33 s	432 ± 30 s	320 ± 19 s	397 ± 13 s
Calcium lactate pentahydrate	650 ± 12 s	435 ± 51 s	314 ± 25 s	368 ± 7 s
Dicalcium phosphate dihydrate	>1800 s	8 ± 1 s	9 ± 1 s	3 ± 0 s
Spray dried lactose	983 ± 49 s	279 ± 15 s	192 ± 10 s	116 ± 64 s

mined by dissolution of the excipients. The solubilities of calcium lactate trihydrate and -pentahydrate are given in Table 1. Spray dried lactose has a solubility of about 200 g/l. Just as could be expected from previous work, a too high water solubility of a filler-binder will prolong the disintegration time (Van Kamp et al., 1986b). This is the reason that tablets compressed from the highly soluble spray dried lactose disintegrate slower than those compressed from the moderately soluble calcium lactates. Tablets compressed from dicalcium phosphate dihydrate did not disintegrate at all. This effect is caused by the fact that dicalcium phosphate dihydrate is practically insol-

uble in water. In previous work it has been found that in spite of a fast and complete water penetration into dicalcium phosphate dihydrate tablets, the tablets will not disintegrate when no disintegrant is present (Van Kamp et al., 1986a).

The effect of the addition of 4% of a super-disintegrant is shown in Table 3. The table shows that all the disintegrants used improve the disintegration of the tablets, but that croscarmellose sodium is the disintegrant of choice for the calcium lactates. In previous work, it has been pointed out that as an effect of a combination of moderate swelling properties and a capillary action, croscarmellose sodium is an effective disintegrant in tablets containing materials with a moderate water solubility (Van Kamp et al., 1986a). For the practically insoluble dicalcium phosphate dihydrate all the super-disintegrants are effective (Van Kamp et al., 1986a).

3.3. Formulation examples

Because calcium lactate pentahydrate is the most promising one of the two calcium lactates, the efficacy of this product as a directly compressible filler-binder is illustrated in two different tablet formulations and compared with almost similar formulations containing dicalcium phosphate dihydrate (Table 4). All the tablets contain 5% theophylline monohydrate as a model active ingredient. Formulations I and II contain calcium lactate pentahydrate and calcium phosphate dihydrate, respectively, as single filler-binder. Formulations III and IV contain a combination of microcrystalline cellulose and one of the calcium salts, because it has been shown in previous work that tablets with excellent compaction properties can be prepared from blends of dicalcium phosphate dihydrate and microcrystalline cellulose (Bolhuis et al., 1979). For the tablets containing dicalcium phosphate dihydrate, sodium starch glycolate was chosen as a disintegrant because of the effectivity of this disintegrant for insoluble filler-binders (Van Kamp et al., 1986a).

The tablet properties are listed in Table 4. As well for tablets containing one calcium salt as for tablets containing a combination of microcrystalline cellulose and a calcium salt, the highest crushing strengths were found for tablets containing calcium lactate pentahydrate.

As could be expected from previous work (Lerk et al., 1974), the addition of 25% microcrystalline cellulose increased the crushing strength of tablets with dicalcium phosphate dihydrate. The Table shows, however, that tablets with calcium lactate pentahydrate as a single filler-binder have about the same crushing strength as tablets with a blend of dicalcium phosphate and microcrystalline cellulose. For this reason, the addition of the second filler-binder microcrystalline cellulose is not necessary if the tablets contain calcium lactate pentahydrate instead of dicalcium phosphate dihydrate. The friability of tablets compressed from formulations I, III and IV were lower than 1%, but tablets

Table 4
Tablet formulations and properties of tablets, compressed at 20 kN at a velocity of 300 mm s^{-1}

Formulation	I	II	III	IV
Theophylline monohydrate	5.0%	5.0%	5.0%	5.0%
Calcium lactate pentahydrate	90.5%	–	65.5%	–
Dicalcium phosphate dihydrate	–	90.5%	–	65.5%
Microcrystalline cellulose, type 102	–	–	25.0%	25.0%
Croscarmellose sodium	4.0%	–	4.0%	–
Sodium starch glycolate	–	4.0%	–	4.0%
Magnesium stearate	0.5%	0.5%	0.5%	0.5%
Tablet properties				
Crushing strength	86 ± 5 N	47 ± 3 N	130 ± 8 N	84 ± 6 N
Disintegration time	229 ± 9 s	4 ± 1 s	173 ± 9 s	10 ± 1 s
Friability	0.7%	100.0%	0.3%	0.4%

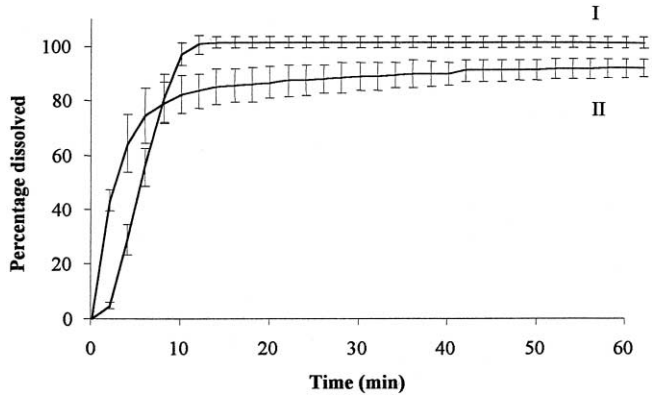


Fig. 5. Dissolution rate of theophylline from tablets according to formulation I and II, respectively (Table 4).

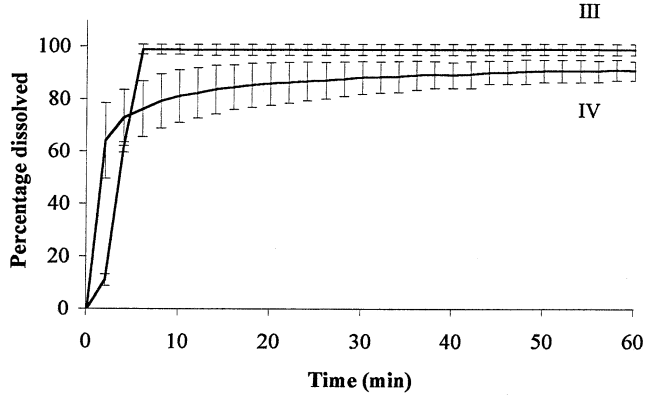


Fig. 6. Dissolution rate of theophylline from tablets according to formulation III and IV, respectively (Table 4).

compressed with dicalcium phosphate dihydrate as single filler-binder (formulation II) had a friability of 100%. This high friability must be attributed to the high brittleness of the material (Schmidt and Herzog, 1993).

The shortest disintegration times were found for tablets containing dicalcium phosphate dihydrate (formulations II and IV). Tablets with calcium lactate pentahydrate (formulations I and III) show indeed a longer disintegration time, but this time is acceptable if the higher tablet strength is taken into account. Moreover, it should be born in mind that the disintegration tests were accomplished without the use of disks.

The Figs. 5 and 6 show the dissolution rate of theophylline from tablets compressed from the four different formulations. Tablets containing dicalcium phosphate dihydrate as a single filler-binder (Fig. 5, formulation II) show indeed a fast start of the dissolution rate, but the rate slows down and dissolution is not complete after 60 min. Moreover, the standard deviation is rather high. This effect is caused by the fact that the tablets disintegrate in more or less large particles. Because of the poor solubility of dicalcium phosphate dihydrate, a further decrease of the size of these particles is a slow process. Fig. 6 shows that the addition of microcrystalline cellulose (Formulation IV) does not improve the dissolution rate of theophylline. The dissolution of theophylline from tablets containing calcium lactate pentahydrate (Fig. 5, formulation I) or a blend of calcium lactate pentahydrate and microcrystalline cellulose (Fig. 6, formulation III) starts slower as an

effect of the longer disintegration time. Dissolution is complete, however, after 10 min for tablets containing calcium lactate pentahydrate (formulation 1) and even 5 min for tablets containing calcium lactate pentahydrate and microcrystalline cellulose.

4. Conclusions

This study shows that a special, free-flowing form of calcium lactate pentahydrate is an effective filler-binder for tablets, prepared by direct compaction. The binding properties of this product are much better than those of calcium lactate trihydrate and dicalcium phosphate dihydrate, respectively. In contrast to dicalcium phosphate dihydrate, calcium lactate pentahydrate can be used as a single filler-binder in tablet formulations and does not need a second filler-binder such as microcrystalline cellulose.

The disintegration time of tablets containing calcium lactate pentahydrate is determined by dissolution of the excipient but can be shortened by the addition of a suitable disintegrant such as croscarmellose sodium.

Tablet formulations with theophylline monohydrate as a test drug show that the drug release can be improved when calcium lactate pentahydrate is used instead of dicalcium phosphate dihydrate, even if 25% of the calcium salt is replaced by microcrystalline cellulose.

According to the results of this study calcium lactate pentahydrate (Puracal® DC) is a promising filler-binder for direct compaction of tablets for both pharmaceutical and nutraccuticals purposes.

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