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Process characteristics and compaction of spray-dried emulsions containing a drug dissolved in lipid

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Abstract

The objective of the present study is to prepare directly compressible powders, containing a poorly water-soluble drug dissolved in medium-chain triglycerides (MCT), by spray drying o/w-emulsions in a pilot plant spray dryer. In addition to the lipid phase, the emulsions contained a water-soluble carrier (a sugar), a water-insoluble carrier (magnesium alumino metasilicate) and a combined emulsifier and film-forming agent (gelatine). A factorial design was used to investigate the effect of formulation variables on the spray drying process and powder properties. The factors varied were soluble carrier type (trehalose or mannitol), insoluble carrier particle size distribution (granular or fine powder) and amount of lipid phase in the emulsion (low or high). Compressibility and compactibility of the spray-dried emulsions were mainly affected by the content of lipid in the powders and decreased on increasing the amount of lipid. Increasing the particle size of the insoluble carrier decreased spray drying process yield and lipid encapsulation efficiency whereas compactibility and handling properties were improved. Incorporation of a soluble carrier becoming amorphous on spray drying resulted in tablets with an increased mechanical strength compared to powders containing a crystalline soluble carrier.

Keywords: Spray drying; Dry emulsion; Poorly soluble drug; Compressibility; Compactibility; Lipid formulation

1. Introduction

The use of high throughput screening in drug discovery has led to an increasing number of new drug molecules having a low aqueous solubility and hence a poor oral bioavailability when administered as a conventional tablet or capsule. Incorporation of a poorly water-soluble drug in an o/w-emulsion, wherein the drug is dissolved or dispersed, has been reported to improve the bioavailability for a range of drugs (Humberstone and Charman, 1997). The increased

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bioavailability is caused by elimination of the dissolution step or, in case of dispersed drug, an increased dissolution rate. Additionally, the lipid digestion products may contribute to solubilisation of the drug molecules during transport to the unstirred water layer of the intestinal membrane as previously reviewed (Charman et al., 1997).

Lipid encapsulation by drying o/w-emulsions can be used in the attempt to produce powders preserving an improved bioavailability. In addition to rotary evaporation (Porter et al., 1996) and freeze-drying (Corveleyn and Remon, 1999), spray drying has been applied. Oral administration of vitamin E acetate, formulated as a capsule containing spray-dried emulsion, has been shown to result in a bioavailability comparable to an o/w-emulsion (Takeuchi et al., 1991b). In another study, a spray-dried emulsion reconstituted in water resulted in a significantly higher AUC of a model drug compared to a cyclodextrin complex (Dollo et al., 2003).

Since the description of spray-dried o/w-emulsions in the early 1960s (Richter and Steiger-Trippi, 1961), reports have been made on encapsulation of lipid droplets using different formulation principles. The carriers applied have been small water-insoluble particles (Takeuchi et al., 1991a, 1992a,b), water-soluble film-formers (Nakamoto et al., 1975; Christensen et al., 2001a,b, 2002) or a combination of a surface-active protein and one or more water-soluble components (Pedersen et al., 1998; Dollo et al., 2003). The work performed has mainly addressed lipid droplet size distribution following redispersion of the dried products. Dependent on the formulation principle, the droplet size distribution is affected by carrier composition, lipid content, lipid type and drying process variables. In addition, the investigations have concerned stability of lipid encapsulation (Christensen et al., 2001a, 2002; Dollo et al., 2003) and storage-induced changes in lipid distribution in the particles (Pedersen et al., 1998). Stability is potentially an issue if the powders contain an amorphous solid following spray drying as recrystallisation of amorphous components on storage might result in decreased product performance. References are often made to the observations on absorption of cyclosporin in a rat perfusion study (Tarr and Yalkowsky, 1989) to conclude that a reduction in lipid droplet size causes a further increase in bioavailability. But perfusion does not account for the intestinal processing of lipids which has the potential to reduce the droplet size of an ingested emulsion. Recently, Odeberg et al. (2003) concluded from a human absorption study that the bioavailability of cyclosporin was practically unchanged comparing oral formulations having mean lipid droplet sizes of ∼0.2 μm and ∼18 μm. Therefore, dependent on the drug in question, a complete preservation of the initial droplet size distribution need not be fulfilled in order to improve bioavailability.

Apart from incorporation of spray-dried HPMC-emulsions in tablets (Christensen et al., 2001b), requiring a granulation step to overcome problems related to spray-dried powder physical properties, not much attention has been paid to the manufacture of tablets containing spray-dried emulsions. The objective of this study is to prepare directly compressible spray-dried emulsions containing a poorly water-soluble drug dissolved in medium-chain triglycerides (MCT), a sugar, a porous water-insoluble carrier and a film-forming agent. The effect of lipid content, sugar type and insoluble carrier particle size distribution on the spray drying process and powder properties was investigated.

2. Materials and methods

2.1. Materials

The emulsions and solutions for spray drying were prepared using a model drug (Lu 28-179, solubility in medium-chain triglycerides ∼49 mg/g, intrinsic solubility in water ∼0.03 μg/ml, H. Lundbeck A/S, Denmark), medium-chain triglycerides (density 0.93–0.96 g/ml, Ph. Eur. grade, Delios V, Grünau Illertissen, Germany), gelatine (Ph. Eur. grade, Rousselot Gelatin 275 FG 8, Rousselot, France), trehalose dihydrate (high purity grade, Hayashibara Company, Japan), mannitol (Ph. Eur. grade, Pearlitol 160 C, Roquette Freres, France) and magnesium alumino metasilicate (Neusilin UFL2, fine powder and Neusilin US2, granular, Fuji Chemical Industry Company, Japan).

Acetonitrile (gradient grade, Riedel-deHaën, Germany) and citric acid monohydrate (analysis grade, Merck KGaA, Germany) were used for HPLC-analysis. Coulometric Karl Fischer reagent (HYDRANAL-

Coulomat AG, Riedel-deHaën, Germany) was used for Karl Fischer titration.

2.2. Preparation of emulsions and solutions for spray drying

Lu 28-179 was dissolved in MCT to form a clear solution. Gelatine and sugar were dissolved in water at 50 °C by stirring and throughout the rest of the process, a temperature of about 50 °C was maintained. The pH in the aqueous solution was adjusted to the isoelectrical point of the gelatine before mixing with the MCT solution. A crude emulsion was formed by mechanical stirring with a dispersing unit (Ultra-Turrax T 25 basic equipped with a S 25 N-25 G dispersing head, IKA Labortechnik, Germany) for 3 min at 19,000 rpm. Further homogenisation was subsequently performed with a high-pressure homogeniser (EmulsiFlex C5, Avestin, Canada) by applying two passages at a pressure of 138–152 MPa. Neusilin was added to the emulsion and gentle stirring was performed for 15 min to complete the preparation before spray drying started. The stirring continued during the spray drying process to avoid sedimentation of Neusilin. The compositions of the emulsions were as shown in Table 1. Providing an example, the actual amounts used in the preparation of an emulsion containing 115 g lipid phase, Neusilin US2 and trehalose were as follows: 4.6 g Lu 28-179 was dissolved in 110.4 g MCT to obtain the lipid phase. 105 g trehalose dihydrate and 20 g gelatine were dissolved in 382 g water including the NaOH added during pH adjustment. Following mixing of the two phases and homogenisation, 58 g Neusilin US2 was added.

For the evaluation of spray-dried sugars, 20% (w/w) solutions of either trehalose (anhydrous) or mannitol were prepared by dissolving the sugars in water.

2.3. Spray drying process conditions

Spray drying was performed in a pilot plant spray dryer (Mobile Minor, GEA Niro A/S, Denmark) equipped with a chamber extension section to increase the height of the drying chamber. The total dimensions of the drying chamber were 0.84 m cylindrical height with a diameter of 0.80 m and a 60° conical base. Drying airflow was 80 kg/h at a chamber pressure of −5 mbar. A 1.5 mm two-fluid nozzle operating at 0.5 bar was used to atomise the feed in mixed-flow mode. The inlet air temperature was 200 °C and the emulsion feed-rate was regulated by a programmable logic controller to maintain an outlet air temperature of 115 °C. A cyclone was used to collect the spray-dried powders from the outlet air.

2.4. Characterisation of excipients, emulsions and spray-dried powders

2.4.1. Emulsion droplet size distribution

Volume size distributions were determined using laser diffraction (HELOS KF, Sympatec, Germany) applying the Fraunhofer theory. Samples withdrawn from the emulsions before the addition of Neusilin were used to determine the droplet volume size distribution using a flow through cell (SUCELL, Sympatec, Germany). The emulsions were diluted with water prior to the measurements and the mean of two determinations calculated. The median of the volume size distribution ($d_{50\%}$) was used to describe the average droplet size. The width of the volume size distribution was described using SPAN calculated according to Eq. (1):

$$\text{SPAN} = \frac{d_{90\%} - d_{10\%}}{d_{50\%}} \quad (1)$$

where $d_{10\%}$ and $d_{90\%}$ represent the 10% and 90% quantiles.

Table 1
Composition of emulsions for spray drying

Technical property	Materials	Feed content[a] (g)	Fraction of solids[b] (w/w)
Lipid phase	MCT with 40 mg Lu 28-179/g	52.5 or 115	0.411
Insoluble carrier	Neusilin UFL2 or Neusilin US2	52.5	0.187
Soluble carrier	Trehalose or mannitol	95.0	0.339
Emulsifier/film-forming agent	Gelatine	17.6	0.063
Homogenous phase	Water	400	–

[a] Referring to the dry state of the solid materials.
[b] Referring to a lipid phase content of 115 g. Using 52.5 g, the lipid phase fraction of solids is 0.241 (w/w).

2.4.2. Sugar physical state

Differential scanning calorimetry (DSC) thermograms (DSC 2920, TA Instruments, USA) were recorded of 2–3 mg samples in aluminium pans at a scanning rate of 10 °C/min. To allow evaporated water to escape during analysis, pans having holes were used and the lids were not sealed to the pans.

2.4.3. Moisture content

The amount of water present in the excipients before preparation of the emulsions was determined by halogen drying (Halogen Moisture Analyzer HR73, Mettler-Toledo, USA) at a temperature of 150 °C. The results were used to calculate the amount of excipient corresponding to the desired content of dry solids. The amount of water in the spray-dried powders was determined by coulometric Karl Fischer titration (756 KF Coulometer equipped with a 774 Oven sample processor, Metrohm, Switzerland) at an oven temperature of 150 °C.

2.4.4. Spray drying process yield

The amount of dry solids (including MCT solution) fed to the spray dryer and the weight of the collected spray-dried powder were determined. Following subtraction of the moisture content in the spray-dried powder, the w/w fraction of the theoretical maximum process yield dry solids (including MCT solution) was calculated.

2.4.5. Content of MCT solution in spray-dried powders

The content of Lu 28-179 in the spray-dried powders and in the MCT solution used to prepare the emulsions was determined by reversed-phase HPLC-analysis. The column (YMC-Pack Pro C18, particle size 5 μm, 250 mm × 4.6 mm internal diameter) was heated to a temperature of 45 °C. The mobile phase (35%, v/v, 25 mM citrate buffer, pH 6.2, and 65%, v/v, acetonitrile) had a flow of 1.5 ml/min. The content of Lu 28-179 was used to calculate the MCT solution w/w fraction of the collected powders. The encapsulation efficiency was calculated as the ratio between MCT solution w/w fraction in the dry powder and MCT solution w/w fraction of the emulsion dry solids (including MCT solution).

2.4.6. Density

Pycnometric density was determined with five purges and five runs on a helium gas displacement pycnometer (AccuPyc 1330, Micromeritics, USA). Bulk density was determined by pouring approximately 50 ml powder into a tared graduated 50:1 ml cylinder and measuring the volume and mass. Three determinations were performed and used to calculate the mean pycnometric density and bulk density.

2.4.7. Particle size distribution

Particle size distributions were determined using the laser diffraction apparatus as described for emulsion droplet size. Spray-dried emulsions and Neusilin were analysed applying a dry powder feeder (RODOS/VIBRI, Sympatec, Germany) and an injector pressure of 0.2 bar with the exception of Neusilin UFL2 where 1.0 bar was needed to break up agglomerates. Due to cohesiveness, spray-dried mannitol and trehalose were measured in a glass container (CUVETTE, Sympatec, Germany) after dispersion in MCT. For all particulate materials, the mean of three determinations was calculated to obtain $d_{50\%}$ and SPAN.

2.4.8. Powder compressibility and compactibility

The powders were compacted with a compaction simulator (Pedersen and Kristensen, 1994). When necessary, lubrication was applied to the punches and the die by the use of a 5% suspension of magnesium stearate in acetone. Powder samples weighing approximately 500 mg were compacted with 15.0 mm flat-faced punches and stored in an airtight container. The compression time displacement profile was a simulation of an excentric press with a cycle time of 2.2 s.

The compressibility was characterised as suggested by Walker (1923) assuming a relationship between the relative volume (V) of the tablets in-die and the logarithm of maximum pressure (P_{max}) applied by the upper punch:

$$100V = -W\log(P_{max}) + C \quad (2)$$

Using the notation in Eq. (2) as proposed by Sonnergaard (1999), the compressibility, W, expresses the change in volume in percent of the powder volume when the pressure is increased by a factor 10 within the range of pressures producing a linear relationship. C is a constant.

Approximately 24 h after compaction, the tablets were weighed and the height measured (Digimatic Indicator, Mitutoyo, Japan). The tablets were then subjected to a diametral load with a tablet hardness tester (Kristensen et al., 2002). The piston of the hardness tester operated at a speed of 75 μm/s and a PC was used to record the force required to cause fracture.

The compactibility (MPa) was characterised using specific crushing strength (SCS) calculated according to Eq. (3):

$$\mathrm{SCS} = \frac{\text{force (N) to cause fracture}}{\text{tablet diameter (mm)} \times \text{tablet height (mm)}} \quad (3)$$

which differs from the formula used by Fell and Newton (1970) by not including the constant term $2/\pi$. Using Eq. (3), a tablet with a height of 2 mm having a SCS of 1 MPa corresponds to a tablet crushing strength of 30 N.

2.5. Experimental design and statistical analysis

A randomised 2^3 full factorial design with two replications was conducted. The factors and levels used in the preparation of the emulsions were: amount of MCT solution (low or high) containing 40 mg Lu 28-179/g, Neusilin type (Neusilin UFL2, fine powder or Neusilin US2, granular) and sugar type (trehalose or mannitol) and PC software (MODDE 6.0, Umetrics AB, Sweden) were applied to perform analysis of variance (ANOVA) based on multiple linear regression except responses with missing values where partial least squares analysis was performed. The *P*-values reported were based on the full model with all main effects and interactions.

3. Results and discussion

3.1. Emulsion droplet size distribution

No significant effect of sugar type or the level of MCT solution on droplet $d_{50\%}$ (Table 2) was observed indicating a robust emulsification process resulting in an average droplet $d_{50\%}$ of 1.8 μm. The average droplet SPAN was 1.3. Increasing the content of MCT solution resulted in decreased SPAN values (Table 3) caused by a tendency of $d_{90\%}$ to decrease (data not

Table 2
Mean response variables of the 2^3 factorial design[a]

Factorial levels[b]	Droplet size $d_{50\%}$ (μm)	Droplet size SPAN	Moisture content (%, w/w)	Process yield (w/w)	MCT solution w/w fraction	Encapsulation efficiency	Pycnometric density (g/cm^3)	Bulk density (g/ml^3)	Particle size $d_{50\%}$ (μm)	Particle size SPAN
52.5, US2, T	1.8	1.4	3.6	0.62	0.16	0.70	1.507	0.37	109	1.27
115, US2, T	1.9	1.2	3.0	0.55	0.30	0.76	1.387	0.39	112	1.25
52.5, UFL2, T	–	–	2.5	0.91	0.23	0.98	1.425	0.36	33	1.77
115, UFL2, T	1.7	1.2	2.8	0.85	0.39	0.97	1.288	0.30	34	1.64
52.5, US2, M	1.7	1.4	3.0	0.75	0.20	0.86	1.427	0.37	104	1.47
115, US2, M	1.8	1.2	2.5	0.74	0.38	0.95	1.297	0.37	107	1.44
52.5, UFL2, M	1.8	1.4	2.3	0.91	0.22	0.94	1.412	0.34	31	1.83
115, UFL2, M	1.7	1.2	2.9	0.78	0.39	0.98	1.284	0.33	41	1.60

[a] Droplet size was considered to be part of a 2^2 design with four replications because the level of Neusilin did not affect the emulsification.
[b] MCT solution (52.5 g or 115 g), Neusilin (US2 or UFL2) and sugar (trehalose, T, or mannitol, M).

Table 3
Summary of ANOVA including main effects and the Neusilin–sugar interaction[a]

Factors and interaction	Droplet size $d_{50\%}$	Droplet size SPAN	Moisture content	Process yield	MCT solution w/w fraction	Encapsulation efficiency	Pycnometric density	Bulk density	Particle size $d_{50\%}$	Particle size SPAN
MCT solution	NS	_***	_***	_***	+***	+*	_***	NS	+***	_***
Neusilin type	NA	NA	+***	_***	_***	_***	+***	+***	+***	_***
Sugar type	NS	NS	+***	_**	_***	_**	+***	NS	NS	_***
Neusilin–sugar	NA	NA	***	***	***	***	***	NS	**	**

[a] The change in responses when the factorial levels change from low to high are denoted + (increase) or – (decrease). The high levels are 115 g MCT solution, Neusilin US2 and trehalose. The level of significance is indicated by *, ** or *** corresponding to a *P*-value lower than 0.05, 0.01 or 0.001, respectively. No significant effect, corresponding to a *P*-value higher than 0.05, is indicated by NS. NA denotes not applicable. Droplet size was analysed as a 2^2 design with four replications because the level of Neusilin did not affect the emulsification process.

shown). Droplet $d_{50\%}$ and SPAN were slightly higher than those reported for spray-dried HPMC-emulsions having a comparable content of MCT (Christensen et al., 2001a).

3.2. Sugar physical state

The DSC thermogram of spray-dried trehalose (Fig. 1) did not allow a reliable identification of the glass transition of amorphous trehalose previously reported to be 115 °C (Taylor and York, 1998) to 120 °C (Naini et al., 1998) for a dry sample. However, assum-

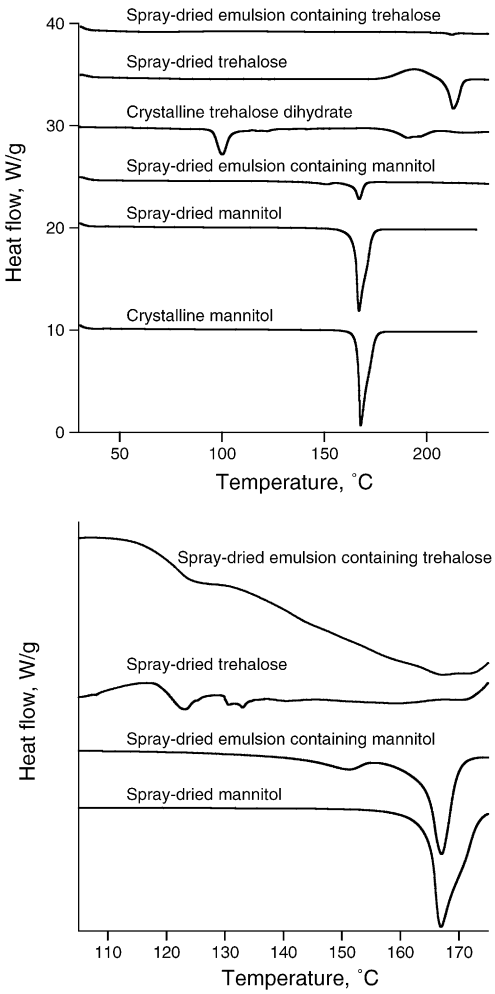

Fig. 1. DSC thermograms of the spray-dried powders and the crystalline sugars (top) and close-ups of melting and glass transitions of the spray-dried powders (bottom).

ing that moisture had evaporated from the sample during the scan, the change in baseline observed at approximately 120 °C is in accordance with the expected value of the glass transition. Furthermore, the thermogram did not show the endothermic peak at about 96 °C observed for crystalline trehalose dihydrate (Fig. 1) corresponding to the loss of crystal water (Naini et al., 1998). No thermal events were observed until about 180 °C where the exotherm recrystallisation of crystalline anhydrous trehalose started followed by its melting at 213 °C (Taylor and York, 1998). Therefore, the spray-dried trehalose was concluded to be amorphous. The spray-dried mannitol and the crystalline starting material (Pearlitol 160 C) both showed a sharp peak at 167 °C (Fig. 1) corresponding to the melting of crystalline mannitol modifications I or II (Burger et al., 2000). This was in agreement with previous findings (Naini et al., 1998) where spray-dried mannitol was crystalline modification I despite the high drying rate favouring formation of an amorphous state as observed for lactose, sucrose and trehalose. Comparing the thermograms of the spray-dried emulsions with the sugar thermograms (Fig. 1) supports that the physical state of trehalose and mannitol in the spray-dried emulsions was amorphous and crystalline, respectively. The presence of a small broad peak at 151 °C for the spray-dried emulsion containing mannitol indicates the presence of the modification III mannitol polymorph having a lower melting point than modifications I and II (Burger et al., 2000).

3.3. Moisture content

The average moisture content in the collected spray-dried emulsions was 2.8% ranging between 2.3% and 3.6% (Table 2). As shown in Table 3, all the factors and the Neusilin–sugar interaction affected the moisture content. They were all having the opposite effect relative to their influence on the powder MCT solution w/w fraction. Therefore, it was concluded that the effects on moisture content were due to the changes in the amount of powder solids able to contain moisture. In addition, the effect of Neusilin type (Table 3) was caused by a concurrent effect on particle size. The larger particles produced using Neusilin US2 (Table 2) resulted in higher moisture content due to an increased average diffusion path of water. Furthermore, spray-dried trehalose had higher moisture content than spray-dried mannitol (Table 4). The effect of sugar type was therefore also due to a difference in moisture content of the sugars following spray drying.

3.4. Process yield, content of MCT solution and encapsulation efficiency

The average process yield was 0.76 and the observed variation (Table 2) was caused by differences in the amount of powder adhering to the drying chamber wall, the cyclone and the piping leading from the drying chamber to the cyclone. Increasing the level of MCT solution decreased the process yield (Table 3). The observed effect was not due to loss of unencapsulated MCT solution droplets as encapsulation efficiency improved when increasing the level of MCT solution (Table 3). It is therefore more likely that the stickiness was related to the MCT solution w/w fraction in the powders. Increasing content of MCT solution in the powders caused more particles adhering to the internal surfaces of the spray dryer.

Replacing Neusilin UFL2 with Neusilin US2 decreased the process yield, MCT solution w/w fraction and encapsulation efficiency (Table 3). The atomisation produced a significant amount of droplets not containing insoluble carrier in the case of Neusilin US2 because of the larger particle size. This led to more particles not containing insoluble carrier and having

Table 4
Results from the characterisation of Neusilin and spray-dried sugars

Material	Moisture content[a] (%, w/w)	Process yield (w/w)	Pycnometric density (g/cm^3)	Bulk density (g/ml^3)	Particle size $d_{50\%}$ (μm)	Particle size SPAN
Neusilin US2	–	–	2.108	0.16	112	2.03
Neusilin UFL2	–	–	2.242	0.09	3	3.99
Spray-dried trehalose	2.0	0.82	1.444	0.46	13	2.44
Spray-dried mannitol	0.2	0.81	1.446	0.41	18	2.14

[a] Moisture content determined by Karl Fischer titration.

an increased content of MCT solution. These particles would, therefore, be expected to have an increased tendency to adhere explaining the observed effects. In addition, the larger Neusilin US2 containing particles travelling further following atomisation, and having higher moisture content as previously described, are more likely to form deposits in the drying chamber (Masters, 2002). The total effect was an increased amount of deposits having a higher content of MCT solution than the collected spray-dried emulsion.

Substituting mannitol with trehalose had similar effects on process yield, MCT solution w/w fraction and encapsulation efficiency as the use of Neusilin US2 as insoluble carrier (Table 3). This was not expected as no difference in process yield was observed spray drying the sugar solutions (Table 4). Stickiness of spray-dried amorphous trehalose is affected by increasing moisture content contrary to spray-dried crystalline mannitol (Naini et al., 1998). The effects could, therefore, be caused by an increased stickiness of amorphous trehalose relative to crystalline mannitol when combined with Neusilin. This hypothesis is supported by the observed interactions between insoluble carrier and sugar type (Table 3). The lowering effect of trehalose on process yield, MCT solution w/w fraction and encapsulation efficiency was less significant when the insoluble carrier was Neusilin UFL2. In this case, the insoluble particles were more evenly distributed in the atomised droplets and resulted in a lower moisture content possibly reducing stickiness of amorphous trehalose. An interaction between the level of MCT solution and sugar type could be observed for MCT solution w/w fraction ($P < 0.05$). The effect of increasing the level of MCT solution was larger for mannitol compared to what was observed for trehalose. The reason was probably the previously described higher encapsulation efficiency of the spray-dried emulsions containing mannitol.

3.5. Powder density

The average pycnometric density of the collected powders was 1.38 g/cm^3. The MCT solution had a density of about 1 g/cm^3 which was lower than the density of the carriers used (Table 4). Therefore, increasing the MCT solution w/w fraction was expected to decrease the powder pycnometric density. The effects of Neusilin, sugar type and the Neusilin–sugar interaction were only due to their influence on MCT solution w/w fraction (Table 3) as neither the levels of Neusilin type nor sugar type caused the pycnometric densities of the carriers to vary accordingly (Table 4).

The average poured bulk density of the collected powders was 0.35 g/ml and density was increased for powders containing Neusilin US2 (Table 3). During the determinations, it was observed that powders containing Neusilin US2 resulted in less voids when filling the cylinder. Therefore, the observed effect on bulk density was probably an improved flowability caused by the larger particle size of the spray-dried emulsions containing Neusilin US2 (Table 2). The Neusilin–MCT solution interaction was significant ($P < 0.05$) even though the effect of MCT solution on bulk density was not. Increasing the level of MCT solution caused the volume of voids in the cylinder to increase only when the spray-dried emulsions contained Neusilin UFL2. The reason for the observed interaction between Neusilin and MCT solution was, therefore, probably related to differences in powder flowability.

3.6. Particle size distribution

The average spray-dried powder particle $d_{50\%}$ was 71 μm and the average SPAN 1.5. As shown in Table 3, the $d_{50\%}$ was dependent on the level of MCT solution, Neusilin type and the interaction between Neusilin and sugar type. In addition, the interaction between MCT solution and sugar type was significant ($P < 0.05$). However, based on the values in Table 2, only the effect of Neusilin type was considered to have a magnitude of interest in relation to the following discussions on compressibility and compactibility. As expected, Neusilin US2 caused the spray-dried powder $d_{50\%}$ to increase due to the larger $d_{50\%}$ relative to Neusilin UFL2 (Table 4).

A decrease in spray-dried powder SPAN relative to the Neusilin types (Table 4) was observed. All variables and the Neusilin–sugar interaction affected SPAN (Table 3). Replacing mannitol with trehalose only caused SPAN to decrease if the powders contained Neusilin US2. An interaction of MCT solution with Neusilin ($P < 0.01$) was caused by a larger reduction in Neusilin UFL2 SPAN relative to Neusilin US2. No straightforward explanations of the observed effects and interactions exist. However, it is likely that the key determinants were the concurrent changes in particle

$d_{50\%}$ and the way the variables affected the composition of the deposits.

3.7. Compressibility

From the compression profiles of the insoluble carriers and spray-dried sugars (Fig. 2), it is noted that Neusilin had the highest compressibility in terms of W. This was caused by the highly porous Neusilin structure which is evident comparing the pycnometric and bulk densities (Table 4). The spray-dried sugars displayed a much smaller reduction in relative volume compared to Neusilin. Their compressibility was not affected by the different physical states of the sugars. The spray-dried sugars had lower pycnometric densities than those reported for freeze-dried amorphous trehalose, 1.53 g/cm^3 (Zhang and Zografi, 2001), and precipitated mannitol modifications I or II (1.47–1.49 g/cm^3) (Burger et al., 2000), respectively. The presence of interparticular voids might have contributed to compressibility in addition to particle rearrangement and deformation.

The compressibility of the spray-dried emulsions is displayed in Fig. 3. The powders were grouped according to Neusilin type because of the interactions between Neusilin and sugar type (Table 3). Fig. 3a shows that the replications of powders containing Neusilin UFL2 have near identical compression behaviour. It is evident that two distinct patterns exist correlating with the level of MCT solution. Using the high level of MCT solution caused a decreased compressibility and a lower pressure was needed to obtain maximum reduction in relative volume. The reduced compressibility was caused by the significant increase in powder w/w fraction of the incompressible MCT solution (Table 3).

The powders containing Neusilin US2 (Fig. 3b) displayed only little variation in compressibility described by W. The appearance of the profiles indicated a similar

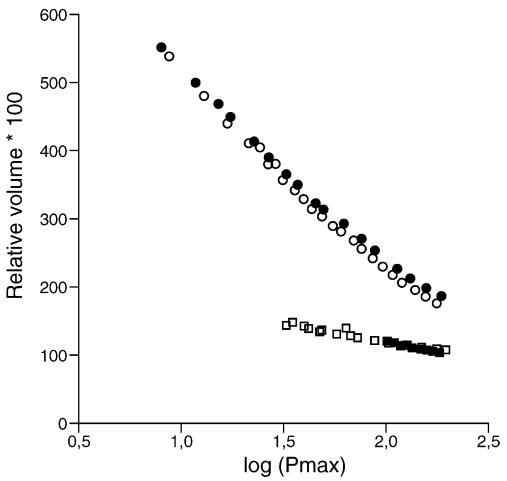

Fig. 2. Walker-plot representing compressibility of Neusilin and spray-dried sugars based on one determination; Neusilin US2 (◯), Neusilin UFL2 (●), mannitol (□) and trehalose (■).

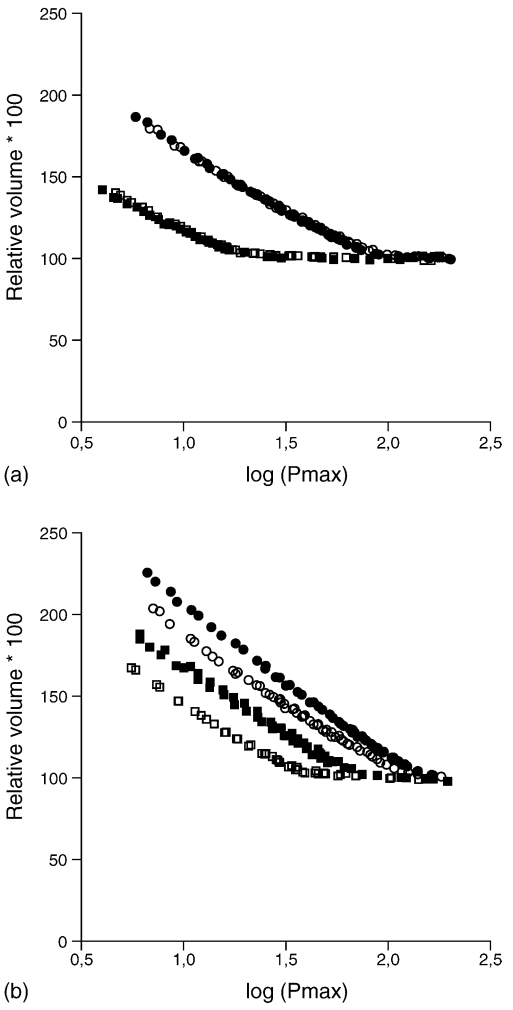

Fig. 3. Walker-plot representing compressibility of spray-dried emulsions containing Neusilin UFL2 (a) and US2 (b), each curve based on the two replicates; 52.5 g MCT solution and trehalose (●), 52.5 g MCT solution and mannitol (◯), 115 g MCT solution and trehalose (■) and 115 g MCT solution and mannitol (□).

behaviour of the replicates. However, the combination of trehalose and high level of MCT solution did show higher variation than the others. A correlation of compressibility to the powder MCT solution w/w fraction (Table 2) could be observed in terms of pressure needed to obtain maximum reduction in relative volume. The top-down arrangement of the profiles corresponds to an increasing MCT solution w/w fraction and hence a decreasing fraction of compressible material. In contrast to powders containing Neusilin UFL2, the sugar type affected powder MCT solution w/w fraction (Table 2). Therefore, the difference in compressibility was not considered directly related to sugar type but was caused by changes in MCT solution w/w fraction.

3.8. Compactibility

The difference in compactibility of the Neusilin types relative to the spray-dried sugars (Fig. 4) was according to the differences in compressibility (Fig. 2). The more compressible Neusilin generally formed stronger compacts than the sugars. However, the type of Neusilin or sugar affected the mechanical strength of the tablets even though only little difference in compressibility was observed. In particular, a difference between the sugars was evident. A pressure above approximately 100 MPa was required for bonding of trehalose to occur whereas mannitol tablets could be produced at pressures above approximately 30 MPa. The observed compactibility of mannitol was slightly lower than previously reported for granulated mannitol modifications I or II (Burger et al., 2000).

The compactibility profiles of spray-dried emulsions containing Neusilin UFL2 (Fig. 5a) was affected by the powder content of MCT solution w/w fraction. Increasing the level of MCT solution lowered the pressure where no further increase in SCS could be ob-

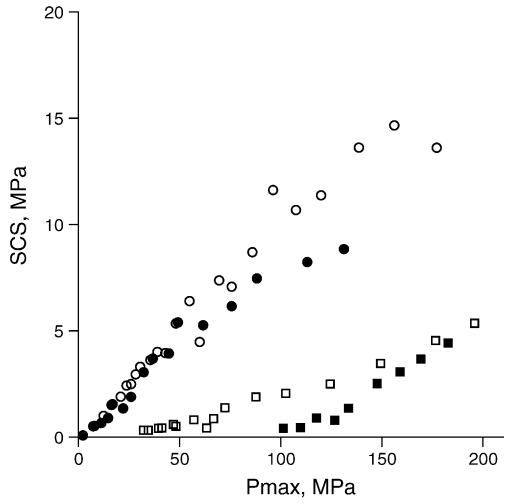

Fig. 4. SCS of Neusilin and spray-dried sugars based on one determination; Neusilin US2 (◯), Neusilin UFL2 (●), mannitol (□) and trehalose (■).

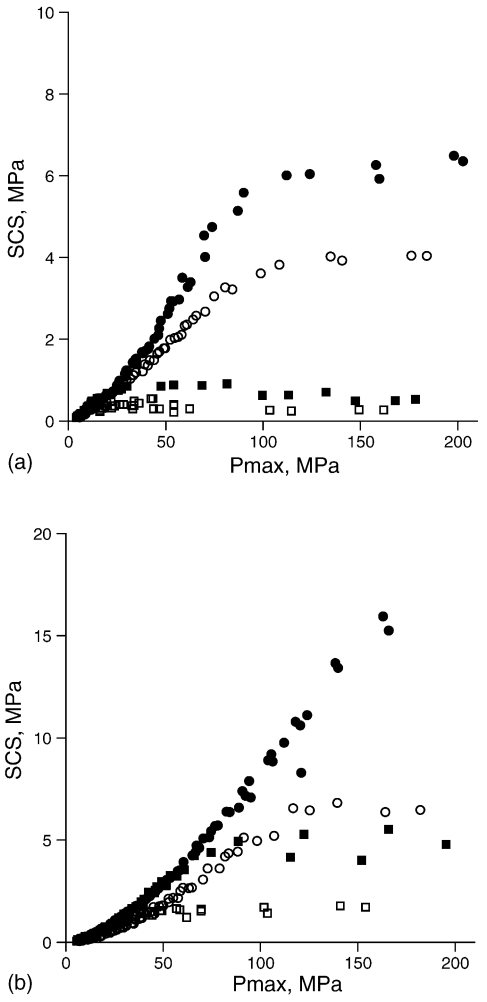

Fig. 5. SCS of powders containing Neusilin UFL2 (a) or US2 (b), each curve based on the two replicates; 52.5 g MCT solution and trehalose (●), 52.5 g MCT solution and mannitol (◯), 115 g MCT solution and trehalose (■) and 115 g MCT solution and mannitol (□).

served and the maximum value of SCS obtained. The result was tablets having an insufficient mechanical strength. Inclusion of trehalose resulted in a higher maximum SCS compared to mannitol. This was unexpected as the sugars had a similar compressibility (Fig. 2) and trehalose formed weaker compacts than crystalline mannitol (Fig. 4). The compactibility of spray-dried emulsions containing Neusilin US2 (Fig. 5b) was also determined by powder MCT solution w/w fraction. The differences caused by sugar type were probably mainly due to the effect of sugar type on powder MCT solution w/w fraction as previously discussed. However, trehalose resulted in higher SCS compared to mannitol at pressures below 70 MPa. The effect was present even when the MCT solution w/w fraction in the powders containing trehalose was higher. Comparing the Neusilin types (Fig. 5a and b), a general improvement of SCS using Neusilin US2 could be observed (note the different scales). However, it must be noted that the effect was confounded with a reduction in powder MCT solution w/w fraction substituting Neusilin UFL2 with Neusilin US2 (Table 3).

4. Conclusions

The present study showed that directly compressible powders containing a poorly water-soluble drug dissolved in MCT could be produced by spray drying an o/w-emulsion. Compressibility and compactibility of the spray-dried emulsions were mainly governed by the MCT solution w/w fraction in the powders but was also affected by the particle size distribution of the insoluble carrier and the sugar type.

Increasing the level of MCT solution caused the mechanical strength of the tablets to decrease. Dependent on the desired mechanical strength of the tablets, a MCT solution load of 20–40% (w/w) could be achieved with the formulations described.

The particle size distribution of the insoluble carrier was affecting the spray drying process and the spray-dried emulsion physical properties when using a pilot plant spray dryer. Small particles were required to obtain a high process yield and a high MCT solution encapsulation efficiency. Large particles were needed for the production of free flowing powders and to increase the mechanical strength of the tablets. However, increased process yield and encapsulation efficiency for large particles might be obtained using a spray dryer having a larger drying chamber reducing the amount of deposits.

The type of sugar was observed to have the most significant effect using an insoluble carrier containing particles which were large compared to the droplets in the emulsion. This is ascribed to the fact that the trehalose is in an amorphous state after spray drying whereas mannitol is in a crystalline state. However, trehalose in general resulted in tablets having a higher mechanical strength compared to mannitol. Dependent on the required load of MCT solution and desired mechanical strength of the tablets, the more stable crystalline mannitol might be preferred to the amorphous trehalose.

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