Evaluation of the suitability of various lubricants for direct compaction of sorbitol tablet formulations.

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Original Article

ABSTRACT

There is an increasing interest in using polyols, such as sorbitol, in pharmaceutical tablet formulations due to their sweet taste and reduced calorie content and noncariogenic characteristics. Sorbitol is a common tableting excipient and plays a major role in the manufacture of chewable and sublingual tablets. One limitation of sorbitol as a tableting excipient is that its hygroscopic nature may cause pronounced friction, as well as, sticking to the punch surfaces. Therefore, the aim of the present study was to evaluate the suitability of various lubricants for reducing friction and preventing sticking during the compaction of sorbitol-containing tablets. The efficiency of the most commonly used lubricant, magnesium stearate, was compared to that of sodium stearyl fumarate (Pruv®), microprilled poloxamer 407 (Lutrol® micro 127) and PEG 4000. Compaction studies were performed using both an eccentric tablet press and a rotary tablet press. In addition to their compaction properties, the effect of the investigated lubricants on the tablet properties was evaluated. Considering both the lubricant efficiency and the influence on tablet properties of the investigated lubricants, Pruv® was found to be most suitable for compaction of the investigated sorbitol tablet formulations. However, the best overall lubricant performance, accompanied by excellent tablet properties, was observed with a mixture (1:1) of magnesium stearate and Pruv®, indicating synergism between these lubricants.

KEY WORDS: Neosorb®, direct compaction, lubrication, ejection, friction, sticking, tensile strength, disintegration

INTRODUCTION

Polyols (sugar alcohols) such as sorbitol, are common excipients in pharmaceutical dosage forms, as well as, in food products. Due to their sweet taste but reduced calorie content and noncariogenic characteristics, they are particularly useful as sugar substitutes. Sorbitol is described as having a pleasant, cooling, sweet taste with a sweetness of approximately 60 % compared to that of sucrose (1). Chemically, sorbitol is a D-glucitol which is a hexahydric alcohol related to mannose and is an isomer of mannitol. Sorbitol occurs naturally in a wide variety of ripe berries. However, it is primarily produced industrially by high-pressure catalytic hydrogenation or by electrolytic reduction of the D-glucose. Crystalline sorbitol occurs as an odourless, hygroscopic powder and it exhibits a

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complex monotropic polymorphism (2, 3). Efforts have been made to identify the existing polymorphic forms. In addition to five different anhydrous crystalline polymorphic forms, one amorphous form and the hydrate of sorbitol have been identified (4, 5).

Because of its physico-chemical properties, sorbitol is commonly used in different pharmaceutical dosage forms as a sweetening agent, humectant, plasticizer for soft gelatine capsules or filler-binder in tablet formulations. Sorbitol was the first polyol that was modified for use as a suitable filler-binder in direct compaction (6). Among the existing polymorphic forms γ-sorbitol, which is obtained by spray-drying, or a special crystallization technique, is postulated to be the most stable polymorphic form with the best compaction properties (3, 6, 7). However, one major limitation for the use of sorbitol as filler-binder in tablet formulations is that its hygroscopic nature may cause strong friction at the tablet-die interface during tablet compaction and ejection. Moreover, sticking of tablets to the punch surfaces during tablet take-off may also occur.

To reduce friction at the tablet-die interface, tablet formulations are mixed with lubricants, whereas anti-adherents are used to prevent sticking. However, it is well known that efficient lubricants often also have anti-adherent properties (8). Magnesium stearate is the most commonly used tablet lubricant because it reduces friction efficiently even at low concentrations of 0.25 – 0.5 % and it also exhibits good anti-adherent properties (9). Despite its excellent lubricant performance, magnesium stearate is reported to have a negative effect on the compactibility of powder blends (10, 11). Depending on the deformation behavior of the powder particles in a tablet formulation, magnesium stearate can reduce the physical strength of the tablets significantly which is attributed to the formation of a thin lubricant film around each of the host particles during blending (12). As a result of this physical barrier, the interparticulate bonding strength between the particles is weakened. Therefore, tablets consisting of excipients that undergo plastic deformation are greatly affected, whilst brittle materials were found to be less susceptible to magnesium stearate (10, 13). In addition to the decreased bonding properties, magnesium stearate is also known to decrease the wettability due to its pronounced hydrophobic nature, and thus it can cause delayed tablet disintegration and prolonged dissolution rates (12, 14, 15).

Sodium stearyl fumarate has been suggested as another suitable lubricant for tableting. It has been shown that sodium stearyl fumarate has fewer negative effects on tablet strength and dissolution rate than magnesium stearate (16, 17). If tablets are intended to be dissolved in water prior to ingestion, e.g. effervescent tablets, lubrication of the tablet formulation with water soluble excipients is most preferable. For this purpose solid polyethylene glycols, e.g. PEG 4000 and PEG 6000, have been used as lubricants (18). Microprilled poloxamers are also readily soluble in water and therefore may be used as hydrophilic lubricants in tableting (19).

The objective of the present study was to investigate the suitability of various lubricants for reducing friction, as well as, for preventing sticking during direct compaction of various Neosorb® P60W tablet formulations. The efficiency of the most commonly used lubricant magnesium stearate was compared to that of sodium stearyl fumarate (Pruv®), microprilled poloxamer 407 (Lutrol® micro 127) and PEG 4000.

MATERIALS

Sorbitol (Neosorb® P60W, Roquette Frères, France), microcrystalline cellulose (Avicel® PH200, FMC BioPolymer, Ireland), and crospovidone (Kollidon® CL, BASF, Germany) were used for the preparation of directly compressible powder blends. The powder blends were lubricated with magnesium stearate

(Fagron, Germany), sodium stearyl fumarate (Pruv®, JRS Pharma, USA), PEG 4000 P (Macrogol 4000 powder, Fagron, Germany), and microprilled poloxamer 407 (Lutrol® micro 127, BASF, Germany), respectively. The lubricants were used as provided by the suppliers. Some physical properties of the lubricants are summarized in Table 1. All other reagents used in this study were of analytical grade.

Table 1 Comparison of some physical properties of the employed lubricants

	MgSt	Pruv	Lutrol micro 127	PEG 4000
Particle Morphology	Fine powder, irregular-shaped particles	Fine powder, flat circular-shaped particles	Waxy powder, free-flowing microprilled granules	Fine powder, spherical-shaped particles
Specific Surface Area [m²/g]	1.92 [a]	1.2 – 2.0 [b]	-	-
Melting range [°C] [c]	117 - 150	224 - 245	52 - 57	50 - 58
Lubricant classification	Boundary lubricant	Boundary lubricant	Fluid-film lubricant	Fluid-film lubricant
Lubricant concentration [%] [c]	0.25 - 5	0.5 - 2	2 - 10	2 - 5

[a]According to Certificate of Analysis issued by supplier; Determination by gas adsorption (Ph. Eur. 2.9.26).
[b]According to supplier specification, gas adsorption method.
[c]Data from Reference (8, 20)

METHODS

Physical characterization of Neosorb® and Avicel®

Particle morphology

Samples of Neosorb® and Avicel® were coated with a thin carbon layer and the particle morphology was visualized by scanning electron microscopy (LEO 1525, LEO Elektronenmikroskopie, Oberkochen, Germany) at an accelerating voltage of 5 kV. For comparative purposes the investigated lubricants were also characterized by SEM with regard to their particle morphology.

Melting behavior

The onset of melting was determined by differential scanning calorimetry (DSC7, Perkin Elmer, Beaconsfield, UK). Samples of 10 mg each were heated up at heating rates of 10 K/min in aluminum pans under nitrogen atmosphere. The onset of melting was determined using Pyris® software (Perkin Elmer, Beaconsfield, UK).

Powder densities

The true density of both excipients was measured by helium pycnometry using a 30 cm³ sample cup (Accupyc 1330, Micromeritics, Aachen, Germany). Each measurement comprised 10 purge cycles followed by 10 measuring cycles. Bulk and tapped densities were determined according to the method of the European Pharmacopoeia (Ph. Eur.) (jolting volumeter, STAV 2003, J. Engelsmann, Ludwigshafen, Germany).

Flow properties

Flow properties were determined by measurement of the Hausner ratio and the powder flow rate. The Hausner ratio was calculated as the quotient of tapped and bulk density. The mass-related powder flow rate [g/s] was measured using a flowability tester (BEP2, Copley Scientific, Nottingham, UK) equipped with a stainless steel flow funnel (orifice diameter 10 mm). All measurements were performed in triplicate. The volume-related powder flow rate (cm³/s) was calculated as the quotient of the mass-related powder flow rate and the bulk density of the excipients.

Particle size distribution

The particle size distribution was investigated by laser diffraction using a dry dispersion unit (HELOS/RODOS, Sympatec, Clausthal-Zellerfeld, Germany). Compressed air at 1.5 bar was used to disperse the powder.

Moisture sorption

Moisture sorption isotherms were obtained by gravimetric determination of the water vapor uptake using Schepky hygrostats (21). Prior to

the measurements, the samples were dried over phosphorus pentoxide until the weight remained constant. Subsequently, they were placed on watch-glasses above saturated salt solutions used to adjust the relative humidity to 23% (potassium acetate sesquihydrate), 33% (magnesium chloride hexahydrate), 44% (potassium carbonate sesquihydrate), 66 % (ammonium nitrate), 75 % (sodium chloride), 85% (potassium chloride) and 97.5 % (potassium sulfate), respectively (22). The loaded hygrostats were stored at a temperature of 20°C for 5 days.

Preparation and characterization of lubricated Neosorb powder blends

The Neosorb® concentration in the investigated powder blends was 25, 50 and 75% w/w, respectively. Avicel® was chosen as the filler since it exhibits excellent compaction properties. Kollidon® CL was used as tablet disintegrant at a concentration of 2.5%. Neosorb® was mixed with the filler and the disintegrant using a Turbula blender at 72 RPM for 10 minutes (T2F, W.A. Bachofen, Muttenz, Switzerland). After addition of the lubricants magnesium stearate, Pruv®, Lutrol® micro 127, and PEG 4000, respectively, to each powder blend, mixing was continued for 3 more minutes. All the lubricants were initially tested at a 4% w/w incorporation, since the performance of all lubricants was assumed to be sufficient at this relatively high lubricant concentration. As it is well known that magnesium stearate and Pruv® are very efficient lubricants, these two lubricants were also investigated at concentrations of 1 and 2% w/w. In addition, the effect of lubrication with 1:1 mixtures of the two lubricants at total concentrations of 0.5, 0.75, 1 and 2 % w/w was studied. Prior to compaction, the powder blends were stored in an air-conditioned room at a temperature of 21°C and a relative humidity of 45% for at least 3 days. Flow properties of the lubricated powder blends were determined as described above.

Compaction of lubricated Neosorb® powder blends

Compaction with an eccentric tablet press

To analyze the performance of the different lubricants, compaction of the Neosorb® powder blends containing 4% w/w of lubricant was performed using an instrumented eccentric tablet press (E XI, Fette, Schwarzenbek, Germany) equipped with flat-faced punches of 10 mm diameter. The target tablet weight was 300 mg. Ten tablets were prepared with each powder blend at a compaction speed of 16 strokes/min. at compaction forces of 5, 10, and 15 kN, respectively. The efficiency of each lubricant was characterized by the ejection force measured during compaction, as well as, the R value. R values were calculated as the quotient of the maximum lower and upper punch forces (F_{max}) shown in Equation 1 (23).

$$R = \frac{F_{max(lowerpunch)}}{F_{max(upperpunch)}} \qquad \text{Eq. 1}$$

The closer the R value is to unity, the better the efficiency of lubrication.

Compaction with a rotary tablet press

Selected Neosorb® powder blends were made into tablets using an instrumented rotary tablet press (XL 100, Korsch, Germany) equipped with flat-faced punches of 10 mm diameter. The target tablet weight was 300 mg and the compression speed was 20 RPM with a corresponding dwell time of 74.7 ms. Based on the results obtained with the eccentric tablet press, only the powder blends containing 75% Neosorb® were used for compaction. The performance of the lubricants magnesium stearate and Pruv® was investigated with Neosorb® tablet formulations at lubricant concentrations of 1, 2 and 4% w/w. Powder blends lubricated with different concentrations of 1:1 mixtures of these two lubricants were also compacted.

Characterization of the Neosorb® tablets

After a relaxation time of at least 24 hours following ejection of the tablets, the crushing strength, the diameter and the thickness of 10 tablets were determined using a hardness tester (TBH 30, Erweka, Heusenstamm, Germany). The tablet tensile strength was calculated using Equation 2 developed by Fell *et al.* (24).

$$\sigma = \frac{2 * F}{\pi * d * h} \qquad \text{Eq. 2}$$

Where σ is the tablet tensile strength (MPa), F the crushing strength (N), d the tablet diameter (mm), and h the tablet height (mm). The disintegration times of six tablets were measured with a disintegration tester (ZT 72, Erweka, Germany) according to the method of the Ph. Eur. for uncoated tablets. The disintegration apparatus was operated with magnetic guided discs allowing for an automated determination of the tablet disintegration time.

RESULTS AND DISCUSSION

Physical and bulk powder properties of Neosorb® and Avicel®

It is known that the physical and bulk powder properties of crystalline sorbitol vary depending on the grade of sorbitol used (25). In Table 2 several physical and bulk powder properties of the investigated sorbitol grade Neosorb® P60W are summarized. As Avicel® PH200 was chosen as a filler for the Neosorb® tablet formulations, the bulk powder properties of this excipient are also shown in Table 2.

The melting behavior of sorbitol is a key parameter which characterizes the different polymorphic forms of the excipient. The endothermic event in the DSC thermograms of the investigated sorbitol grade is attributed to melting with a melting onset temperature of 98.9 °C and a heat of fusion of 180.71 J/g.

Table 2 Physical and bulk powder properties of Neosorb® and Avicel®

	Neosorb® P60W	Avicel® PH200
Onset of melting [°C]	98.90 ± 0.72	-
Heat of fusion [J/g]	180.71 ± 2.58	-
True density [g/cm³]	1.492 ± 0.002	1.557 ± 0.001
Bulk density [g/cm³]	0.651 ± 0.001	0.358 ± 0.003
Tapped density [g/cm³]	0.732 ± 0.003	0.454 ± 0.003
Hausner ratio	1.12 ± 0.02	1.27 ± 0.01
Powder flow rate [g/s]	9.49 ± 0.08	4.60 ± 0.24
Powder flow rate [g/cm³]	14.54 ± 0.10	12.85 ± 0.11
Mean particle size (d_{50}) [µm]	191.1 ± 2.9	176.1 ± 4.2

– not determined

This indicates that Neosorb® P60W consists of pure γ-sorbitol (2, 3) which is described as the most stable polymorphic form and is postulated to exhibit the best compaction properties among the existing polymorphic forms (3, 7).

The flow properties of the plain excipients, Neosorb® and Avicel®, were determined by calculating the Hausner ratio and by measuring powder flow rate. In accordance with the Ph. Eur. the Hausner ratio of the investigated sorbitol grade indicated good flowability, whereas Avicel® showed only passable flowability. These results appeared to agree with the mass-related powder flow rate determined for these excipients. However, the difference in flow properties of the two excipients was found to be less pronounced if the volume-related powder flow rate was taken into consideration. This observation results from the large difference in the bulk density of the two compounds which is used to calculate the volume-related powder flow rate. The comparable small difference between the volume-related powder flow rates may furthermore be explained by an apparent similarity of both excipients with regard to particle morphology (Figure 1) and mean particle size.

The physical stability of γ-sorbitol crystals towards moisture also plays a major role with regard to powder processing. Nikolakakis *et al.*,

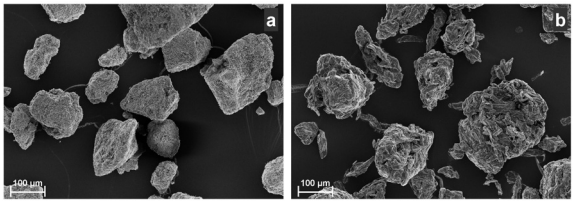

Figure 1 SEM images of (a) Neosorb® P60W and (b) Avicel® PH200.

provided evidence of a plasticizing effect of moisture on γ-sorbitol by plotting the logarithm of the ratio of the yield pressure (P_Y) and the elastic recovery as a function of the moisture content. It was shown that this ratio decreases linearly with increasing moisture content indicating high predominance of plasticity over elasticity at higher moisture content (26). In Figure 2 the water sorption isotherm for the investigated sorbitol grade is shown. The data presented here shows that the powder crystals resist moisture uptake up to a relative humidity of approximately 70 %. After a storage period of 120 hours the water uptake at a relative humidity of 66 % amounted to only 3.4 % (w/w). However, at relative humidities above 70 % (critical hygroscopicity) the Neosorb® samples were observed to show deliquescence. Therefore, it is strongly recommended to avoid processing and storage of the excipient at relative humidities greater than 65 %.

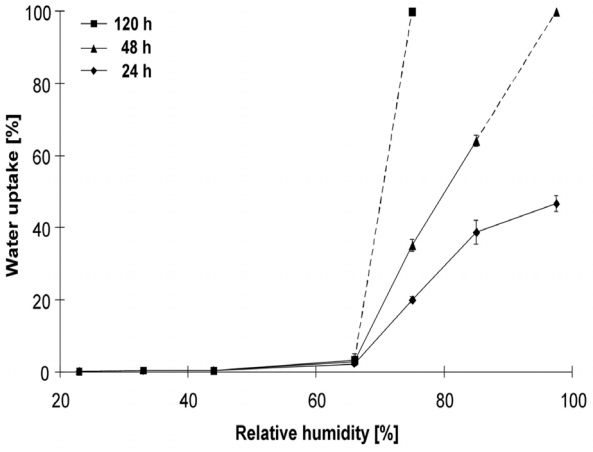

Figure 2 Water sorption isotherm at 20 °C measured after a storage period of 24, 48, and 120 h; means ± SD, n = 3; - - - deliquescence was observed.

Flowability of lubricated Neosorb® powder blends

Each investigated powder blend was characterized with regard to its flowability by determining the Hausner ratio (Figure 3a) and measuring the powder flow rate (Figure 3b). Apparently, an increase of the Neosorb® content leads to a decrease of the Hausner ratio and an increase of the powder flow rate, independent of the lubricant used in the powder blends. These results are in good agreement with the flowability data obtained with the plain excipients Neosorb® and Avicel® (Table 1) because the higher the content of readily flowable Neosorb® in the powder blends, the lower the amount of poorly flowable Avicel®.

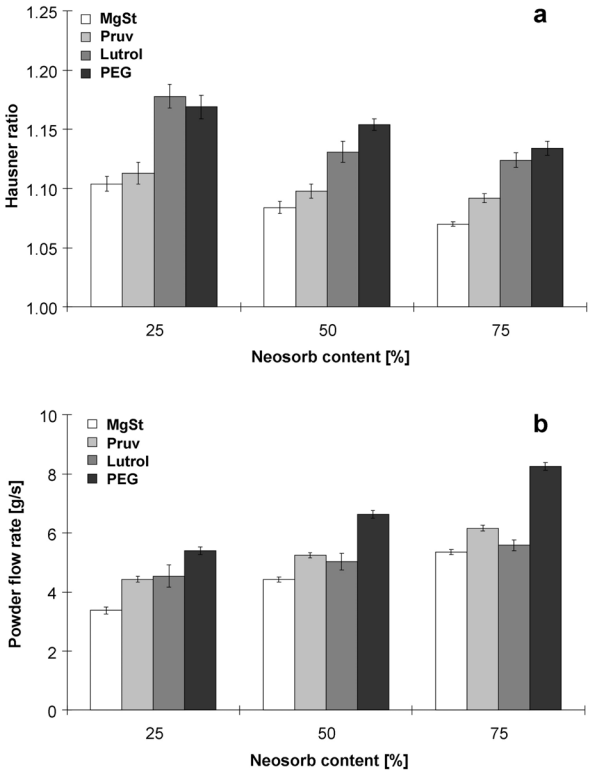

Figure 3 Flow properties of the lubricated powder blends (a) Hausner ratio and (b) powder flow rate; means ± SD, n = 3.

With respect to the various excipients used for lubrication of the powder blends, considerable differences in terms of flowability were observed. The Hausner ratios of powder blends lubricated with either magnesium stearate (MgSt) or Pruv® were determined to be lower than 1.11, independent of the Neosorb® content (Figure 3a). According to the Ph. Eur., Hausner ratios between 1.00 and 1.11 indicate excellent flow properties. In contrast, the Hausner ratios of the powder blends lubricated with Lutrol® or PEG were found to exceed 1.11, but remaining lower than 1.18. Thus, according to the Ph. Eur., the flow properties of the powder blends lubricated with Lutrol® and PEG can still be considered good.

Examining the powder flow rates (Figure 3b), it is interesting to note that the flowability of the powder blends lubricated with magnesium stearate turned out to be worst, whereas the highest powder flow rates were obtained with the powder blends lubricated with PEG. This observation may be explained by the particle morphology of the various lubricant powders. Figure 4 shows SEM images of the different lubricants. In comparison to the powder particles of the lubricants magnesium stearate, Pruv® and Lutrol®, the PEG particles are smooth and spherical leading to a considerable improvement of powder flowability.

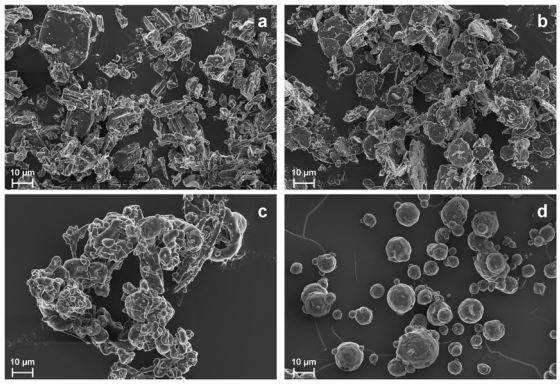

Figure 4 SEM images of (a) magnesium stearate, (b) Pruv®, (c) Lutrol® micro 127, and (d) PEG 4000.

Tabletability and compactibility of lubricated Neosorb® powder blends

Compaction study using an eccentric tablet press

In the first part of the compaction study, tableting of the Neosorb® powder blends was performed using an instrumented eccentric tablet press in order to analyze the performance of the different lubricants. The efficiency of each lubricant was characterized by evaluating the R values, ejection forces and the anti-adherent performance, i.e., the prevention of sticking to the punch surfaces. Table 3 shows the influence of the investigated lubricants and the Neosorb® content on the compaction properties indicated by the R values and the ejection forces measured during compaction.

Table 3 Influence of the Neosorb® content and various lubricants on the compaction and tablet properties; eccentric tablet press; compaction force 10 kN; lubricant concentration 4 % w/w; means ± SD, n = 10 (n = 6 for disintegration time)

	Neosorb [%]	MgSt	Pruv	Lutrol	PEG
COMPACTION PROPERTIES					
R value	25	0.956 ± 0.004	0.975 ± 0.005	0.849 ± 0.010	0.750 ± 0.018 *
	50	0.960 ± 0.008	0.964 ± 0.002	0.830 ± 0.023 *	0.735 ± 0.022 *
	75	0.939 ± 0.009	0.971 ± 0.008	0.820 ± 0.025 *	-
Ejection force [N]	25	50.5 ± 0.2	37.1 ± 0.1	88.3 ± 0.2	92.8 ± 0.6 *
	50	54.0 ± 0.2	44.9 ±0.2	87.1 ± 0.5 *	100.4 ± 0.9 *
	75	54.0 ± 0.4	45.1 ± 0.2	92.4 ± 0.7 *	-
TABLET PROPERTIES					
Tensile strength [Mpa]	25	1.19 ± 0.02	1.55 ± 0.03	3.79 ± 0.08	4.26 ± 0.18 *
	50	1.74 ± 0.04	2.42 ± 0.02	4.18 ± 0.14 *	5.18 ± 0.22 *
	75	2.17 ± 0.05	3.03 ± 0.03	4.58 ± 0.15 *	-
Disintegration time [s]	25	153 ± 10	189 ± 8	402 ± 14	186 ± 11 *
	50	293 ± 13	231 ± 12	280 ± 13 *	224 ± 18 *
	75	308 ± 17	263 ± 12	158 ± 17*	-

*Sticking observed
–Tableting impossible

The anti-adherent performance of the lubricants was determined by visual inspection of the punch surfaces after compaction. Obviously, with the powder blends lubricated with Pruv®, the highest R values and the lowest ejection forces were obtained which is

attributed to a high efficiency of this lubricant. The R values derived from the compaction of the powder blends lubricated with magnesium stearate were found to be similar to those of Pruv®. However, the measured ejection forces were higher, indicating a lower efficiency of magnesium stearate as lubricant. Nevertheless, the anti-adherent performance of both lubricants, Pruv® and magnesium stearate, turned out to be sufficient, as no sticking of powder to the punch surfaces was observed.

In contrast, from the results obtained with Neosorb® powder blends lubricated with either Lutrol® or PEG it is concluded that these two lubricants are inefficient at least at the chosen lubricant concentration of 4 %. Compaction of these powder blends led to low R values and high ejection forces, indicating a poor lubricant efficiency. Moreover, visual inspection of the punch surfaces after compaction revealed pronounced sticking of these powder blends, resulting from a poor anti-adherent performance of the two lubricants. Only the powder blend consisting of 25 % Neosorb® lubricated with Lutrol® showed no sticking to the punch surfaces. The worst compaction properties were observed with PEG as a lubricant. Tableting of the powder blend containing 75 % Neosorb® turned out to be impossible because of pronounced friction induced by sticking of the tablets to the die wall. In summary, from the data presented in Table 3 the rank order of lubricant efficiency was Pruv® ≥ magnesium stearate > Lutrol® micro 127 > PEG 4000.

In addition to the compaction properties, the influence of lubrication on the properties of the Neosorb® tablets was analyzed. The tensile strength and the disintegration time of the tablets prepared with an eccentric tablet press at a compaction force of 10 kN are also presented in Table 3. It is obvious that the tablet properties are significantly affected by, both the type of lubricant and the Neosorb®, content within the powder blends. A general observation was that the higher the Neosorb® content, the higher the tensile strength of the tablets, independent of the lubricant used. As the tensile strength is an indirect measure of the bonding strength within tablets (27), it is hypothesized that an increase of the Neosorb® content leads to an increase of bonding within the tablets. In the literature, directly compactable sorbitol grades are reported to have excellent binding properties which are attributed to the high plasticity of the sorbitol particles and their particle structure (6, 7). The particles of the sorbitol grade Neosorb® P60W consist of very small crystalline needles ultimately resulting in a porous particle structure providing a high surface area for bonding. With regard to the investigated lubricants, it is interesting to note that lubrication of the Neosorb® powder blends with magnesium stearate led to tablets exhibiting the lowest tensile strength, whilst with the powder blends lubricated with Lutrol® or PEG high tablet tensile strengths were obtained. This observation may be explained by the different mechanisms of lubrication, i.e., Magnesium stearate and Pruv® are boundary lubricants with amphiphilic activity and film-forming tendency, whereas Lutrol® and PEG are fluid-film lubricants (8, 28). During the compaction process, fluid-film lubricants are supposed to melt leading to the formation of a continuous viscous fluid thin layer which separates tablet surface and metal surface (28). After the compaction pressure is removed, solidification of the melted component is assumed to contribute to bonding within the tablets ultimately resulting in tablets with a higher tensile strength. However, one limitation for the use of fluid-film lubricants in conventional tablet formulations is their tendency to cause sticking to punch surfaces. In fact, as a result of sticking, an extremely rough tablet surface was obtained with the formulations lubricated with Lutrol® or PEG and thus the appearance of these tablets was unacceptable.

The Neosorb® content and the lubricant type also turned out to have a major effect on tablet

disintegration. Although all tablets were found to disintegrate within several minutes, fulfilling the requirements for disintegration of uncoated tablets according to the Ph. Eur., considerable differences were observed. At a low Neosorb® content of 25 % the tablets lubricated with the boundary lubricants magnesium stearate and Pruv® disintegrated much faster than the tablets containing the water soluble lubricant Lutrol®. The comparably slow disintegration of the Lutrol®-containing tablets is an effect of the high tablet tensile strength. Interestingly, although lubrication with PEG also led to tablets with a high tensile strength, disintegration of these tablets was as fast as that of the Pruv®-containing tablets. This observation may be explained by the defects on the tablet surfaces caused by sticking which lead to a large contact area for water resulting in enhanced tablet disintegration.

With increasing Neosorb® content, disintegration of the non-sticking tablets was found to slow down. On the one hand, this may be attributed to the increase of the tablet bonding strength with increasing Neosorb® content. On the other hand, due to its high solubility, the predominant mechanism of disintegration of the tablets with a high Neosorb® content of 75 % is supposed to be tablet dissolution leading to slow disintegration rather than fast disintegration induced by rapid water penetration and subsequent widening of the pores (29). As a result of the hydrophobizing effect through lubricant film formation on the surface of the Neosorb particles, the surface wettability is reduced and thus the dissolution rate of the tablets is slowed down. In contrast, the disintegration of tablets lubricated with Lutrol® turned out to be considerably faster at a high Neosorb content of 75% than at a low Neosorb® content of 25%. Poloxamers such as Lutrol are known to exhibit a pronounced solubilizing efficiency leading to an enhancement of the wettability and the dissolution rate of poorly soluble substances (30). In this study, with an increase of the content of water-soluble Neosorb®, the amount of the water-insoluble component microcrystalline cellulose is reduced in the tablet formulation, and thus tablet disintegration primarily occurs by tablet dissolution at a Neosorb® content of 75%. The fast disintegration of the Lutrol®-containing tablets at this high Neosorb® content is therefore assumed to be attributed to the solubilizing effect of Lutrol® leading to an enhancement of the rate of dissolution.

Compaction study using a rotary tablet press

In the second part of the compaction study, only the two most efficient lubricants from the first part of the compaction study, magnesium stearate and Pruv®, were used for the lubrication of the powder blends. Powder blends consisting of 75% Neosorb® and lubricant at concentrations of 1, 2 and 4 %, respectively, were compacted using a rotary tablet press. It was confirmed that the efficiency of the lubricant Pruv® was superior to that of the most commonly used lubricant magnesium stearate, i.e., ejection forces derived from compaction of the powder blends lubricated with Pruv® were found to be lower than those obtained during compaction of powder blends lubricated with magnesium stearate (Table 4).

Table 4 Influence of lubricant and lubricant concentration on the compaction and tablet properties; rotary tablet press; compaction force 10 kN; Neosorb® content 75 % w/w; means ± SD, n = 10 (n = 6 for disintegration time)

	Lubricant [%]	MgSt	Pruv
COMPACTION PROPERTIES			
Ejection force [N]	1	381.9 ± 12.4 *	215.5 ± 6.2 *
	2	54.0 ± 0.8	45.1 ± 0.7
	4	46.0 ± 0.4	37.7 ± 0.5
TABLET PROPERTIES			
Tensile strength [Mpa]	1	3.17 ± 0.12 *	3.84 ± 0.08 *
	2	2.83 ± 0.07	3.74 ± 0.03
	4	1.75 ± 0.09	3.03 ± 0.02
Disintegration time [s]	1	253 ± 8 *	184 ± 7 *
	2	266 ± 16	188 ± 12
	4	299 ± 10	195 ± 14

* Sticking observed

Interestingly, at the lowest lubricant concentration of 1%, for both lubricants the measured ejection forces were drastically higher than those obtained at lubricant concentrations of 2 and 4%, respectively. These high values are the result of die wall sticking, as friction is increased at the interface of the tablet surface and the die wall.

Moreover, sticking to the punch surfaces was observed with both the powder blend lubricated with Pruv® and the powder blend lubricated with magnesium stearate. Therefore, at a lubricant concentration of 1% the anti-adherent performance of both lubricants was considered inadequate. This observation is contrary to the results presented in earlier publications where magnesium stearate concentrations between 0.5 and 1% were found to be sufficient for the compaction of various sorbitol tablet formulations. For instance, Michaud reported that placebo tablets containing only sorbitol (Sorbidex®) and 1% of magnesium stearate could be successfully prepared by direct compaction without sticking (31). For this reason, it is assumed that the anti-adherent performance of the employed lubricants is considerably affected by the physico-chemical properties of the investigated sorbitol grades.

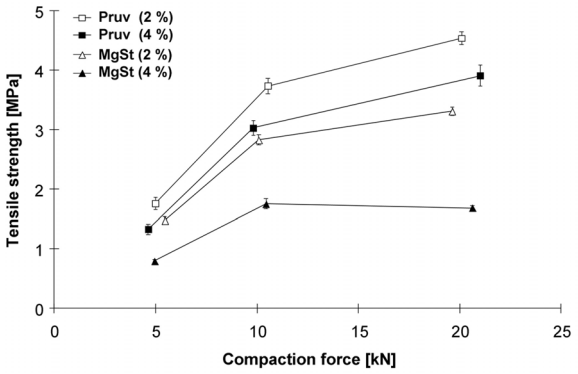

Figure 5 Influence of the lubricant type and the lubricant concentration on the tabletability of Neosorb® tablet formulations; means ± SD, n = 10.

Properties of tablets made with the rotary tablet press were examined determining the tabletability and by measuring the disintegration times. Tabletability is the tensile strength of a tablet in dependence of the applied compaction force. The influence of the lubricant type and the lubricant concentration on the tabletability of the investigated Neosorb® powder blends is presented in Figure 5. It is apparent that the tabletability of the powder blends is strongly affected by both the lubricant type and its concentration. The tensile strength of tablets containing magnesium stearate was considerably lower than that of tablets containing Pruv®. For example, at a compaction force of 10 kN and a lubricant concentration of 2%, the tensile strength of tablets containing magnesium stearate was 2.83 MPa (± 0.07), whereas the tensile strength of tablets containing Pruv® was 3.74 MPa (± 0.03). With an increase of the lubricant concentration a decrease of the tablet tensile strength was observed. The tensile strength of the tablets containing magnesium stearate was reduced from 2.83 MPa to only 1.75 MPa (± 0.09). In contrast, the tensile strength of the tablets containing Pruv® decreased from 3.74 MPa to 3.03 MPa (± 0.02), which indicates an excellent tabletability even at a high lubricant concentration of 4%.

The observed decrease of the tablet hardness with increasing concentrations of the two lubricants is caused by film formation of the lubricant around the host particles (12). This lubricant film may act as a physical barrier, and it therefore interferes with the binding of powder particles resulting in comparably soft tablets. However, the effect of the lubricant film on the tablet hardness depends stongly on the lubricant type and on the deformation characteristics of the excipients used in the tablet formulation. Sorbitol and microcrystalline cellulose are examples of excipients with a high lubricant sensitivity resulting from their primarily plastic deformation behavior during compaction (6, 32-35). However, because brittle fragmentation is also likely to occur during compaction of crystalline sorbitol, the

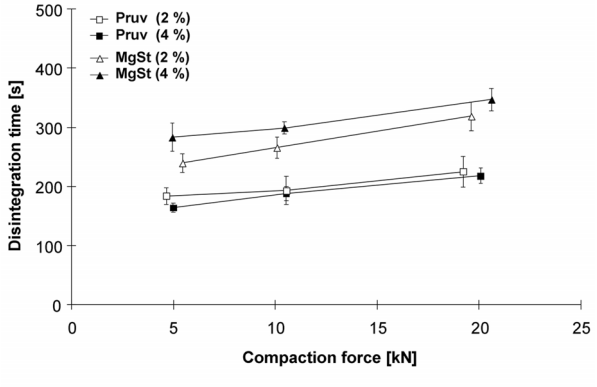

Figure 6 Influence of the lubricant type and the lubricant concentration on the disintegration time of Neosorb® tablets; means ± SD, n = 6.

excipient is reported to be less susceptible to magnesium stearate than microcrystalline cellulose (11).

In addition to their excellent tabletability, the tablets lubricated with Pruv® also turned out to show better disintegration properties than those lubricated with magnesium stearate. Figure 6 shows the influence of the lubricant type and concentration on the disintegration times of Neosorb® tablets. Tablets lubricated with Pruv® disintegrated more rapidly than the tablets containing magnesium stearate. This observation is attributed to the pronounced hydrophobic nature of magnesium stearate compared to the relative hydrophilicity of Pruv®, which leads to poor wettability of the tablet surface ultimately resulting in prolonged tablet disintegration (12, 14, 15).

Considering both the lubricant efficiency and their effect on tablet properties, it is concluded that lubrication of Neosorb® tablet formulations using Pruv® is preferable to using magnesium stearate.

Tabletability and compactibility of Neosorb® powder blends lubricated with 1:1 mixtures of magnesium stearate and Pruv®

Tableting of Neosorb® powder blends lubricated with 1% of either magnesium stearate or Pruv® resulted in pronounced sticking to the punch surfaces, indicating that the anti-adherent performance of each lubricant was insufficient (see previous section). Nevertheless, preliminary studies revealed a possible synergistic effect of both lubricants, if a mixture of magnesium stearate and Pruv® was used for the lubrication of the investigated Neosorb® tablet formulation. In order to analyze the lubricant efficiency of 1:1 mixtures of magnesium stearate and Pruv®, Neosorb® powder blends with a total concentration of lubricant of 0.5, 0.75, 1 and 2%, respectively, were prepared.

Figure 7 shows that the ejection forces measured during the compaction of the powder blends were below 100 N at a total lubricant concentration of 1 %, indicating a good lubricant efficiency. Even at a total lubricant concentration of 0.75 % the ejection forces of approximately 200 N were considered acceptable. Moreover, it is interesting to note that sticking of powder to the punch surfaces was not detected with the powder blends lubricated with 0.75 % and higher. A total lubricant concentration of 0.5 % turned out to be inadequate, as compaction of the powder blends led to unacceptably high ejection forces of approximately 500 N and to sticking to the punch surfaces.

Lubrication of the powder blends with a 1:1 mixture of magnesium stearate and Pruv®

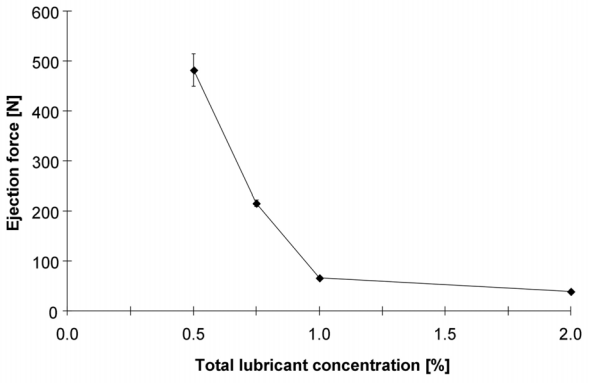

Figure 7 Influence of the total lubricant concentration on the ejection force of Neosorb® tablets; magnesium stearate Pruv® (1 1); means ± SD, n = 10.

resulted in tablets with excellent properties. The influence of the total lubricant concentration on the tablet tensile strength and the disintegration time of tablets is shown in Figure 8. It is apparent that both the tablet tensile strength and the disintegration times of the tablets are only slightly affected by the total lubricant concentration. However, even at a comparably high lubricant concentration of 2% the tablet tensile strength was found to exceed 3 MPa and the tablets disintegrated within 200 seconds.

In summary, a synergistic effect of the lubricants magnesium stearate and Pruv® was observed. In contrast to the lubrication with the plain lubricants, a 1:1 mixture of both lubricants allowed a reduction of the total lubricant concentration from 2% to 1%.

CONCLUSION

In contrast to the fluid-film lubricants Lutrol® micro 127 and PEG 4000, the boundary lubricants Pruv® and magnesium stearate turned out to be efficient lubricants for the compaction of the Neosorb® tablet formulations. However, tablets prepared with Pruv® as the lubricant showed superior properties in terms of tablet tensile strength and disintegration time. Therefore, considering both the lubricant efficiency and the effect on tablet properties, it is concluded that lubrication of Neosorb® tablet formulations using Pruv® is preferable to magnesium stearate.

In addition, a synergistic effect between magnesium stearate and Pruv® can be assumed. Tableting of powder blends lubricated with 1% of either magnesium stearate or Pruv® resulted in pronounced sticking to the punch surfaces, which indicated that the anti-adherent performance of each lubricant was insufficient. Interestingly, the required amount of lubricant for the investigated Neosorb® tablet formulations could be reduced to a total lubricant concentration of 1%, if a 1:1 mixture of magnesium stearate and Pruv® was used. Lubrication with this mixture resulted in acceptable ejection forces during compaction (below 100 N), excellent tablet properties, and sufficient anti-adherent performance.

Finally, from the results obtained in this study and previously published results it is obvious that the physico-chemical properties of sorbitol has a major effect on its performance in tableting. Sorbitol as a tableting excipient is commercially supplied by many manufacturers providing various sorbitol grades. Sorbitol grades provided by different manufacturers may be manufactured using different processes and thus they are likely to have different particle morphology and powder properties. This is expected to affect the lubricant requirements for tablet formulations.

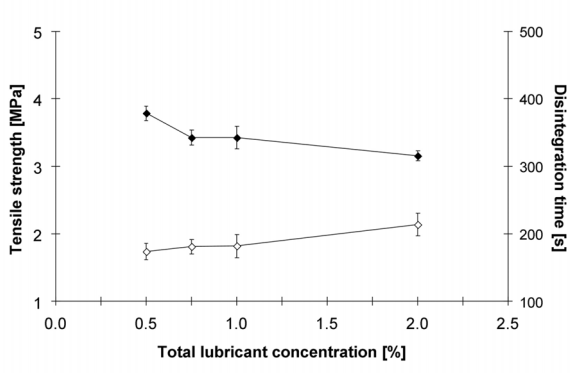

Figure 8 Influence of the total lubricant concentration on the tensile strength (closed symbols; means ± SD, n = 10) and on the disintegration time (open symbols; means ± SD, n = 6) of Neosorb® tablets lubricated with magnesium stearate Pruv® (1 1).

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