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RESEARCH ARTICLE

Polyols as filler-binders for disintegrating tablets prepared by direct compaction

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Abstract

Background: Although polyols are frequently used as tablet excipients in lozenges, chewing tablets, and orodisperse tablets, special directly compressible (DC) forms are recommended as filler-binder in common disintegrating tablets. *Aim*: In this article, DC types of isomalt, lactitol, mannitol, sorbitol and xylitol are evaluated. *Method*: Tablets of both lubricated and unlubricated DC polyols and theophylline tablets were compressed at different forces using a compaction simulator or a motorized hydraulic press. Disintegration times (without disks) and dissolution rate were measured according to Ph.Eur. *Results*: Compaction profiles show that the DC forms of isomalt, mannitol and sorbitol have sufficient compactibility and a low lubricant sensitivity. The crushing strengths of tablets, prepared from DC lactitol and xylitol, are too low for practical use. Because of their reduced hygroscopicity and smaller capping tendency as compared with DC sorbitol, DC types of isomalt and mannitol seem to be the most convenient filler-binders. Because of their high water solubility, tablets prepared from polyols erode rather than disintegrate. Tablet formulations with theophylline as a test drug and DC isomalt or DC mannitol as filler-binder show that both products have their own limitations: DC mannitol gives more adhesion problems than DC isomalt. On the other hand, the disintegration time and drug dissolution rate for tablets containing DC mannitol is faster than for tablets containing DC isomalt. *Conclusions*: Of the DC polyols investigated, both DC isomalt and DC mannitol are the most suitable filler-binders for disintegrating tablets, prepared by direct compaction.

Key words: *Direct compaction; direct compression; filler-binders; polyols; tablets*

Introduction

Nowadays, there is an increasing interest in sugar substitutes such as mono- and disaccharide alcohols, also called polyols, in pharmaceutical tablet formulations. The reason for this interest is their taste, reduced calorie content, and noncariogenic characteristics. In addition, the majority of these polyols can be consumed by diabetics without any significant increase in body glucose, insulin, or lactic acid concentration unlike the conventional saccharides such as sucrose, glucose, and lactose. As polyols do not possess a carbonyl group, they are not subject to the Maillard reaction; hence, polyols are chemically more stable than related saccharides.

Polyols are polyhydric alcohols, which are prepared from sugars by reducing aldehyde or keton sites to a primary secondary hydroxyl group through catalytic hydrogenation, enzymatic conversion or fermentation, or through a combination of these. An example is the conversion of glucose to sorbitol through catalytic hydrogenation. Polyols are also called sugar alcohols because part of their structures resembles sugar of which the aldehyde or keto group is reduced to an alcohol group.

Similar to other chemicals, the tableting properties of the different polyols are strongly dependent on crystal modification, amorphous content, crystal form, and for agglomerates, in addition, size and porosity. Similar to most other excipients, polyols are not suitable as filler-binders for direct compaction without any physical modification, because their flow or compaction properties are inadequate for practical purposes. For this reason, polyols with enhanced physicomechanical properties have been developed using different techniques such as sieving, crystallization, spray drying, granulation, agglomeration, and co-processing, or a combination of these methods. About 10 years ago, only sorbitol and mannitol were

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available in special directly compressible (DC) forms[1]. Even now, special forms of isomalt, lactitol, and xylitol are marketed as filler-binders for direct compaction.

Sorbitol was the first sugar alcohol used in direct compaction of tablets. Sorbitol is produced by the catalytic hydrogenation of D-glucose. Chemically, it is an isomer of mannitol. The most significant differences are their hygroscopicity and solubility in water; sorbitol is hygroscopic at relative humidities (RHs) above 65%, whereas mannitol is nonhygroscopic; the aqueous solubility of sorbitol is higher than that of mannitol. Sorbitol exists in different crystalline polymeric forms (α-, β-, γ-, and δ-sorbitol) and an amorphous form. γ-Sorbitol is the most stable form and has better compaction properties than the other crystalline polymorphic forms, although the compatibility is strongly dependent on particle structure produced by the manufacturing process[2,3]. Sorbitol for direct compaction is γ-sorbitol. It is prepared by spray drying or crystallization and marketed by different companies. The first products on the pharmaceutical market were Sorbitol Instant (Karion Instant®, now with the brand name Parteck® SI) from Merck and Neosorb® 20/60 DC from Roquette. Sorbitol Instant (Parteck SI) is produced by a special spray-drying process, which causes the sorbitol to crystallize in an interwoven, filamentary microstructure. It is available as a fine powder (SI 150) and as a coarser grade (SI 400). Neosorb is a crystallized γ-sorbitol. The hygroscopicity of sorbitol limits its use in common tablet formulations[1].

Mannitol is prepared by catalytic hydrogenation of carbohydrate solutions of glucose and/or fructose. It is often obtained with the isomer, sorbitol, from which it is isolated. Debord et al.[4] studied the compressibility of different polymorphic forms of mannitol. They concluded that the α-form compressed better than the β-form, the δ-form, and an unidentified form. The particle shape had a great influence on the compressibility. For the same particle size, a granulated powder had better compaction properties than native crystals. Wet granulation of α-mannitol powder gave a good excipient for direct compaction. An important advantage of mannitol over sorbitol is its lower hygroscopicity. Nowadays, different DC forms of mannitol differing in particle size and density are available. Most known are the Pearlitol® DC, SD mannitol granular powders from Roquette, and Parteck M200 from Merck.

Lactitol is produced by the catalytic hydrogenation of lactose. It is approximately 0.4 times as sweet as sucrose and is widely used as a replacement for sucrose in foodstuff. It is available in a number of different grades, including monohydrate, anhydrous, and directly compressible. Granulated lactitol is designed for use as a direct compaction tablet diluent, and it is marketed as Finlac® DC by Danisco. Granulated lactitol is prepared with help of a water granulation process[5]. The product is composed of microcrystalline agglomerates with a mean particle size of 160 μm.

Agglomerated xylitol is available as Xylitab® (Danisco). Xylitab 300 is granulated with a xylitol solution. As it is a pure xylitol granulate, it complies with the monographs for xylitol in the USP/NF, Ph.Eur., and JP.

Isomalt is a mixture of two disaccharide alcohols, derived from the hydrogenation of isomaltulose. The principal components are the disaccharide alcohols, 6-*O*-α-D-glucopyranosyl-D-sorbitol (GPS) and 1-*O*-α-D-glucopyranosyl-D-mannitol dihydrate (GPM). Isomalt is the only polyol produced from sucrose. Monographs on isomalt are described in both Ph.Eur.5 and USP/NF 24. Two good flowing, agglomerated forms containing small primary particles, especially designed for direct compaction, were marketed recently by BENEO-Palatinit. In galenIQ® 720, the ratio GPS:GPM is 1:1 and in galenIQ 721 the ratio is 3:1. As the water solubility of GPS is higher than that of GPM, the products have different solubilities[6].

The aim of this study was to evaluate five frequently used DC polyols: isomalt, lactitol, mannitol, sorbitol, and xylitol as filler-binders for direct compaction. Although these polyols are also used frequently in lozenges, chewing tablets, and orodisperse tablets, because of their taste, negative heat of solution, and high water solubility, this study describes only their use as directly compressible filler-binder in common, disintegrating tablets.

Materials and methods

Materials

The DC polyols used were sorbitol (Parteck SI 150) from Merck (Darmstadt, Germany); mannitol (Pearlitol 200 SD) from Roquette frères (Lestrem, France); lactitol (Finlac DC) and xylitol (Xylitab 300) from Danisco (Kotka, Finland); and isomalt (galenIQ 721) from BENEO-Palatinit (Mannheim, Germany). In this article, these polyols will be referred to as DC sorbitol, DC mannitol, DC lactitol, DC xylitol, and DC isomalt, respectively. The other materials used were magnesium stearate Ph.Eur. from Centrachemie (Etten Leur, The Netherlands), theophylline monohydrate Ph.Eur. from Genfarma (Maarssen, the Netherlands), and crospovidone (Kollidon® CL) from BASF (Ludwigshafen, Germany).

Methods

The bulk density was determined by pouring 50 g of powder into a calibrated plastic cylinder and observing the volume taken up by the powder. Tap density was determined after 500 taps according to DIN 53194. The presented data are the mean value of six measurements.

Flow properties of the polyols were determined by measuring the minimum aperture of the vessel through

which the material is still flowing[7]. The Hausner ratio was calculated from bulk and tap densities[8].

The particle size distribution was measured using laser diffraction (Sympatec RODOS SR 480; Sympatec, Clausthal-Zellerfeld, Germany). Compressed air was used to disperse the powder.

N_2 adsorption-desorption isotherms of the polyols were measured at 77.35 K using Micromeritics TriStar (Micromeritics Instrument Corp., Norcross, GA, USA) to determine the specific surface areas. Before measurement, the sample was outgassed with nitrogen for 18 hours (Micromeritics VacPrep 061; Micromeritics). The BET equation was used to calculate the specific surface areas, according to the N_2 adsorption isotherms at the relative pressures between 0.05 and 0.25.

The morphology of the particles was investigated by using scanning electron microscopy (SEM) analysis (JEOL 6301F; Jeol Ltd., Tokyo, Japan).

To study compaction properties, flat-faced tablets of 500 mg with a diameter of 13 mm were prepared on a programmable compaction simulator (ESH testing; Brierley Hill, UK) at different compression forces. Before compression, the excipients were mixed with 0.5% magnesium stearate in a Turbula mixer (model 2P; W.A. Bachofen, Basel, Switzerland) at 90 rpm. The speed of the upper punch was 300 mm/s. This speed simulates high-speed tableting machines[9].

For the measurement of lubricant sensitivity and disintegration time, tablets were prepared from both pure polyol or from blends of polyol and 0.5% magnesium stearate. Mixing with the lubricant was performed for 2 or 30 minutes in the Turbula mixer. Before compressing the unlubricated material, the die was prelubricated with magnesium stearate. Flat-faced tablets of 500 mg and a diameter of 13 mm were compressed with a force increase of 2 kN/s at 20 kN on a mechanical hydraulic press (ESH testing, Brierley Hill, UK).

Tablet formulations containing DC isomalt or DC mannitol were prepared with theophylline monohydrate as a test drug (Table 1). The drug and the excipients except magnesium stearate were mixed for 15 minutes in the Turbula mixer at 90 rpm. After the addition of magnesium stearate, the mixing was continued for an additional 2 minutes. Flat-faced tablets of 500 mg weight, 13 mm diameter were compressed at 10 kN and 20 kN, respectively, using the mechanical hydraulic press.

Table 1. Formulation of theophylline tablets.

Materials	Mixture(%)	Tablet(mg)
Theophylline monohydrate	5.0	25.0
DC isomalt or DC mannitol	90.5	451.5
Crospovidone	4.0	20.0
Magnesium stearate	0.5	2.5

The tablet crushing strength ($n = 10$) was determined using a Schleuniger 6M tester (Dr. Schleuniger Producttronic, Solothurn, Switzerland). Disintegration times were determined using the Ph. Eur. apparatus without disks. The presented data are the mean value of six measurements. The dissolution rate of theophylline monohydrate from the tablets was measured in the Ph. Eur. paddle apparatus (Prolabo, Paris, France) in phosphate buffer solution (pH 6.8). The drug concentration was measured spectrophotometrically using an Ultrospec 4052 TDS apparatus (LKB, Zoetermeer, The Netherlands) at 268 nm. The presented data are the mean value of three measurements.

Results and discussion

Powder characteristics, particle structure, and flow properties

Figure 1 shows scanning electron micrographs of the five DC polyols. The figure shows that all the products were composed of granules, but they differ strongly in primary particle structure. Granules of both DC sorbitol and DC mannitol were built up of very small crystalline needles, whereas no small crystalline particles are visible in the granules of DC isomalt, DC xylitol, and DC lactitol. In Table 2, the mean particle size, specific surface area, bulk density, tapped density, Hausner ratio, and flow through apertures of the five polyols are compared.

The particle structures are reflected by the specific surface area (Table 2). The specific surface area of DC sorbitol is about four times higher than the surface area of DC isomalt or DC xylitol. The bulk density of the materials varies between 0.46 for DC isomalt and 0.63

Table 2. Physical properties of polyols for direct compaction.

	DC isomalt	DC lactitol	DC mannitol	DC sorbitol	DC xylitol
Mean particle size (μm)	220	125	152	360	209
Specific surface area (m^2/g)	0.32	0.95	0.69	1.22	0.29
Bulk density (g/cm^3)	0.46	0.58	0.52	0.45	0.63
Tapped density (g/cm^3)	0.52	0.71	0.56	0.51	0.74
Hausner ratio	1.14	1.22	1.09	1.13	1.17
Flow through aperture (mm)	2.5	>18	2.5	5	>18
Water solubility at 20°C (g/100 g)[10]	40	36	15	67	38

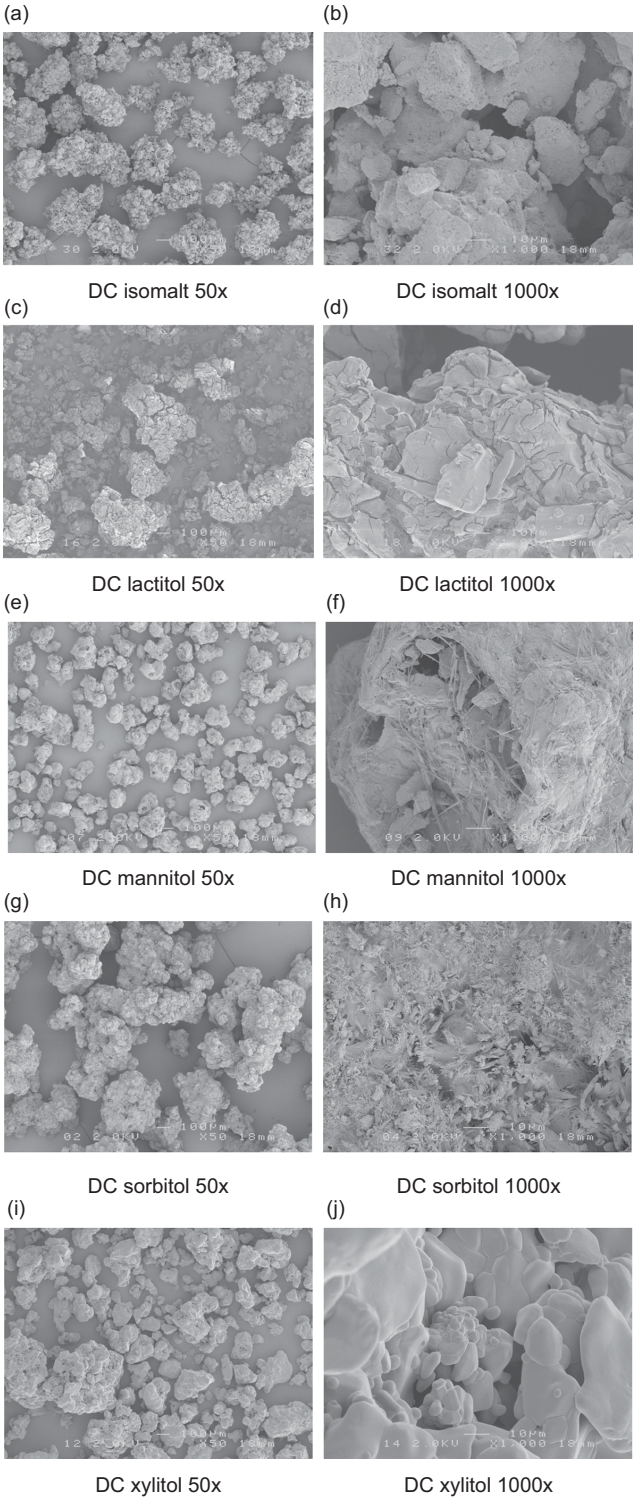

Figure 1. (a–j) Scanning electron microscopic pictures of directly compressible polyols.

for DC xylitol. Comparing flow-ability, expressed as Hausner ratio, shows that all the polyols have good to excellent flow properties. This may be due to the favorable particle form (see Figure 1) and particle size distribution. However, differences can be seen in flowability through orifices. DC sorbitol does not flow through the smallest orifice, whereas DC lactitol and DC xylitol do not even flow through the widest orifice, this in spite of their reasonable Hausner ratio values. As flowability through orifices is more affected by hygroscopicity than the Hausner ratio, the poor flowability of DC lactitol and DC xylitol may be an effect of their hygroscopicity.

Compaction properties

Figure 2 shows the compaction profiles of the polyols, compressed at 300 mm/s using the compaction simulator. The tablets were lubricated with 0.5% magnesium stearate. The figure shows that DC sorbitol has extremely good binding properties. This is caused by both the high plasticity and the open crystalline matrix of small interwoven filamentary crystals (see Figure 1h), giving a high surface for bonding[11,12]. However, at higher forces the tablets show capping, just as was reported previously by Deurloo et al.[13]. Of the other polyols, DC isomalt and DC mannitol have better compaction properties than DC lactitol, whereas DC xylitol could not be compressed at high speed because of capping problems. All these products are agglomerates that fragment during compaction. The differences in compaction behavior must hence be caused by differences in deformation behavior of the primary particles in combination with their intrinsic bonding properties. Primary particles of isomalt and mannitol exhibit plastic deformation[14,15] and will form a large surface for bonding. This is not the case with primary particles of DC lactitol and DC xylitol because they exhibit brittle fragmentation[5,16].

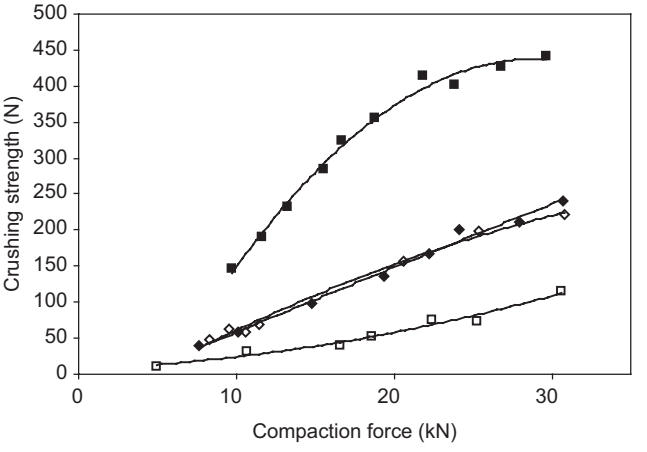

Figure 2. Compaction profiles of different polyols, lubricated with 0.5% magnesium stearate and compressed at 300 mm/s. Closed squares, DC sorbitol; closed diamonds, DC isomalt; open diamonds, DC mannitol; and open squares, DC lactitol.

As unlubricated tablets could not be compressed at high speed using the compaction simulator, for the evaluation of lubricant sensitivity both unlubricated and lubricated tablets were compressed at low speed on an instrumented hydraulic press. The lubricated tablets were mixed for a short (2 minutes) and a prolonged time (30 minutes) with 0.5% magnesium stearate. Moreover, for both unlubricated and lubricated tablets, the pollution of die and punches were inspected visually to judge the sticking tendency of the different polyols. Figure 3 shows the effect of the lubricant on crushing strength of tablets compressed at 20 kN. The figure shows that the lubricant sensitivity is relatively small or even absent. This may be attributed to the granular structure of the products: a lubricant film, formed during the mixing process, will be destroyed by fragmentation of the brittle agglomerates during the early stages of compaction[17]. The positive effect of the lubricant on the crushing strength of xylitol tablets may be caused by the antiadhesive properties of magnesium stearate, reducing tablet damage during ejection. A general recognized problem in tableting sugars and polyols is their sticking tendency, resulting in pollution of die and punches.

For this reason, die and punches were inspected after several compaction cycles of polyols, lubricated with 0.5% magnesium stearate, compressed at 20 kN. Observation of die and punches showed that both DC mannitol and DC xylitol caused a high contamination, whereas a small contamination could be seen for DC lactitol and DC sorbitol. On the other hand, DC isomalt caused no visible contamination of die and punches.

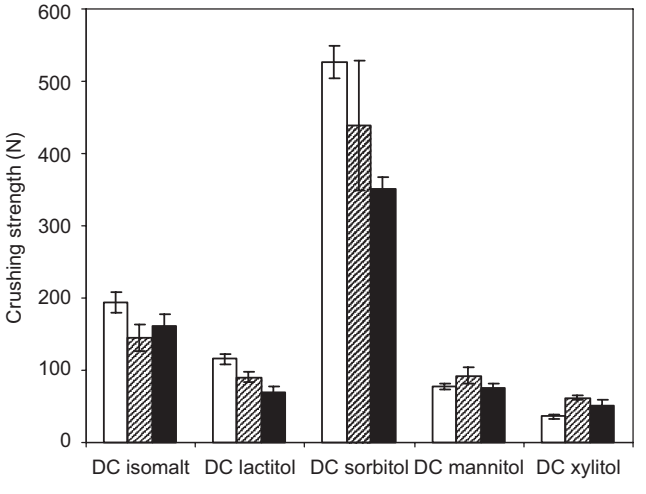

Figure 3. Crushing strength of tablets, compressed at 20 kN from different polyols for direct compaction. The tablets were unlubricated (open bars), or mixed with 0.5% magnesium stearate during 2 minutes (gray bars) or 30 minutes (closed bars).

Hygroscopicity, water solubility, and tablet disintegration

The hygroscopicity of some polyols limits their use as DC filler-binder. In the *Handbook of Pharmaceutical Excipients*[10], sorbitol is described as a hygroscopic powder. It can only be compressed at low relative humidities. After compression, tablets stored at high relative humidity may liquify[18]. For this reason, high percentages of sorbitol should not be used in combination with hygroscopic drugs or other hygroscopic excipients or in combination with unstable drugs. The kinetics of the hygroscopicity of the basic products may differ from that of the DC product: it is claimed that tablets made up of Parteck SI DC sorbitol have a reduced hygroscopicity, as compared with sorbitol powder. The reason is that the tablets are protected by the formation of a hard and smooth film which is formed after compression. This film reduces the ability of moisture to penetrate into the core[12]. Xylitol has a moderate hygroscopicity, but is less hygroscopic than sorbitol. Lactitol is slightly hygroscopic, whereas isomalt and mannitol can be considered as nonhygroscopic[10].

All polyols have a high water solubility (Table 2), but there are large differences. Mannitol (water solubility 15%) is the least soluble; lactitol (36%), isomalt (25%), and xylitol (38%) are more soluble; whereas sorbitol (67%) is close in solubility to sugar. For common, disintegrating tablets, the high solubility of polyols may be a problem in tablet disintegration, although dissolution of the tablets from the outside—'erosion'—guarantee 'disintegration' within a couple of minutes, even if measured without the use of disks and without the addition of a disintegrant. The same phenomenon has been found previously for the disintegration of tablets compressed from different types of the highly soluble anhydrous lactose[19]. Figure 4 shows disintegration time,

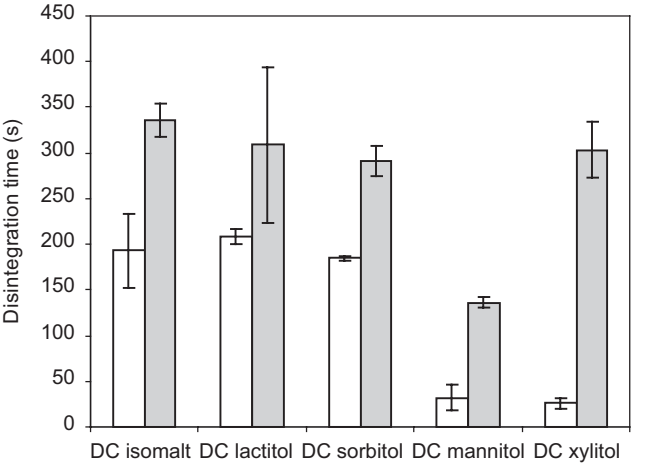

Figure 4. Disintegration time of tablets compressed from different polyols for direct compaction at 20 kN. The tablets were unlubricated (open bars) or lubricated with 0.5% magnesium stearate (gray bars).

measured without the use of disks, of tablets compressed from the different DC polyols at 20 kN. The figure gives disintegration times for both unlubricated tablets and lubricated tablets containing 0.5% magnesium stearate. All tablets were eroded rather than disintegrated. Tablets containing unlubricated DC isomalt, DC lactitol, or DC sorbitol disintegrated in about 200 seconds. Tablets compressed from unlubricated DC mannitol disintegrated in about 75 seconds. This will be caused by the lower solubility of mannitol, enabling a certain amount of water penetration into the tablet (Bolhuis et al., 1985). The fast disintegration of unlubricated DC xylitol tablets is an effect of the very low crushing strength of these (see Figure 3). Lubrication increased the disintegration time of all the tablets with the exception of tablets compressed from DC xylitol with about 100 seconds. This is an effect of the hydrophobic properties of magnesium stearate, which slows down the dissolution rate of the polyols. The disintegration time of DC xylitol tablets was increased more than 250 seconds after lubrication. This is caused by the combination of an increased crushing strength (Figure 3) and the presence of the hydrophobic lubricant.

Theophylline monohydrate tablet formulation

As the nonhygroscopic polyols DC mannitol and DC isomalt exhibit the best overall tableting properties (good compatibility, a low lubricant sensitivity, no capping tendency, and excellent flow properties), tablet formulations with 5% theophylline monohydrate and 90.5% of one of these excipients were prepared (Table 1). As crospovidone is the disintegrant of choice for tablets containing a high percentage of water-soluble material[19], this disintegrant was added in a concentration of 4%. The tablets were lubricated with 0.5% magnesium stearate. Table 3 shows the tableting properties of tablets compressed at 10 and 20 kN, respectively. Just as could be expected from the compression profiles (Figure 2), both tablets containing DC isomalt and DC mannitol have a similar hardness. In contrast to DC mannitol, the disintegration time of tablets containing DC isomalt are strongly dependent on the compaction force used. Tablets containing DC isomalt, compressed at 20 kN, were eroded rather than disintegrated, in about 5 minutes, in spite of the presence of a disintegrant.

Table 3. Crushing strength and disintegration time of theophylline tablets, compressed with DC isomalt and DC mannitol, respectively.

Tablets containing	Compaction force (kN)	Crushing strength (N)	Porosity (%)	Disintegration time (s)
DC isomalt	10	69 ± 3	23.5 ± 0.4	12 ± 2
	20	154 ± 17	16.3 ± 0.2	261 ± 25
DC mannitol	10	69 ± 3	26.6 ± 0.4	13 ± 1
	20	163 ± 12	19.5 ± 1.2	14 ± 1

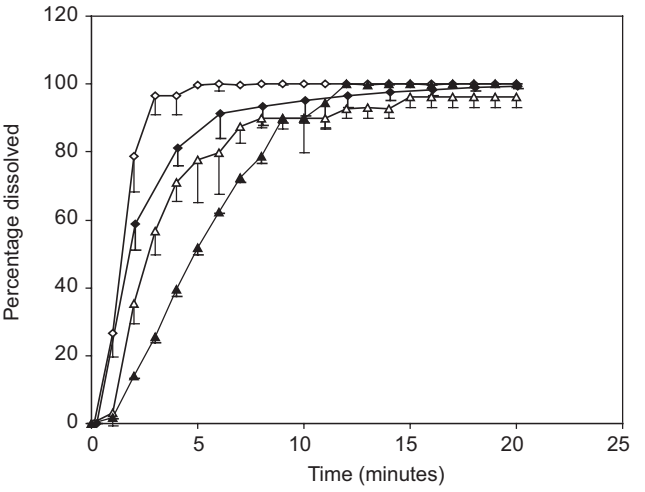

Figure 5. Dissolution rate of theophylline from tablets containing DC isomalt (triangles) or DC mannitol (diamonds) as filler-binders (see Table 1). Compaction force 10 kN (open symbols) and 20 kN (closed symbols), respectively.

Tablets containing DC isomalt, compressed at 10 kN, were disintegrated in 12 seconds. The much better disintegration time of the tablets, compressed with DC isomalt at 10 kN, were disintegrated in 12 seconds. The much better disintegration time of the tablets, compressed with DC isomalt at 10 kN, was caused by water penetration into the porous tablets. In tablets compressed at 20 kN, both a more reduced tablet porosity and the higher water solubility of isomalt, as compared with mannitol, inhibit water penetration. However, erosion of the tablets within a couple of minutes is a guarantee for 'disintegration' of tablets containing DC isomalt, even if compressed at high forces. Figure 5 shows the dissolution rate of theophylline from tablets compressed at 10 and 20 kN, respectively. Although the dissolution time of theophylline from tablets containing DC mannitol was slightly faster, tablets containing DC isomalt also showed a fast and complete drug dissolution.

Conclusion

Although DC polyols are commonly used in lozenges, chewing tablets, and orodisperse tablets, some of them are suitable as filler-binder in disintegrating tablets. With the exception of DC xylitol, the compaction properties of all polyols examined are sufficient for the production of tablets by means of direct compaction. Practical problems that limit their use as filler-binder are linked up with a high water solubility and a high hygroscopicity, just as has been shown for DC sorbitol and DC lactitol. This may give problems with respect to flow properties and adhesion to punches and die. Polyols with a low hygroscopicity and a relatively low water

solubility such as DC isomalt and DC mannitol can be used with success in disintegrating tablets, prepared by direct compaction. Both products have their own advantages and limitations. DC mannitol causes more adhesion problems than DC isomalt. On the other hand, tablets containing DC mannitol show a faster disintegration if compressed at high load. A formulation example with theophylline monohydrate as a test drug shows for DC isomalt that the tablet porosity should not be too low, because this will limit tablet disintegration and drug dissolution rate, although tablet erosion always guarantees a 'disintegration' within a couple of minutes and a consequent fast drug release.

Declaration of interest: The authors report no conflicts of interest.

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