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Research paper

Preparation of maltodextrin nanoparticles and encapsulation of bovine serum albumin – Influence of formulation parameters

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ABSTRACT

Maltodextrin, which is obtained by partial hydrolysis of starch, is water soluble and could serve as hydrophilic carrier for the encapsulation of protein-based active pharmaceutical ingredients. We investigated three different commercial maltodextrins (Dextrose Equivalents (DE) 4.0–7.0, DE 13.0–17.0 and DE 16.5–19.5) with focus on their ability to form nanoparticles by inverse precipitation.

Successful particle formation was observed for DE 13.0–17.0 and DE 16.5–19.5 but not for DE 4.0–7.0. The process was investigated using acetone as anti-solvent and poloxamer 407 as stabilizer. A tunable size between 170 nm and 450 nm was achieved by varying the type of maltodextrin and the stabilizer concentration. Particles were spherical in shape and were stable over a time period of 14 days. Maltodextrin nanoparticles (MD NPs) were tested on A549 cells and did not show any cytotoxic effects. This underlines the potential of maltodextrin as material for drug delivery systems. Bovine serum albumin (BSA) as a model protein was successfully encapsulated into MD NPs with encapsulation efficiencies of approx. 70% and loading rates of up to 20%.

1. Introduction

Proteins and peptides are representing a growing class of active pharmaceutical ingredients (APIs) [1,2]. In order to overcome their unfavourable pharmacokinetic profiles [3], they are often applied as parenteral solution or encapsulated into drug delivery systems (DDS). PLGA and its derivatives are pharmaceutically known and approved polymers that have been utilized for the preparation of such DDS [4–6]. However, the encapsulation of these highly hydrophilic proteins into the hydrophobic matrix of PLGA is often inefficient.

Polysaccharides are instead natural biopolymers having abundant resources in nature and usually low manufacturing costs. Additionally, they are considered as safe, hydrophilic and biodegradable, turning them into ideal candidates as material for DDS preparation [7]. Starch is one of the most studied polysaccharides for drug delivery. It consists of a complex macromolecular structure based on glucose units, forming amylose and amylopectin substructures [8]. Maltodextrin (MD) is produced from starch by partial hydrolysis and is more hydrophilic when compared to starch [9]. MDs are classified by dextrose equivalents (DE), which is a measured value for the amount of reducing sugars present in the polymer. A low DE indicates a high fraction of polysaccharides and a low fraction of glucose, whilst a high DE refers to a high fraction of glucose. These biocompatible components are the reason that MD is already a known excipient for different pharmaceutical applications [10].

First attempts to form particles based on MD were already successfully established, for example using spray drying [11,12] and self-assembly techniques with chitosan [13] or gum arabic [14,15]. However, the described methods resulted either in large particles in the micrometers size range [16] or the preparation process involved toxic substances [17].

Nanoprecipitation is a fast and mild technique for small particle preparation, suitable for the encapsulation of proteins [18]. The method was introduced by Fessi et al. [19]. This process is widely known *e.g.* for the preparation of PLGA NP [6] and gelatin NP [20,21]. In this process, PLGA is dissolved in an organic solvent and precipitated by adding the solution to an anti-solvent, in this case an aqueous phase. The organic solvent should be miscible with the aqueous phase and easy to remove via evaporation. The process was also optimized for waxy maize starch acetate (SA) by Tan et al. [22]. They dissolved SA in acetone and obtained a nano-suspension by dropwise addition of water. The starch concentration, the water to organic phase ratio and the

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system polarity have been identified as critical parameters.

The aim of this study was to evaluate the use of hydrolyzed starch and to find a mild and reproducible method for maltodextrin nanoparticle formation. Therefore, nanoparticle preparation by inverse precipitation was studied. Parameters were investigated in order to establish a reproducible and straight forward method. We further performed a short toxicity evaluation of the obtained maltodextrin particles with A549 cells, a well described cell line serving as model for the respiratory tract. This cell model was taken due to the potential of these particles for pulmonary application. Furthermore, particles were loaded with BSA as a model protein to demonstrate the particles ability as DDS for macromolecules.

2. Materials and methods

2.1. Materials

Three maltodextrins with different dextrose equivalents (DE 4.0–7.0, DE 13.0–17.0, and DE 16.5–19.5), glucose monohydrate, α-lactose monohydrate (lactose), and bovine serum albumin (BSA) were obtained from Sigma Aldrich (St. Louis, USA). Poloxamer 407 is a non-ionic, tri-block copolymer surfactant composed of polyethylene oxide and polypropylene oxide, used in several pharmaceutical formulations for topical and oral delivery, and was purchased from Caesar & Loretz GmbH (Hilden, Germany). Organic solvents of analytical grade (methanol, acetone) were bought from VWR (Bruchsal, Germany).

A549 cells (ACC 107) were received from the "Deutsche Sammlung von Mikroorganismen und Zellkulturen" (DSMZ, Braunschweig, Germany) and cultured in Gibco RPMI 1640 from ThermoFisher Scientific (Waltham, USA). The medium was supplemented with 10% fetal calf serum (FCS) and 1% penicillin streptomycin from PAN (Aidenbach, Germany). Gibco Hankś Balanced Salt Solution (HBSS) was bought from ThermoFisher Scientific. 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) was purchased from Roche (Mannheim, Germany).

2.2. Preparation of maltodextrin nanoparticles

Nanoparticles were prepared from maltodextrin by an inverse precipitation in methanol and acetone as anti-solvents. Briefly, maltodextrin was dissolved in milliQ water to obtain solutions of 5 mg/mL. A volume of 1 mL of the maltodextrin solution was added to 9 mL anti-solvent with a syringe pump (Legato, Kd scientific, US) whilst stirring. The injection flow rate was set to 35 mL/min. The process was optimized for acetone as anti-solvent, adding poloxamer 407 as stabilizer in various concentrations (0.1%, 0.05%, 0.025%, 0.01%; m/v). Samples were stirred for 15 min for equilibration before analysis.

2.3. Physiochemical characterization of maltodextrin nanoparticles

The particles were analysed with a focus on size and size distribution, represented by the polydispersity index (PdI), using the Zetasizer Nano ZS (Malvern, Malvern, UK). Physicochemical properties were studied for 14 days to evaluate particle storage stability at room temperature.

Particle morphology was examined by scanning electron microscopy (SEM EVO HD15, Carl Zeiss Microscopy GmbH, Jena, Germany). Therefore, samples were placed on a silica wafer, air-dried, and sputtered with a gold layer of approximately 15 nm thickness prior to imaging (Quorum Q150R ES, Quorum Technologies Ltd, East Grinstead, UK). The accelerating voltage was 5 kV.

2.4. Safety assessment

Cell viability was evaluated using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. For assessing the cytotoxicity of maltodextrin nanoparticles, 2×10^4 A549 cells were seeded into 96 well plates and cultured overnight. The cells were incubated with maltodextrin nanoparticles for 4 h and 24 h. To this end, maltodextrin NP formulations (from maltodextrin DE 13.0–17.0 and DE 16.5–19.5, stabilized with 0.025% poloxamer) were dried by evaporation and dissolved in medium to obtain solutions of 5, 0.5, 0.05 and 0.005 mg/mL. As control, maltodextrin with a DE of 13.0–17.0 and 16.5–19.5, poloxamer 407 and α-lactose monohydrate, each dissolved in medium in the same concentrations, were applied.

In all cases, following incubation of cells with NP or materials, cells were washed once with 200 µL HBSS buffer. A volume of 100 µL fresh HBSS buffer, containing 10% (v/v) MTT reagent (stock solution: 5 mg/mL) was added and incubated for 4 h. HBSS buffer was aspirated and 100 µL DMSO was added and incubated for 20 min. Absorbance was measured at 550 nm with the Tecan Infinite® 200 microplate reader (Tecan Deutschland GmbH, Crailsheim, Germany). All incubation steps were performed at 37 °C. Cell viabilities were calculated in comparison to negative control (untreated cells as 100% value of cell viability) and positive control (1% Triton™ X-100 solution as 0% value of cell viability).

Table 1
Maltodextrin nanoparticles were prepared using acetone as anti-solvent and different amounts of stabilizer (Poloxamer 407). The formation of nanoparticles using Maltodextrin 4.0–7.0 was possible in presence of a high amount of stabilizer (1:1.8). Maltodextrins with an increased dextrose equivalent (> 13) allowed a reproducible production of small particles. The size increased when reducing the poloxamer amount. The same procedure led to smaller particles for Maltodextrin 13.0–17.0. Data are presented as mean ± SD of 3 batches.

	Poloxamer [%]	Maltodextrin [mg/mL]	Poloxamer [mg]	Size [d·nm]	PdI
Maltodextrin 4.0–7.0					
	0.5	5	45	158.0 ± 0.6	0.053
	0.25	5	22.5	178.4 ± 0.1	0.078
A1	0.1	5	9	228.8 ± 7.6	0.157
A2	0.05	5	4.5	Aggregates	0.555
A3	0.025	5	2.25	Aggregates	0.792
A4	0.01	5	0.9	Aggregates	0.847
A5	0	5	0	Aggregates	0.926
Maltodextrin 13.0–17.0					
B1	0.1	5	9	172.8 ± 17.8	0.049
B2	0.05	5	4.5	174.8 ± 15.8	0.034
B3	0.025	5	2.25	182 ± 15.6	0.035
B4	0.01	5	0.9	221.7 ± 16.5	0.024
B5	0	5	0	531.8 ± 149.3	0.077
Maltodextrin 16.5–19.5					
C1	0.1	5	9	171.8 ± 4.5	0.055
C2	0.05	5	4.5	210.9 ± 22.9	0.043
C3	0.025	5	2.25	272 ± 70.7	0.028
C4	0.01	5	0.9	446.8 ± 206.5	0.065
C5	0	5	0	699.2 ± 348.9	0.124

2.5. Loading of maltodextrin nanoparticles

Maltodextrin nanoparticles were loaded with BSA as model drug. The protein was added to the aqueous maltodextrin phase before nanoparticle formation, in order to obtain concentrations of 0.5 mg/mL and 1 mg/mL. Particles were prepared afterwards by adding 1 mL of the aqueous BSA/maltodextrin solution to 9 mL acetone, containing 0.025% poloxamer 407 as stabilizer, using a syringe pump with an injection flow rate of 35 mL/min. For determining the protein encapsulation efficiency (EE) and loading rate (LR), loaded nanoparticles were separated from free protein by centrifugation at 9500 rcf for 30 min at 4 °C (Rotina 420R, Tuttlingen, Andreas Hettich GmbH & Co.KG). The resulting pellet was dissolved in milliQ water and analysed via UV absorbance at 280 nm (BSA). In addition, the supernatant was dried by evaporation and then resuspended in milliQ water in order to

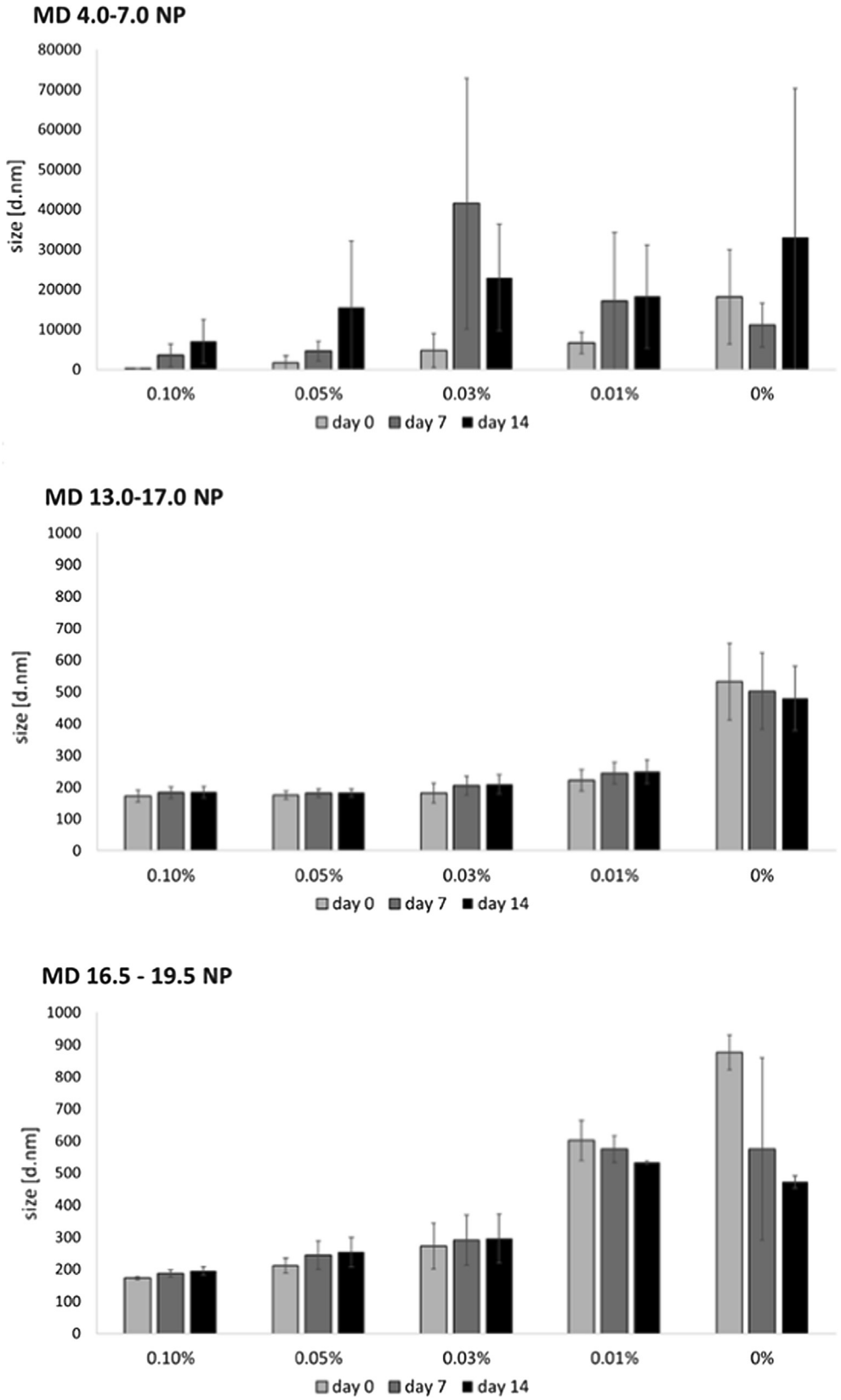

Fig. 1. Maltodextrin nanoparticles were prepared using acetone as anti-solvent and different amounts of stabilizer (poloxamer 407). Size was determined with the Zetasizer Nano ZS on the day of preparation (day 0), day 7 and day 14. Data are presented as mean ± SD of 3 batches.

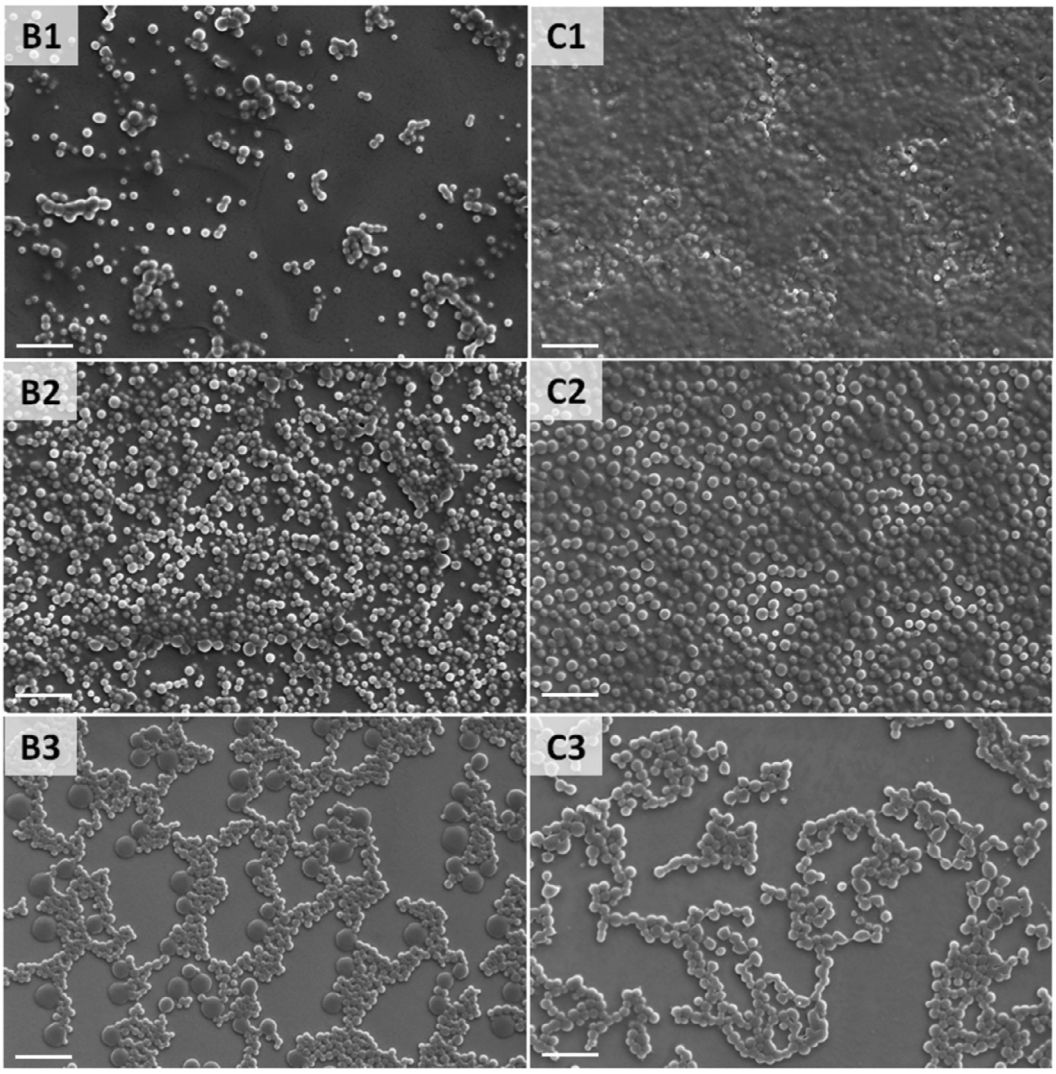

Fig. 2. SEM micrographs of maltodextrin 13.0–17.0 (B) – and maltodextrin 16.5 – 19.5 (C) nanoparticles, stabilized with poloxamer 0.1% (1), 0.05% (2), and 0.025% (3); scale bar = 3 μm. Particles are homogenously distributed but tend to fuse as a consequence of the reduced poloxamer concentration (B3).

Table 2
Cytotoxicity of different materials as well as nanoparticle formulations on A549 cells. No hints for cytotoxic effects were determined after 4 h and 24 h of incubation. Data are presented as mean ± SD of 3 wells. NP: nanoparticles made of maltodextrin.

Conc [mg/ml]	Maltodextrin 13.0–17.0	NP 13.0–17.0	Maltodextrin 16.5–19.5	NP 16.5–19.5	Poloxamer 407	Lactose
4 h						
5	97.2 ± 10.4	95.5 ± 3.5	98.3 ± 12.5	105.1 ± 1.1	109.3 ± 2.1	107.1 ± 5.4
0.5	106.7 ± 3.3	98.0 ± 3.5	95.3 ± 5.8	100.5 ± 3.7	104.0 ± 2.8	107.1 ± 0.4
0.05	103.2 ± 3.8	103.0 ± 1.0	91.8 ± 1.7	101.6 ± 2.6	104.8 ± 1.5	96.4 ± 3.7
0.005	103.7 ± 3.3	98.0 ± 0.4	100.1 ± 5.6	98.3 ± 2.5	96.2 ± 4.0	98.2 ± 4.5
24 h						
5	117.0 ± 3.1	99.4 ± 5.5	114.9 ± 2.7	119.5 ± 1.2	130.5 ± 2.2	113.5 ± 3.3
0.5	114.7 ± 2.7	109.6 ± 8.6	111.0 ± 4.6	120.8 ± 3.2	116.5 ± 5.7	111.9 ± 3.7
0.05	114.1 ± 4.6	93.8 ± 0.3	108.4 ± 4.1	118.6 ± 2.0	113.0 ± 0.8	104.1 ± 2.3
0.005	114.9 ± 3.1	100.9 ± 0.3	95.8 ± 5.5	100.1 ± 2.3	115.7 ± 5.4	98.4 ± 9.3

calculate for the free protein amount. EE (Eq. (1)) and LR (Eq. (2)) of BSA in the NPs were defined and calculated according to the following equations:

$$EE[\%] = \frac{mass(protein\ \ in\ \ the\ \ particles)}{mass(protein)total} * 100 \quad (1)$$

$$LR[\%] = \frac{mass(protein\ \ in\ \ the\ \ particles)}{massMD} * 100 \quad (2)$$

3. Results and discussion

Maltodextrin is a highly water soluble material. In order to prepare maltodextrin nanoparticles, we used an inverse precipitation method. Briefly, maltodextrin was dissolved in an aqueous phase (water), which was added to the anti-solvent under set conditions, leading to precipitation of the material. Different maltodextrin types DE 4.0–7.0, DE 13.0–17.0 and DE 16.5–19.5 as well as two anti-solvents, methanol and

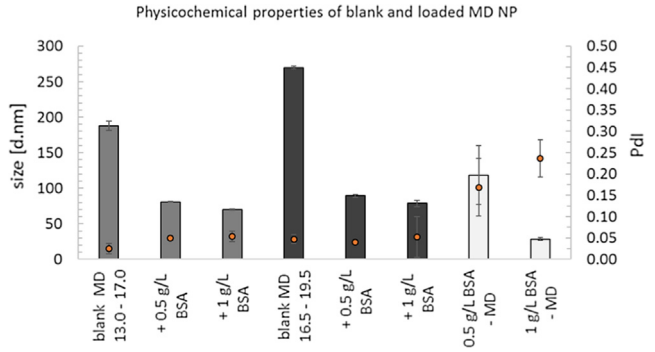

Fig. 3. Physicochemical properties of blank and loaded maltodextrin 13.0–17.0 (mid grey columns) and maltodextrin 16.5–19.5 (dark grey columns) nanoparticles (concentration = 0.5 mg/mL). Loaded particles were prepared by coprecipitation with either 0.5 g/L BSA or 1 g/L BSA into a 0.025% poloxamer in acetone solution. Particles were homogenously distributed (PdI < 0.05, represented by the orange dots), but showed smaller particle sizes of approximately 80 nm, when loaded with BSA. The precipitation of BSA without MD (light grey columns) showed high PdI values (orange dots), indicating an inhomogeneous system.

acetone, were tested. With methanol as anti-solvent, all types of maltodextrin showed larger aggregates visible by eye (data not shown). Maltodextrin DE 13.0–17.0 and DE 16.5–19.5 showed stable nanoparticles in acetone, thus the process was optimized regarding particle size for this anti-solvent by adding poloxamer 407 in different concentrations to the organic phase.

The resulting nano-formulations (from maltodextrin DE 4.0–7.0, DE 13.0–17.0 and DE 16.5–19.5; using acetone as anti-solvent with and without poloxamer 407 as stabilizer) can be found in Table 1. To produce stable maltodextrin DE 4.0–7.0 nanoparticles, a comparable high amount of poloxamer was necessary (> 9 mg per 5 mg maltodextrin). Reducing the poloxamer amount resulted in aggregation of the particles (large size with high standard deviation and high PdI). In contrast to maltodextrin 4.0–7.0, maltodextrins with a higher DE (13.0–17.0 as well as 16.5–19.5) allowed a reproducible formation of particles with a narrow size distribution (represented by a PdI < 0.1). Thus these approaches seem to be better suited for the preparation of the DDS.

For both types of maltodextrin (DE 13.0–17.0 and DE 16.5–19.5), nanoparticles with a reproducible size between 170 and 270 nm could be prepared. The particle size was depended on the type of maltodextrin and on the poloxamer concentration in an inversely proportional relationship.

We assume that there is a range of glucose chain lengths allowing the formation of nanoparticles by the applied method. Longer glucose chains (DE 4.0–7.0) as well as glucose itself (applied as glucose monohydrate, data not shown) did not succeed. Glucose monohydrate showed a transparent solution after inverse precipitation, leading to the assumption that the solubility in water was too high for precipitation, while MD DE 4.0–7.0 led to the formation of aggregates. More details of the commercial maltodextrins, *e.g.* molecular weight, as well as maltodextrins with DEs > 19.5 would be necessary to confirm this hypothesis.

Storage stability at room temperature of all formulations was tested for 14 days. As expected from the first data, MD 4.0–7.0 was not stable with high fluctuations in particle sizes, probably arising from the sedimentation of larger aggregates. Formulations of maltodextrin (DE > 13) were constant in size and PdI for at least 14 days (Fig. 1). However, if no stabilizer was applied, the fluctuation in particle size increased over time.

The particle morphology was investigated by scanning electron microscopy (SEM). Micrographs of maltodextrin DE 13.0–17.0 and DE 16.5–19.5 are displayed in Fig. 2. Particles were spherical with smooth surface. Further, the data are in accordance with size measurements done by dynamic light scattering, using the Zetasizer Nano ZS (Table 1). In contrast, SEM images of maltodextrin DE 4.0–7.0, especially with lower concentrations of poloxamer (< 0.1%) were characterized by heterogeneous areas which did not allow an interpretation (data not shown). However, particles could be detected for maltodextrin DE 4.0–7.0, stabilized with 0.1% poloxamer (Supplementary Fig. 1).

A reduction of stabilizer improved the visualization by SEM as no stabilizer covered the sample. Particles were shown in more detail and were homogenous in size and shape. The relatively small concentration of poloxamer 0.025% (B3 and C3) gave the impression of 'sticky' or 'melting' particles with some of them tending to fuse. This might be an artifact due to the drying process on the silica wafer necessary for SEM sample preparation. However, it underlined the increasing destabilization of the particles as a consequence of the reduction of the poloxamer amount.

The safety of maltodextrin NP was evaluated by a cytotoxicity assay with A549 cells as an *in vitro* model for the alveolar space. Additionally, materials used for nanoparticle preparation and lactose as reference material, known from pulmonary formulations on the market, were

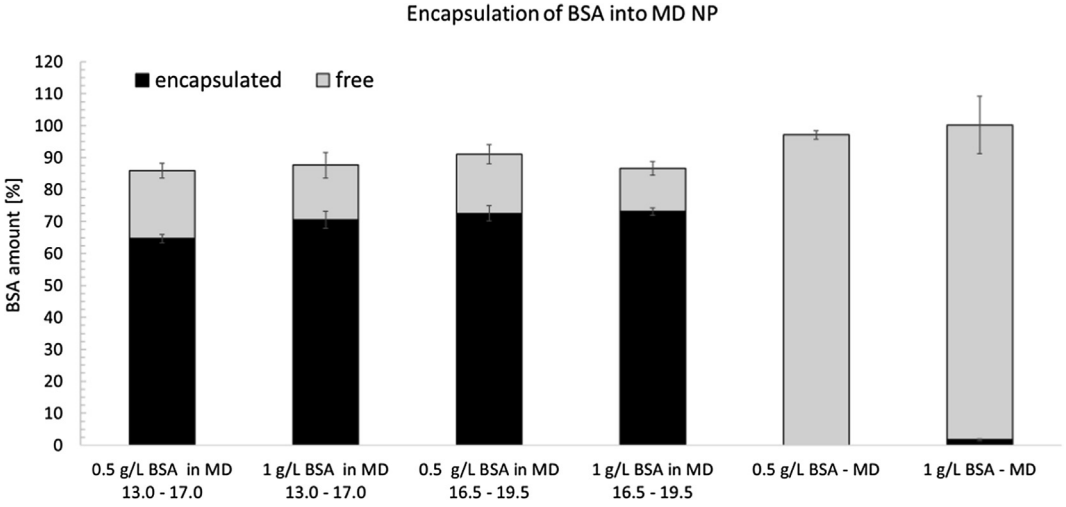

Fig. 4. Encapsulated amount of 0.5 g/L and 1 g/L BSA into maltodextrin 13.0–17.0 and maltodextrin 16.5–19.5 nanoparticles (0.5 g/L). As control, BSA was also precipitated without maltodextrin (two columns on the right). All particles were prepared using a 0.025% poloxamer in acetone solution. All BSA could be found in the supernatant for the samples, precipitated without maltodextrin. For the samples, coprecipitated with maltodextrin a high amount of BSA (~70% of the applied BSA amount) could be found in the pellet.

tested. Lactose and poloxamer 407 showed cell viabilities around 100% for all tested concentrations. Dissolved maltodextrin nanoparticles also did not show any cytotoxicity in the tested concentration range (Table 2).

For evaluating maltodextrin NPs as DDS for proteins, BSA was used as model protein. The encapsulation of BSA into MD NPs was performed for the formulations B3 (MD 13.0–17.0) and C3 (MD 16.5–19.5), each containing 0.025% poloxamer as stabilizer. Encapsulation was performed as coprecipitation of maltodextrin and BSA. Therefore, the protein was dissolved in maltodextrin solution, before performing the inverse precipitation. Fig. 3 emphasizes that particle size dramatically decreased from approx. 180 nm and 270 nm for blank maltodextrin 13.0–17.0 and 16.5–19.5, respectively, to approx. 80 nm, when BSA was encapsulated. The size of the loaded particles was independent from the maltodextrin type and slightly smaller for the higher amount of BSA. All formulations showed narrow size distributions, represented by a PdI < 0.05. As control, BSA was precipitated without maltodextrin showing high PdI values, indicating an inhomogeneous system and the need for encapsulation.

As control, BSA was added after maltodextrin nanoparticle formation. Here, a difference in size could not be observed (data not shown), in contrast to the encapsulation *via* coprecipitation indicating the interaction of BSA with maltodextrin and the influence of cargo/protein on particle formation and appearance. We assume that the reduced BSA-loaded particle size indicates an influence of the BSA itself as stabilizer which could explain this observation. Regarding the proteinaceous load we cannot exclude aggregation of BSA or any change of the protein tertiary structure due to acetone.

Maltodextrin NPs encapsulated approx. 70% of the applied BSA amount. No pellet was found after centrifugation of BSA controls precipitated without maltodextrin, emphasizing the successful encapsulation of BSA intro maltodextrin NPs (Fig. 4). A loading rate of 10% and 20% was quantified for the BSA in maltodextrin NPs (0.5 g/L and 1 g/L, respectively). The release rate was not determined as particles dissolve in relevant aqueous media within seconds. Thus, an immediate release took place.

Based on the data so far, the development of a pulmonary formulation is of interest. Nanoparticles might be agglomerated to clusters suitable for aerosol administration. They will release an encapsulated API in an aqueous environment without any cytotoxic implication on lung cells. Further studies are planned to investigate this application.

4. Conclusion

We successfully prepared stable maltodextrin nanoparticles from two commercial types of maltodextrins with a DE > 13, using an inverse precipitation method. The particle size strongly depended on the type of maltodextrin and the amount of stabilizer, reaching from a controllable size of approximately 170–450 nm. The formulations did not show any cytotoxic effects on A549 cells and could be successfully loaded with the model protein BSA, showing encapsulation efficiencies of approx. 70% and loading rates of up to 20%.

We expect maltodextrin nanoparticles to be an interesting drug carrier for pulmonary applications. Maltodextrin is water soluble, biodegradable and non-toxic in high concentrations (5 mg/ml). In future, we want to investigate if and how a pulmonary drug formulation with a high fine particle fraction based on maltodextrin nanoparticles can be prepared. For the future, we assume that a freeze-drying process can stabilize the particles and might also lead to an improved storage stability of encapsulated proteins.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejpb.2019.07.003.

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