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Lubricant sensitivity in relation to bulk density for granulations based on starch or cellulose

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Summary

The study described in this paper was concerned with the susceptibility to lubrication with magnesium stearate of tablets compressed from granulations based on native starches or on modified celluloses. Different properties of the granulations, like particle size, flowability and surface area, were analyzed in relation to the tablet lubricant sensitivity ratio, being the ratio between the decrease in crushing of tablets due to mixing with a lubricant and the crushing strength of tablets prepared without a lubricant. Different linear relationships between the lubricant sensitivity ratio of tablets and the bulk density of the powders were found, for granulations prepared from different starting materials. Flowability proved to be the predominant mechanism in the formation of a lubricant film on the granulations. Poor flow properties, which are characterized by low bulk densities, retard or impede the formation of a lubricant film during mixing.

Introduction

In a previous study the characteristics of native starches have been investigated (Bos et al., 1987). Rice starch showed a much better compactibility than corn, potato and tapioca starch. Moreover, the binding capacity proved to be almost insensitive to mixing with the lubricant magnesium stearate. However, rice starch exhibited worst flowability as compared with the other starches, caused by its fine particle size. The flowability could be improved by granulation, but the sensitivity to lubrication increased as well, resulting in a decreased binding capacity of the lubricated granulations and consequently in tablets with lower crushing strengths.

The same is observed for microfine cellulose, marketed amongst others as Elcema^R. The granular grades of Elcema^R possess better flowability, but exhibit highest sensitivity to lubrication with magnesium stearate, as compared with the powder grades of Elcema^R (Vromans et al., 1988). However, the use of a lubricant in tablet formulations is necessary in order to facilitate the ejection of the tablet from the die, to prevent sticking of the tablets to the punches and to minimize wear on dies and punches. Magnesium stearate is the most

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commonly used lubricant. Next to the desired effect of an excellent die wall lubrication, magnesium stearate also has some unwanted side effects: poor wettability of the tablets, increased disintegration time and decreased tablet strength. These effects are caused by the formation of a hydrophobic film around the excipient particles (Strickland et al., 1956; Bolhuis et al., 1975). Not all types of tablet excipients are sensitive to lubrication. De Boer et al. (1978) illustrated that the sensitivity of excipients to magnesium stearate depends on the compression behaviour and on the bonding mechanism of the material. Fragmenting materials were hardly influenced by lubrication. This phenomenon was explained by the assumption that lubricant-free surfaces are created by fragmentation of the particles during consolidation of the particle system.

In a later study, Vromans et al. (1988) showed that for different types of lactose, the sensitivity to lubrication was related to the bulk density of the powder. Different explanations for this phenomenon were proposed. Firstly, a low bulk density is an indication for poor flowability of a powder, which might delay or even prevent the formation of a lubricant film during the mixing process. Secondly a lower bulk density will result in a larger contribution to particle rearrangement and consequently in more friction during consolidation. This could disturb an already formed lubricant film and enhance bond formation.

Roblot-Treupel and Puisieux (1986) studied the distribution of magnesium stearate on granules. They found that the lubricant was located in the cavities of the particles. Lerk and Sucker (1988) also found that part of the magnesium stearate was trapped in cavities of granulation particles.

The present study was set up to investigate:

- the effect of granulation on the lubricant susceptibility of different native starches and celluloses and;
- the occurrence of single linear relationships between lubricant sensitivity and bulk density for granulations prepared from starch and cellulose, respectively, similar to those found by Vromans et al. (1988) for lactose.

Granulations with different properties were prepared. The granulation properties such as particle size, flowability and surface area were analyzed and related to the lubricant sensitivity ratio, being the ratio between the decrease in crushing strength of tablets due to mixing with a lubricant and the crushing strength of tablets prepared without a lubricant. An attempt is made to elucidate the relationship between granulation properties and sensitivity to mixing with a lubricant. Knowledge of the predominant factors affecting the formation of a lubricant film on granular material may contribute to the development of granulations, having both good flow properties and good binding properties after lubrication.

Materials and Methods

Materials

The materials used were: rice starch Pharm. Eur. grade (Chemiefarma, Maarssen, The Netherlands), corn starch U.S.P. grade (Lamers en Indemans, 's Hertogenbosch, The Netherlands), tapioca starch (product of Thailand), potato starch Ph. Eur grade (Avebe, Foxhol, The Netherlands), modified rice starch (developed by Erawan Pharmaceutical Research and Laboratory Co., under the name Eratab^R, marketed by Avebe, Foxhol, The Netherlands, under the name Primotab^R ET), Elcema^R P050, P100, F150 and the two granular grades G250 and G400 (Degussa A.C., Frankfurt, F.R.G.), magnesium stearate (Centrachemie, Etten-Leur, The Netherlands) and talc (Centrafarm, Etten-Leur, The Netherlands). Methylcellulose 15 mPa s (A.C.F. Chemiefarma, Maarssen, The Netherlands) was used in granulation liquids. Prior to use and after granulation, all materials were stored for at least 1 week at 20 (±1)°C and 45 (±5)% RH.

Granule preparation

Granulations were prepared from rice starch, corn starch and Elcema^R P050, P100 and F150. Different granulation techniques were applied:

Fluid-bed granulation (method: fluid-bed): In a fluid-bed granulator (UNI-Glatt, Glatt GmbH, Binzen/Lörrach, F.R.G.) the material was mixed with the granulation liquid, which was sprayed onto the powder mass and dried in the fluid-bed granulator.

Wet massing and screening (method: frewitt): In a planetary mixer (model KM 250, Kenwood Ltd, Hants, U.K.) the material was mixed with the granulation liquid, which was added dropwise. After mixing the wet mass was forced through a Frewitt 1000 μm screen (Erweka GmbH, Mainz, F.R.G.). After drying at 40 °C in a tray drier, the granules were passed again through a Frewitt 1000 μm screen.

Wet massing and extrusion: In a planetary mixer (model KM 250, Kenwood Ltd, Hants, U.K.) the material was mixed with the granulation liquid, which was added dropwise. After mixing, the wet mass was forced through a granulator (model GA65, Alexanderwerk, Remscheid, F.R.G.). After drying at 40 °C in a tray drier, the granules were either used as such (method: alexander) or passed through a Frewitt 1000 μm screen (method: alex/frew).

Granulation in a rotating dish (method: dish): In a rotating dish (Erweka GmbH, Mainz, F.R.G) the granulation liquid was sprayed on the material. After sufficient build-up of the granules, they were dried at 40 °C in a tray drier.

Briquetting: After tabletting the material at either 75 MPa (method: 75 MPa briq) or 300 MPa (method: 300 MPa briq), the tablets were crushed in a mortar, with a pestle.

The granulation liquids used were respectively: a 2% w/v rice starch paste for rice starch, a 2% w/v corn starch paste for corn starch and water (method: W) or a 3% w/v methylcellulose solution (method: MC) for Elcema^R. After preparation, the granulations were classified with a vibrational sieving machine (Fritsh, Idar-Oberstein, F.R.G.), in two different sieve fractions of, respectively 106–300 and 300–600 μm.

Three commercial granulations: Elcema^R G250 and G400, prepared from Elcema^R P100, and Primotab^R, a rice starch granulation, were also investigated.

Flow characteristics

As an indication of the flowability of a particulate system, the bulk density was measured by pouring a weighed amount of the material into a small measuring glass with an internal diameter of about 16 mm. The results are the mean of three measurements.

The flowability of the materials was determined by estimation of the ability of the powders to flow freely through funnels of standard dimensions, as described by Klein (1968). The flowability is indicated with the number of the smallest funnel through which the powder flows freely. The funnel bearing number one has the smallest outflow opening and the funnel bearing number five, the largest outflow opening. This method only discriminates roughly between the flowability of the different materials. For a better discrimination, the flowability of the starch granulations was also determined as the mass flow (10^{-3} kg/s) through funnel number two. The results are the mean of three measurements. The volume flow (10^{-6} m^3/s) was calculated from the mass flow and the bulk density.

Surface area

The volume specific surface area (S_v: m^2/m^3) was determined with the aid of a permeametry apparatus, built according to the principle of Lea and Nurse (Allen, 1975). The weight specific surface area (S_{perm}: m^2/kg) was calculated from the volume specific surface area and the true density. The results are the mean of two measurements.

The weight specific surface area (S_{N2}: m^2/kg) was also measured by nitrogen adsorption, with a Quantasorp gas adsorption apparatus (Quantachron corporation, Syosset, U.S.A.). The results are the mean of at least two measurements.

Tablet preparation

Tablets were prepared by manually introducing 500 mg of either lubricated or unlubricated excipient into a 13 mm die of a compression device, mounted between the plates of a hydraulic press (Hydro Mooi, Appingedam, The Netherlands). The applied load rate for all tablets was 2 kN/s. The tablets were compressed at a load level of 75 or 150 MPa. If necessary the die was prelubricated by compression of a magnesium stearate tablet.

Lubricant sensitivity

The lubricant sensitivity was expressed as the lubricant sensitivity ratio (LSR). This is the ratio between the decrease in crushing strength of tablets due to mixing with lubricant and the crushing strength of unlubricated tablets prepared without magnesium stearate:

$$\mathrm{LSR} = (S_0 - S_{\mathrm{lub}})/S_0,$$

where S_0 and S_{lub} are the crushing strengths of tablets prepared without and with a lubricant, respectively. For the preparation of lubricated tablets, the powder was mixed with 1% w/w magnesium stearate, unless stated otherwise, in a Turbula mixer (model 2P, W.A. Bachoven, Basle, Switzerland) for 30 min at a rotation speed of 90 rpm prior to tabletting.

After tabletting the tablets were stored for at least 20 h at 20 °C and 45% RH before the crushing strength was measured with a Schleuniger instrument (model 4M, Dr K. Schleuniger, Zurich, Switzerland). The results are the mean of at least eight measurements.

Results and Discussion

The flow characteristics of different native starches and starch granulations as well as the properties of the prepared tablets are summarized in Table 1. A plot of the lubricant sensitivity ratio (LSR) of the tablets against the bulk density of the primary particles, i.e. the ungranulated starches, shows a linear relationship (Fig. 1). A similar linear relationship is found for the rice starch granulations (Fig. 1). It should be noted that the two corn starch granulations do not fit on the relationship for the rice starch granulations.

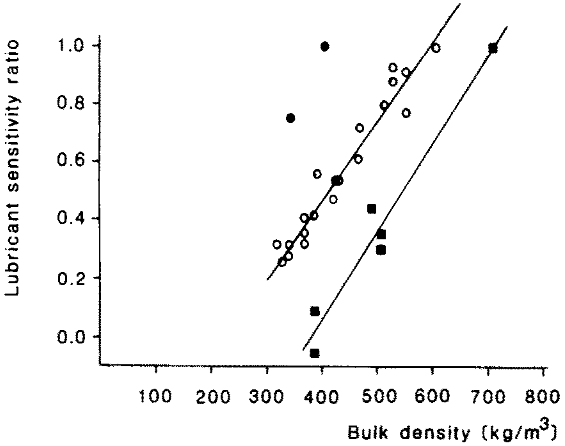

Fig. 1. Lubricant sensitivity ratio of tablets prepared from native starch or from starch granulations, as a function of the bulk density of the material. (●) Corn starch granulations, (○) rice starch granulations (correlation coefficient = 0.97), (■) native starch (correlation coefficient = 0.98).

The data for the microfine cellulose products, Elcema^{R} P50, P100 and F150, and the cellulose granulations, both the commercially available Elcema^{R} products (G250 and G400) and the granulations prepared by different methods from different Elcema grades, are given in Table 2. Elcema^{R} F150, a fibrous grade of microfine cellulose with a particle size range of 100–200 μm, exhibits a lower bulk density than the powder grades Elcema^{R} P50 and P100. Elcema^{R} P50 has a particle size range of 40–70 μm and Elcema^{R} P100 of 50–150 μm. In Fig. 2 the LSR of tablets, compressed from Elcema^{R} P50, P100 and F150 and from granulations prepared from these materials, are plotted against the bulk density of the particulate system. The results show a linear

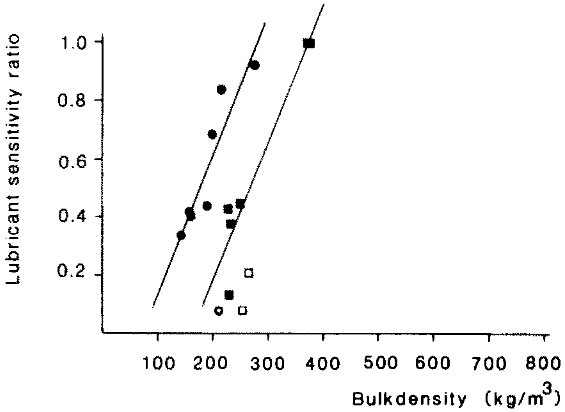

Fig. 2. Lubricant sensitivity ratio of tablets prepared from Elcema^{R} F150 (○), Elcema^{R} P50 and P100 (□), granulations based on Elcema^{R} F150 (●) and granulations based on Elcema^{R} P50 and P100 (■), as a function of the bulk density of the powders (correlation coefficient for the granulations based on Elcema^{R} F150 = 0.93 and for granulations based on Elcema^{R} P50 and P100 = 0.95).

TABLE 1

Flow characteristics of starch and starch granulations and crushing strength and lubricant sensitivity ratio of tablets prepared from these materials

Starch	Granulation method	Sieve fraction (μm)	Flow properties				Tablet properties			
			BD	FN	MF	VF	CL	S_0	S_{lub}	LSR
Rice	ungranulated	unfrac. [a]	388 (2) [b]	> 5	0 [b]	0	75	89 (17) [b]	81 (11) [b]	0.09
							150	169 (34)	177 (18)	−0.05
Corn	ungranulated	unfrac. [a]	507 (11)	> 5	0	0	75	31 (2)	20 (2)	0.36
							150	60 (4)	42 (3)	0.30
Tapioca	ungranulated	unfrac. [a]	491 (4)	> 5	0	0	150	70 (4)	39 (4)	0.44
Potato	ungranulated	unfrac. [a]	708 (15)	> 5	0	0	150	68 (10)	0	1
Rice	Fluid-bed	106–300	394 (18)	1	1.05 (0.03)	2.67	75	117 (2)	50 (2)	0.56
		300–600	390 (5)	2	0.88 (0.01)	2.27	75	79 (2)	46 (3)	0.42
Rice	Alexander	106–300	345 (9)	1	0.86 (0.01)	2.50	75	96 (5)	66 (2)	0.32
							150	172 (5)	123 (6)	0.28
		300–600	375 (16)	2	0.88 (0.02)	2.34	75	94 (6)	64 (3)	0.32
Rice	Frewitt	106–300	331 (7)	1	0.90 (0.01)	2.72	75	78 (5)	53 (3)	0.32
							150	133 (6)	99 (7)	0.26
		300–600	390 (6)	2	1.06 (0.01)	2.72	75	71 (2)	41 (3)	0.42
Rice	Alex./Frew.	106–300	373 (3)	1	0.90 (0.01)	2.42	75	101 (4)	60 (2)	0.41
							150	176 (18)	112 (7)	0.36
		300–600	423 (3)	2	1.06 (0.01)	2.50	75	78 (2)	41 (2)	0.48
Rice	Dish	106–300	427 (7)	1	1.26 (0.01)	2.94	75	85 (7)	39 (2)	0.54
							150	153 (7)	79 (4)	0.48
		300–600	437 (14)	1	1.26 (0.01)	2.89	75	83 (3)	38 (2)	0.54
Rice	75 MPa briq.	106–300	470 (2)	2	1.13 (0.01)	2.41	75	97 (11)	27 (1)	0.72
							150	184 (17)	68 (3)	0.61
		300–600	513 (5)	2	1.30 (0.01)	2.54	75	85 (8)	17 (1)	0.80
Rice	300 MPa briq.	106–300	530 (4)	1	1.39 (0.01)	2.62	75	94 (4)	7 (1)	0.93
							150	179 (10)	21 (4)	0.88
		300–600	609 (1)	2	1.60 (0.01)	2.63	75	73 (3)	0	1
Rice	Primotab^R	106–300	554 (1)	2	1.12 (0.03)	2.01	75	81 (6)	8 (2)	0.91
							150	143 (10)	34 (2)	0.77
Corn	Frewitt	106–300	345 (2)	1	0.72 (0.03)	2.10	75	27 (1)	7 (1)	0.75
		300–600	407 (11)	2	1.11 (0.01)	2.74	75	27 (2)	0	1

BD, bulk density (kg/m^3); FN, funnel number; MF, mass flow ($\times 10^{-3}$ kg/s); VF, volume flow ($\times 10^{-6}$ m^3/s); CL, compression load (MPa); S_0, crushing strength unlubricated (N); S_{lub}, crushing strength lubricated (N); LSR = lubricant sensitivity ratio.

[a] Unfractionated.

[b] Mean (standard deviation).

relationship between the LSR and the bulk density, for the granulations prepared from Elcema^R F150. A similar linear relationship is seen for the granulations based on Elcema^R P50 and P100, including the commercially available Elcema^R granulations: G250 and G400. These granulations are based on Elcema^R P100 and have particle size ranges of, respectively, 200–300 and 130–260 μm. The non-granular products do not fit in the linear relationship found for the granulations.

In summary, linear relationships between the lubricant sensitivity and the bulk density are found for the different granular forms of starch and of cellulose, similar as reported by Vromans et al. (1988) for lactose. These results question the mechanism or combination of mechanisms behind this relation. Concerning film formation of magnesium stearate it can be stressed that:

– A low bulk density is an indication for poor flowability, which results in poor film formation

TABLE 2

Flow characteristics of cellulose and cellulose granulations and crushing strength and lubricant sensitivity ratio of tablets prepared from these materials

Cellulose	Granulation method	Sieve fraction (μm)	Flow properties		Tablet properties			
			BD	FN	CL	S_0	S_{lub}	LSR
Elcema^{R} F150	ungranulated	unfrac. [a]	216 (7) [b]	> 5	75	116 (7) [b]	107 (6) [b]	0.08
Elcema^{R} P050	ungranulated	unfrac. [a]	254 (6)	> 5	75	60 (2)	55 (4)	0.08
Elcema^{R} P100	ungranulated	unfrac. [a]	266 (23)	> 5	75	104 (8)	82 (5)	0.21
Elcema^{R} P100	Elcema^{R} G250	unfrac. [a]	375 (9)	> 5	75	17 (1)	0	1
Elcema^{R} P100	Elcema^{R} G400	unfrac. [a]	368 (5)	> 5	75	43 (2)	0	1
Elcema^{R} F150	75 MPa briq.	106–300	200 (4)	> 5	75	110 (2)	35 (4)	0.69
Elcema^{R} F150	300 MPa briq.	106–300	216 (3)	> 5	75	96 (4)	15 (1)	0.84
		300–600	276 (5)	> 5	75	70 (2)	5 (1)	0.93
Elcema^{R} F150	Frewitt W	106–300	144 (6)	> 5	75	104 (4)	68 (3)	0.34
		300–600	158 (8)	> 5	75	93 (2)	54 (3)	0.42
Elcema^{R} F150	Frewitt MC	106–300	190 (3)	> 5	75	64 (4)	36 (2)	0.44
		300–600	162 (13)	> 5	75	76 (4)	45 (2)	0.41
Elcema^{R} P050	Frewitt W	106–300	230 (4)	> 5	75	106 (3)	93 (4)	0.13
		300–600	250 (4)	2	75	112 (3)	64 (3)	0.45
Elcema^{R} P100	Frewitt W	106–300	232 (3)	2	75	124 (2)	77 (4)	0.38
		300–600	227 (2)	2	75	124 (5)	70 (2)	0.43

BD, bulk density (kg/m^3); FN, funnel number; CL, compression load (MPa); S_0, crushing strength unlubricated (N); S_{lub}, crushing strength lubricated (N); LSR, lubricant sensitivity ratio.

[a] Unfractionated.

[b] Mean (standard deviation).

during mixing with a lubricant (flowability-mechanism).

- A low bulk density can result in a larger contribution to particle rearrangement during compaction, which could disrupt an already formed lubricant film and reduce lubricant sensitivity (disruption-mechanism).
- A low bulk density is an indication for a high intra-granular porosity. In the pores of granules the lubricant can be packed away, resulting in a decreased film formation (pack-away-mechanism).
- During consolidation, fragmentation of the granules might take place, creating clean lubricant free surfaces (fragmentation-mechanism).

The following discussion is concerned with the discrimination between the different possible mechanisms of formation of a lubricant film on starch or cellulose based granulations.

Bulk density

In Fig. 3 a survey plot is given of the relation between the LSR and the bulk density, for both non-granular primary particles (e.g. native starches) and for granulations prepared from these primary particles (e.g. rice starch granulations).

Rice starch (A in Fig. 3) exhibits a lower bulk density than corn starch (B in Fig. 3). This is

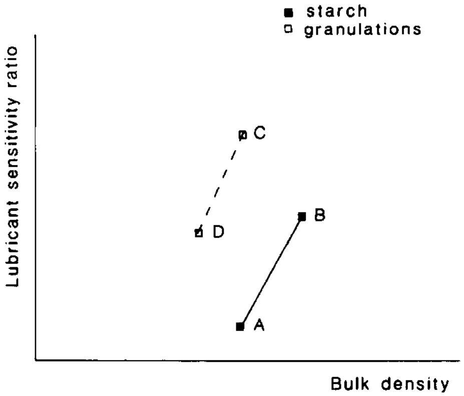

Fig. 3. Lubricant sensitivity ratio of tablets versus bulk density. A, rice starch; B, corn starch; C and D, rice starch granulations.

caused by the more irregular shape and smaller particle size of rice starch (mean particle diameter 8 μm) as compared to corn starch (mean particle diameter 15 μm), resulting in poor flowability for rice starch (Bos et al., 1987). Realizing that starches deform plastically under compression and consist of primary particles with no intra-particular porosity, the action of a fragmentation- or pack-away-mechanism can be excluded. Consequently, the decrease in the LSR of 0.36 for corn starch to 0.09 for rice starch (Table 1 and Fig. 3) may be attributed to the poorer flowability of rice starch, expressed by the lower bulk density, as compared with corn starch. The poor flowability of rice starch retards lubricant film formation during mixing. After prolonged mixing with magnesium stearate, it is possible to increase the LSR of rice starch to 1 (Bos et al., 1987).

The LSR for rice starch (A in Fig. 3) increases dramatically by preparing a rice starch granulation with the same bulk density (C in Fig. 3). Granulation introduces intra-granular porosity:

$$V_{t,C} = V_{e,C} + V_{i,C} = V_{t,A} = V_{e,A}$$

where V_t represents the total pore volume per bulk volume, V_e is the extra-particular pore volume per bulk volume and V_i denotes the intra-particular pore volume per bulk volume. Action of a pack-away-mechanism of magnesium stearate in the pores of the granules, as well as a fragmentation-mechanism, creating clean lubricant-free surface areas during compaction of the granules, would both result in a decreased sensitivity of the granules for the lubricant, expressed by a decreased LSR. The contrary is found. The same bulk density of both rice starch and the prepared granulation may exclude the effect of a disruption-mechanism. Realizing that granulation increases particle size and thus flowability, it may finally be concluded that in this case the flowability-mechanism will be the predominant factor affecting the formation of a lubricant film around the granules.

For the rice starch granulations the LSRs were found to vary from 1, for the 300 MPa briquettes, to 0.26, for the Frewitt granulation (Table 1). The survey plot in Fig. 3 shows that a decrease in bulk density (D vs C in Fig. 3) results in a decrease in LSR. This implies decreasing lubricant sensitivity with decreasing flowability of the rice starch granulations.

It also may be assumed that two granulations with different bulk densities but with the same particle size fractions (C and D in Fig. 3), will have the same extra-particular porosity: $V_{e,C} = V_{e,D}$. A decreased bulk density corresponds with an increased total porosity ($V_{t,D} > V_{t,C}$), therefore the granulation with a lower bulk density (D) will have a higher intra-particular porosity than the granulation with a higher bulk density (C): $V_{i,D} > V_{i,C}$. A granule with a higher porosity has more space to pack-away lubricant, resulting in less sensitivity to mixing with a lubricant and in a decreased LSR.

In conclusion, the decreasing lubricant sensitivity with decreasing bulk density of rice starch granulations may be caused by both the flowability- and the pack-away-mechanism. However, the other mechanisms cannot yet be excluded.

The granulations prepared from corn starch are more sensitive to lubrication than the rice starch granulations, with comparable bulk densities (Fig. 1). This might be attributed to the difference in surface texture of the granulations, since a major difference between rice and corn starch is the difference in particle shape. Corn starch has a more smooth surface and is more prone to film formation, whereas rice starch has a more angular shape, resulting in granulations with a more irregular surface than the corn starch granulations.

Flowability

The data presented in Table 1 show that the flow through funnels of standard dimensions does not discriminate between the granulations. Measurement of the volume flow through funnel number two does not give any further information. No relationship between the LSR and the volume flow of rice starch granulations exists (correlation coefficient = 0.21). However, when the flowability is expressed as the mass flow through funnel number two, a significant relationship (correlation coefficient 0.84) is found between the LSR and the mass flow of the rice starch granulations (Fig. 4).

With increasing mass flow, the shear forces

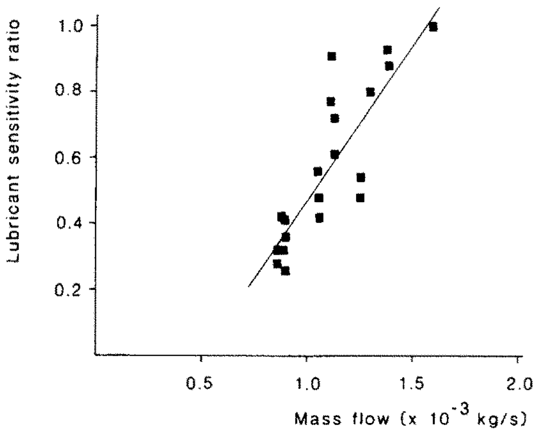

Fig. 4. Lubricant sensitivity ratio of tablets prepared from rice starch granulations, as a function of the mass flow (correlation coefficient = 0.84).

during mixing may be assumed to increase, facilitating the lubricant film formation and thus increasing the LSR. Comparing Figs 1 and 4, it is seen that the correlation between the LSR and the mass flow is less significant, than between the LSR and the bulk density, indicating that the flow-mechanism is of influence, but not the only factor affecting the lubricant sensitivity.

Mixing

In order to discriminate between the different (possible) mechanisms of lubricant film formation, additional mixing experiments were performed with magnesium stearate, talc and two rice starch granulations with different bulk densities (Frewitt granulation, fraction 300–600 μm, bulk density 390 kg/m^3 and dish granulation, fraction 300–600 μm, bulk density 437 kg/m^3). The results are given in Table 3.

If the packing-away of magnesium stearate into the pores plays a dominant role in the prevention of the formation of a lubricant film, the mixing of a granulation with a magnesium stearate tablet should result in an increased LSR. When the lubricant is added as a tablet, no excess magnesium stearate powder is available to be packed away into the pores. The lubricant film will be formed by shearing off layers of magnesium stearate, from the tablet. After mixing for 30 min with a magnesium stearate tablet the LSR was smaller than after mixing with 0.5% or 1% magnesium stearate. This is probably due to the difference in initial distribution of the magnesium stearate in the powder blend; more time is required for magnesium stearate to shear off from a tablet than from evenly distributed powder particles.

After mixing for 2 h the LSR for granulations mixed with a tablet magnesium stearate was the same as for granulations mixed with either 0.5% or 1% of magnesium stearate (Table 3).

TABLE 3

Lubricant sensitivity ratio of starch granulations after mixing with talc and magnesium stearate (Mgst.)

Mixed with	Mixing time (min)	S_0	S_{lub}	LSR
Frewitt granulation, sieve fraction 300–600 μm				
0.5% Mgst.	30	73 (3) [a]	40 (2) [a]	0.45
	120	73 (3)	28 (1)	0.62
0.5% Mgst. + 2% talc	30	73 (3)	40 (2)	0.45
	120	73 (3)	29 (2)	0.61
1% Mgst.	30	71 (2)	41 (3)	0.42
	30	67 (2)	36 (1)	0.47
	120	67 (2)	27 (2)	0.59
1% Mgst. + 2% talc	30	74 (2)	39 (3)	0.47
	120	67 (2)	27 (1)	0.59
tablet Mgst. 500 mg	30	74 (2)	51 (2)	0.31
	120	73 (2)	30 (2)	0.60
2% talc	30	74 (2)	58 (3)	0.22
	120	67 (2)	42 (2)	0.38
Dish granulation, sieve fraction 300–600 μm				
0.5% Mgst.	30	80 (3) [a]	37 (2) [a]	0.54
	30	86 (3)	42 (3)	0.52
	120	86 (3)	30 (2)	0.66
0.5% Mgst. + 2% talc	30	80 (3)	44 (3)	0.45
	30	86 (3)	41 (3)	0.53
	120	86 (3)	33 (4)	0.62
1% Mgst.	30	83 (3)	38 (2)	0.54
	30	78 (4)	36 (2)	0.54
	120	78 (4)	29 (2)	0.62
1% Mgst. + 2% talc	30	83 (4)	37 (2)	0.55
	120	78 (4)	30 (3)	0.62
tablet Mgst. 500 mg	30	83 (4)	49 (3)	0.41
	120	83 (4)	32 (4)	0.62
2% talc	30	83 (4)	64 (4)	0.24
	120	78 (4)	56 (2)	0.28

S_0, crushing strength unlubricated (N); S_{lub}, crushing strength lubricated (N); LSR, lubricant sensitivity ratio.

[a] Mean (standard deviation)

It should also be noted that after mixing for 2 h, which is excessively long, with either 0.5 or 1.0% magnesium stearate or with a magnesium stearate tablet, the LSR of the two granulations hardly differs at all (Table 3). If the disruption-mechanism were of any influence, a difference in LSR could be expected, since during compaction of material with a lower bulk density more particle rearrangement will take place. Lerk and Sucker (1988) found that the addition of talc decreased the lubrication capacity of magnesium stearate in tabletting mixtures, resulting in an increased ejection force of tablets and in increased contact angles. During mixing with magnesium stearate a discontinuous layer of magnesium stearate is formed around the particles and part of the magnesium stearate is trapped into cavities and behind protruding areas. This latter part is not available for film formation, but it is available to reduce friction during compaction and ejection of the tablet. The addition of a small amount of talc forces magnesium stearate out of the cavities during the mixing and promotes film formation, resulting in increased contact angles. The amount of magnesium stearate used for the film formation is not available at the protrusions to reduce friction during ejection of the tablet, resulting in higher ejection forces. If the lubricant distribution on starch granules depends on the pack-away-mechanism, the addition of talc during mixing with magnesium stearate should result in lower crushing strengths due to enhanced lubricant film formation by the talc, i.e. an increase in LSR. However, after adding talc no increase in the LSR is seen (Table 3).

From the results of these mixing experiments it seems unlikely that the pack-away-mechanism is a predominant factor in the prevention of film formation on the granules. However, its action cannot be excluded.

Surface area

To characterize the ratio between the external and the internal surface area of granules, the surface areas of rice starch and of three rice starch granulations were measured by both nitrogen adsorption and by permeametry. The nitrogen adsorption surface area (S_{N2}) is assumed to be the total area available for binding, whereas the permeametry surface area (S_{perm}) may be assumed to represent the surface area available for film formation during mixing. In Fig. 5 the LSR of the tablets is plotted against the area ratio, defined as the ratio between the nitrogen adsorption- and the permeametry surface area, of rice starch and three rice starch granulations (Table 4). Granulations with relatively more surface area available for binding than for lubricant film formation, expressed by a larger area ratio (the 300 MPa briquettes), may be assumed to be less sensitive to lubrication. However, Fig. 5 shows increasing LSRs with increasing area ratios, therefore the

TABLE 4

Surface area measurements of rice starch granulations

Method	Sieve fraction (μm)	Bulk density (kg/m^3)	Lubricant sensitivity ratio	S_{perm} (m^2/kg)	S_{N2} ($\times$10 m^2/kg)	Area ratio
Frewitt	106–300	331	0.32	86 (4) [a]	81 (5) [a]	9.4
Dish	106–300	427	0.54	73 (2)	68 (3)	9.3
300 MPa briq.	106–300	530	0.93	46 (1)	66 (1)	14.3
Ungranulated	unfractionated	388	0.09	520 (8)	94 (2)	1.8

[a] Mean (standard deviation).

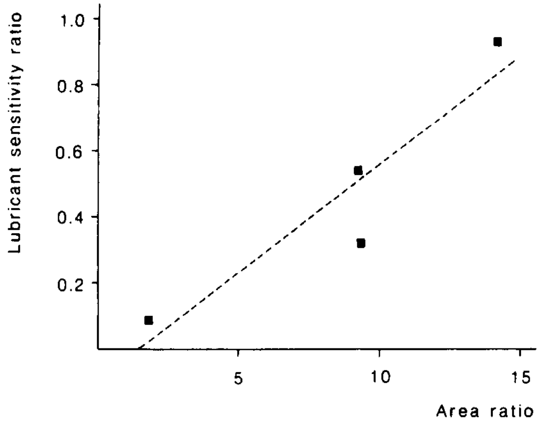

Fig. 5. Lubricant sensitivity ratio of tablets prepared from starch granulations, as a function of the area ratio (= nitrogen adsorption surface area/permeability surface area).

fragmentation mechanism can be excluded. Further investigations are necessary to explain the found relationship.

Considering all the results of the experiments performed on the starch granulations, it may be concluded, that the flowability of a granulation, expressed by its bulk density, will be the predominant factor affecting the sensitivity of a granulation for magnesium stearate film formation.

Cellulose

Finally, for the celluloses analogous relationships as for the starches were found. Both the commercially available granular grades of microfine cellulose, Elcema^R G250 and G400, and the granulations prepared from Elcema^R P050 and P100 meet the same relationship between the LSR of the tablets and the bulk density of the particulate system. The difference in primary particle size does not seem to have any influence. The two starting materials, Elcema^R P050 and P100. have slightly higher bulk densities and smaller LSRs than the granulations (Fig. 2). A similar linear relationship is found for the granulations based on Elcema^R F150 (Fig. 2). The lower bulk density of the Elcema^R F150 granulations might be attributed to the difference in surface texture of the granulations as compared with the Elcema^R P50 and P100 granulations. Elcema^R F150 particles have a fibrous shape, which will result in a more irregular surface of the granulations than the granulations prepared with Elcema^R P50 or P100 and consequently in granulations with a lower bulk density.

Conclusions

Granulations with a uniform particle size range, prepared from materials which are susceptible to lubrication with magnesium stearate, show linear relationships between the lubricant sensitivity ratio of the tablets and the bulk density of the granulation. These relationships were found to be different for the different investigated materials. The flowability of the particulate system proved to be the predominant mechanism in the sensitivity to lubrication with magnesium stearate. This fact should be considered in the development of granulations based on starch or cellulose; granulations with lower bulk densities are preferred above the more lubricant sensitive granulations with higher bulk densities.

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