International Journal of Pharmaceutics: X 9 (2025) 100332

Contents lists available at ScienceDirect

International Journal of Pharmaceutics: X

journal homepage: www.sciencedirect.com/journal/international-journal-of-pharmaceutics-x

Does tablet shape and height influence survival of fluidized bed-granulated living microorganisms during compaction?

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ARTICLE INFO

Keywords:
Probiotics
Saccharomyces cerevisiae
Mass
Height
Shape
Compressibility
Compactibility

ABSTRACT

The provision of effective probiotic formulations requires gentle processing to maintain the viability of the probiotic microorganisms, which is essential for their health-promoting effects. The drying of microorganisms by fluidized bed spray granulation and subsequent processing of the granules into tablets has proven to be a promising process route in previous studies of the same authors. In these, the influence of various factors was considered using cylindrical tablets with a diameter of 11.28 mm and a mass of 450 mg. These flat tablets are unpleasant to ingest and other tablet geometries should be considered for administration of probiotics but to date, no studies exist on the influence of geometric factors of the tableting tool and of the tablets on the survival of microorganisms. To address this aspect, the survival of *Saccharomyces cerevisiae* during the production of flat, round tablets with different tablet masses and thus heights as well as differently shaped convex tablets is determined and related to the physical-mechanical tablet properties to derive process-structure-property relationships. It turned out that higher tablet heights were advantageous regarding microbial survival and mechanical strength which is attributed to a lower elastic recovery. However, the use of differently shaped tools had a smaller influence on microbiological and mechanical tablet properties since the global tablet porosity was hardly affected.

1. Introduction

Probiotic microorganisms can improve patient health if they are taken in sufficient amounts and in a viable form (Joint FAO/WHO Working Group, 2002). To ensure this, suitable dosage forms must be selected and produced under gentle process conditions (Broeckx et al., 2016). During drying, microorganisms can be converted into an inactive, storable state (Lievense and van't Riet, 1993) if the stress on the microorganisms is low enough. Life-preserving drying is possible through freeze drying, spray drying or fluidized bed spray granulation, among others (Broeckx et al., 2016; Lievense and van't Riet, 1993). To enable particularly easy handling and administration and safe dosing of the dried microorganisms, further manufacturing into tablets is often preferred. However, compression is associated with compressive and shear stress on the microorganisms, which can have lethal effects (Plumpton et al., 1986a; Plumpton et al., 1986b; Fassihi and Parker, 1987; Blair et al., 1991; Stadler and Viernstein, 2001; Chan and Zhang, 2002; Ayorinde et al., 2011; Poulin et al., 2011; e Silva et al., 2013; Nagashima et al., 2013; Muller et al., 2014; Vorländer et al., 2020; Vorländer et al., 2023a; Vorländer et al., 2023b; Vorländer et al., 2023c; Vorländer et al., 2023d). Therefore, process and formulation parameters must be chosen with care.

Fluidized bed granules typically have good tabletability, so that only low compression stresses are required to produce mechanically sufficiently strong tablets. In addition, the process is an attractive option for drying microorganisms at relatively low temperatures, especially compared to spray drying. In previous studies by the same authors, yeast cells (*Saccharomyces cerevisiae*) were sprayed onto various carrier materials and the influence of process and formulation parameters was investigated (Vorländer et al., 2023a).

Various aspects and thus possible influencing factors in the tableting of living microorganisms have already been considered in different studies. In particular, the formulation (deformation characteristics such as deformation mechanism and deformation resistance as well as elastic recovery) (Plumpton et al., 1986a; Plumpton et al., 1986b; Fassihi and Parker, 1987; Blair et al., 1991; Stadler and Viernstein, 2001; Chan and

Abbreviations: CFU, colony-forming units; DCP, dicalcium phosphate; LAC, lactose; MCC, microcrystalline cellulose; MgSt, magnesium stearate.

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https://doi.org/10.1016/j.ijpx.2025.100332
Received 22 January 2025; Received in revised form 2 April 2025; Accepted 4 April 2025
Available online 5 April 2025

Zhang, 2002; Ayorinde et al., 2011; Poulin et al., 2011; e Silva et al., 2013; Nagashima et al., 2013; Muller et al., 2014; Vorländer et al., 2020; Vorländer et al., 2023a; Vorländer et al., 2023b; Vorländer et al., 2023c; Vorländer et al., 2023d; Maggi et al., 2000; Stadler and Viernstein, 2003; Brachkova et al., 2009; Klayraung et al., 2009; Villena et al., 2015; Huq et al., 2016; Byl et al., 2018; Sánchez et al., 2018; Oktavia et al., 2020; Shu et al., 2020; Azhar and Munaim, 2021; Hoffmann and Daniels, 2019) and kinetic parameters (dwell time and consolidation time) (Fassihi and Parker, 1987; Vorländer et al., 2023c) were addressed. Usually, flat, round tablets were produced and the influence of geometric aspects was not taken into account.

In principle, tablets can be produced in a wide variety of shapes, for example to make them easier to distinguish or more convenient to swallow. At the same time, the different tablet shapes can have technical process advantages. These include the better suitability of biconvex tablets for film coating processes due to the improved rolling behavior and the reduced formation of twins and multiples (Wilson and Crossman, 1997). In general, a distinction is made between flat, convex (mostly convex, but also concave) and beveled tablets, whereby the radius of curvature determines the height and thus the volume of the calotte and the shape of the bevel is defined by its height and angle. The basic surface shape of the tablets is particularly diverse. Typical shapes include round or elongated tablets (capsule or oval), but various polygons (with rounded corners) such as rhombuses and squares or special shapes are also used (Alexander, 2009). In addition, break notches can be used to improve breakability or embossing can be used for product and brand identification and to mark the dose (Roberts and Rowe, 1986).

Different punch geometries cause different stress effects on powder during compression and by these specific density distributions in the tablets. This is due to the complex particle movements and various interactions between the powder and the tools, which is why the powders are usually not evenly densified and areas of varying density or porosity occur within the tablet (Sinka et al., 2004a). The movement of the particles is influenced in particular by the geometry of the tablet punches. A concave shape of the punch surfaces causes a stronger radial powder movement in the area of the calotte, whereas with flat punches the powder is mainly compacted axially to the direction of force (Eiliazadeh et al., 2003). In addition, frictional effects between the powder and the die influence the powder movement, which is why, for example, external lubrication of the die can change the density distribution in the edge areas of the tablets (Sinka et al., 2004b). In principle, every tablet geometry has characteristic density distributions, which can, however, be influenced by particle characteristics as well as process parameters such as the compaction profile or the tablet height (Sinka et al., 2004a; Eiliazadeh et al., 2003; Han et al., 2008; Diarra et al., 2015). These density gradients influence the mechanical properties of the tablets (Cabiscol et al., 2018), as areas of low density have lower strengths (Diarra et al., 2015).

The density distributions are difficult to access experimentally (Sinka et al., 2004a; Eiliazadeh et al., 2003; Djemai and Sinka, 2006) and have therefore been investigated by various authors using simulative approaches, for example using the finite element method (Sinka et al., 2004b; Han et al., 2008; Diarra et al., 2015; May et al., 2013; Klinzing et al., 2010). Among other things, it was shown that density gradients are significantly more pronounced in biconvex tablets than in flat-faced tablets. While in biconvex tablets a low density area extends vertically through the center of the tablet, flat-faced tablets only show this in the center of the band (Diarra et al., 2015). At the same time, the edges are more dense with a convex shape than with a flat geometry (Diarra et al., 2015). The extent of the density gradients of biconvex tablets is also determined by the tablet height and depends on the radius of curvature (Diarra et al., 2015). Due to the largely uniform density distribution in flat-faced tablets, no significant effect is expected here.

With the different stress and density distributions, it is conceivable that the choice of tablet shape can influence the microbial damage and survival during compaction. However, the extent to which different tablet geometries are associated with different stresses on microorganisms during compression has not yet been published and is therefore the aim of the current study. Fluidized bed granules with yeast cells from an earlier study by the same authors were used for this purpose. These differ in terms of the carrier material used and thus the predominant deformation behavior (ductile to brittle). On the one hand, flat-faced tablets with different masses and therefore heights are produced, and on the other hand tablets with different shapes and sizes but the same projection area-related mass. In addition to the microbiological properties, physical and mechanical parameters such as tablet porosity and tablet strength are determined and linked to each other. In this way, preferred geometry aspects for the production of probiotic tablets are deduced.

2. Materials and methods

2.1. Granules containing living microorganisms

Granules containing viable cells of the yeast *Saccharomyces cerevisiae* (fresh yeast from Deutsche Hefewerke, Nürnberg,Germany) on the basis of dicalcium phosphate (DCP, DI-CAFOS A150, kindly provided by Chemische Fabrik Budenheim KG, Budenheim, Germany), lactose (LAC, Granulac 70, kindly provided by MEGGLE GmbH & Co. KG, Wasserburg am Inn, Germany) or microcrystalline cellulose (MCC, Vivapur 102, kindly provided by J. Rettenmaier & Söhne GmbH + Co KG, Rosenberg, Germany) were produced in a previous study (Vorländer et al., 2023b) and used for the present study. *S. cerevisiae* serves as a model organism in this study due to its similarity to the probiotic yeast *Saccharomyces cerevisiae* subsp. *boulardii* (Edwards-Ingram et al., 2007) and the easy availability of fresh cells with batch-to-batch consistency. Beside the microorganisms and water, the granulation liquid consisted of trehalose and skimmed milk powder as additives to protect the cells during drying. 825 g of the suspension with a solid mass of 310 g (50 % of cell dry weight (CDW), 25 % of trehalose and 25 % of skimmed milk powder) were sprayed on 1 kg of DCP, LAC and MCC, respectively, in a fluidized bed (Solidlab 2, Syntegon Technology GmbH, Waiblingen, Germany). A more detailed description could be found elsewhere (Vorländer et al., 2023a; Vorländer et al., 2023b). Survival during granulation depended on the carrier material and was 19.7 ± 0.9 % with DCP, 13 ± 2 % with LAC and 10.3 ± 0.2 % with MCC. Particle size distribution are shown in of the carrier particles and granules (Fig. S1) was characterized by dynamic image analysis (QICPIC with GRADIS dispersing unit and VIBRI dosing unit, Clausthal-Zellerfeld, Germany). The analysis was repeated three times with a minimum of 100,000 particles analyzed each time.

2.2. Tableting

DCP, LAC, MCC and the corresponding yeast granules were compressed to tablets using a compaction simulator (Styl'One evolution, Medelpharm, Beynost, France). To reduce ejection forces, a suitable amount of magnesium stearate (MgSt, MAGNESIA GmbH, Lüneburg, Germany) as lubricant was added and dispersed with a tumbling mixer (TURBULA, Willi A. Bachofen AG, Muttenz, Switzerland) for 2 min at 49 min^{-1}. Lubrication was necessary for pure DCP (1 wt.-% MgSt) and LAC (0.5 wt.-% MgSt) as well as for the both corresponding granules (both 0.5 wt.-% MgSt). Poor flow properties of MCC (ungranulated carrier material) required addition of 0.5 wt.-% of highly dispersed SiO_2 (Aerosil 200, Evonik Industries AG, Essen, Germany) to ensure homogeneous die filling (mixed for 10 min at 49 min^{-1}). The addition of MgSt was not necessary due to the low ejection forces that occur when tableting MCC or formulations with a high proportion of MCC like the MCC granules. A symmetrical, trapezoidal compression profile with a set consolidation time of 90 ms and a set dwell time of 20 ms was used for displacement-controlled compression.

2.2.1. Variation in tablet mass

The compaction simulator was equipped with round, flat EUR-D tools with a diameter of 11.28 mm. The die was filled with a mass of 450.0 mg, 337.5 mg, 225.0 mg and 112.5 mg, respectively, using a paddle feeder. The applied compression stresses were in the range of 50 to 400 MPa.

2.2.2. Variation in tablet shape

In addition, the compaction simulator was equipped with EUR-D tools of various geometries (Fig. 1). In order to obtain comparable tablets with different projection areas, tablets with a specific weight of 450 mg cm^{-2} were produced in each case. This specific weight was chosen based on the results from the variation in tablet mass, where a higher tablet mass proved to be beneficial and to prevent too low minimal distances of concave punches during compression. Compression stresses up to 550 MPa were applied. In contrast to the previously mentioned studies on the influence of tablet mass, only granules based on MCC were used for the studies on the influence of tablet shape. In addition, another batch of MCC granules was used as for the mass variations. However, it was produced the same way as described earlier (Vorländer et al., 2023b) but with the exception, that yeast cells were obtained from Lallemand-DHW GmbH, Vienna, Austria. The limitation to only one carrier material was made in order to keep the experimental effort manageable, especially in view of the complex analysis of the microbiological tablet properties. The choice of MCC granules is based on their good performance, which was demonstrated during the variation of the tablet mass (survival rate related to tensile strength in Section 3.1).

2.3. Tablet analysis

2.3.1. Microbiological tablet properties

The viability of the yeast cells was determined via counting of colony forming units (CFU). Granules or tablets were suspended in a phosphate buffer, serial diluted and appropriate concentrations were spread on suitable agar plates (please see (Vorländer et al., 2023a; Vorländer et al., 2023b) for details). Each viable microorganism formed a colony during incubation (30 °C, 30 h). These were counted automatically (ProtoCOL3 Plus, Synbiosis, Cambridge, United Kingdom) and used to calculate viability and survival rate (Eq. 1 and Eq. 2).

$$\text{viability}\left[\text{CFU}\,g_{\text{CDW}}^{-1}\right] = \frac{\text{count of colonies}\,[\text{CFU}]}{\text{plated concentration}\left[g_{\text{CDW}}\,L^{-1}\right] \bullet \text{plated volume}\,[\text{L}]} \quad (1)$$

$$\text{survival rate}\,[\%] = \frac{\text{viability (tablet)}\left[\text{CFU}\,g_{\text{CDW}}^{-1}\right]}{\text{viability (granules)}\left[\text{CFU}\,g_{\text{CDW}}^{-1}\right]} \quad (2)$$

Count of colonies is the number of colonies found on one agar plate, plated concentration is the cell dry weight concentration of the plated sample and plated volume is the corresponding volume of the sample (always 100 µL). The objective of the present study was to investigate the influence of tablet weight and shape on the survival of microorganisms during compression. It was found that survival rates were carrier-dependent during granulation, and therefore survival rates were calculated and shown solely for the tableting step. This means that the number of colony forming units in the granules were used as a starting point for calculating the survival rate during tableting (Eq. 2).

2.3.2. Physical tablet properties

2.3.2.1. Porosity. The geometrical dimensions of all tablets were determined to calculate their volume V_t. In the case of convex tablets, changes of the height and volume of the caps during relaxation were neglected since they could not be measured accurate enough to be able to take changes into account. Instead, the data from the tools themselves were used for this volume portion of the convex tablets. The same applies to the caps of the rhombic and oval tablets. Here, it is also assumed that the tablets were uniformly recovered when calculating the volume. This means that although the length of the tablets was measured in two directions, the volume calculation assumed that the shape of the tablet was only scaled. Together with the true density ρ_{true} determined by helium gas pycnometry (Ultrapyc 1200e, Quantachrome Instruments, Boynton Beach, FL, United States) and tablet mass m_t, the tablet porosity ε was calculated by (Markl et al., 2018):

$$\varepsilon = 1 - \frac{m_t}{\rho_{\text{true}}\,V_t} \quad (3)$$

2.3.2.2. Pore size distribution. In addition, the pore size distribution was determined for selected tablets using mercury intrusion (Markl et al., 2018). The determination was carried out in accordance with ISO 15901-1 (Belpore HP, Microtrac, Microtrac Retsch GmbH, Haan, Germany) with a maximum test pressure of 400 MPa and a stepwise pressure increase at a rate of 6–19 MPa min^{-1}.

2.3.2.3. Tensile strength and breaking strength. The breaking force F of always 10 tablets was determined under (diametrical) load between two

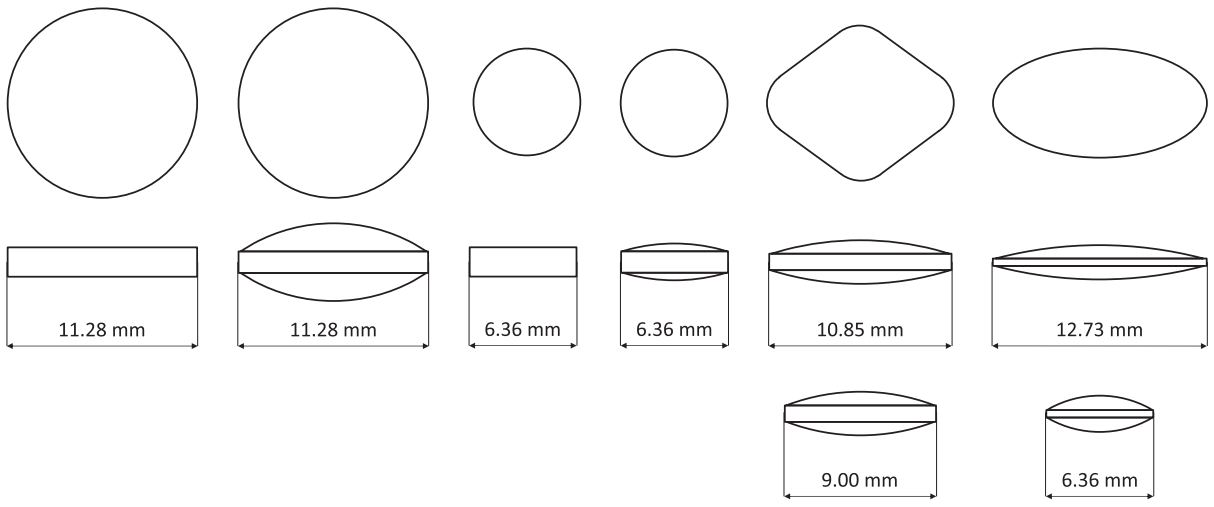

Fig. 1. Schematic illustration of different tablet shapes used: Flat-faced 11.28 mm, convex 11.28 mm, flat-faced 6.36 mm, convex 6.36 mm, rhombic and oval (from left to right).

jaws (manual tablet tester MultiTest 50, Sotax AG, Aesch, Switzerland) (Ph. Eur. 9.3 2.9.8). Together with the geometric parameters, tablet tensile strength σ_t can be calculated for round, flat-faced tablets (Carneiro and Barcellos, 1949; Fell and Newton, 1970) as:

$$\sigma_t = \frac{2\,F}{\pi\,d\,h_t} \tag{4}$$

for round, convex tablets (Pitt et al., 1988) as:

$$\sigma_t = \frac{10\,F}{\pi\,d^2\left(2.84\,\frac{h_t}{d} - 0.126\,\frac{h_t}{h_b} + 3.15\,\frac{h_b}{d} + 0.01\right)} \tag{5}$$

and for elongated, convex tablets (Pitt and Heasley, 2013) as:

$$\sigma_t = \frac{2}{3}\left(\frac{10\,F}{\pi\,d^2\left(2.84\,\frac{h_t}{d} - 0.126\,\frac{h_t}{h_b} + 3.15\,\frac{h_b}{d} + 0.01\right)}\right) \tag{6}$$

d is the diameter of round tablets or the width of the oval tablet, h_t is the total tablet height and h_b is the band height of the convex tablets (total tablet height minus two times cap height). Eqs. (5) and (6) are sometimes the subject of controversy because they do not match Eq. (4) when applied to flat tablets and therefore cannot be reduced to the hertz model (Shang et al., 2013a; Shang et al., 2013b; Al-Sabbagh et al., 2019; Yohannes and Abebe, 2021). Sinka et al. consequently developed an alternative formula for calculating the tensile strength of round, biconvex tablets, which corresponds to Eq. (4) for flat, round tablets (Shang et al., 2013a; Shang et al., 2013b). However, some of the parameters in the equation are formulation-specific, so that the application requires additional experiments (Al-Sabbagh et al., 2019). Furthermore, the transfer to more complex tablet geometries is not readily possible and the application for oval tablets requires the determination of a shape specific geometry factor via finite element method simulation (Yohannes and Abebe, 2021). For rhombic tablets, the applicability has not been considered in any study so far. It is beyond the scope of the present study to investigate this, which is why the breaking force was related to the cross-sectional area (theoretical fracture surface) to get a breaking strength σ_b as an easily accessible surrogate for the strength for tablet with every imaginable shape:

$$\text{flat-faced tablets: } \sigma_b = \frac{F}{d\,h_t} \tag{7}$$

$$\text{convex tablets: } \sigma_b = \frac{F}{d\,h_b + A_{calotte}} \tag{8}$$

For round tablets, $A_{calotte}$ can be calculated as a circle segment based on the radius of curvature of the calotte and the depth of the calotte (11.28 mm: $A_{calotte} = 13.509\ mm^2$; 6.36 mm: $A_{calotte} = 1.857\ mm^2$). For the other punches, the calculation is more complex due to the more complex curvature, which is why the numerical approximation of the CAD program used to design the punches is used (oval: $A_{calotte} = 6.872\ mm^2$; rhombic: $A_{calotte} = 5.830\ mm^2$). The breaking strength and tensile strength are not identical. In order to compare the results from the oval and rhombic tablets with the other geometries, the breaking strength was calculated for all geometries.

3. Results and discussion

3.1. Variation of tablet mass (height)

The geometric tablet property associated with the change in tablet mass is the tablet height. However, the resultant height of the tablets was dependent on the carrier, the tablet mass and the compression stress (Fig. 2 and Table S1). Due to these dependencies, instead of tablet height, the tablet mass is considered during presentation and discussion of results.

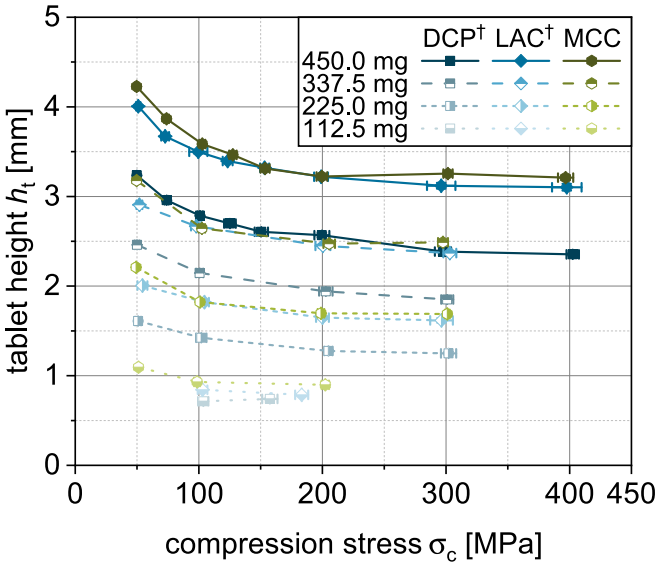

Fig. 2. Dependency of tablet height of applied compression stress, tablet mass (112.5 to 450 mg) and carrier material during compaction of yeast containing granules. (†) Lubrication with 0.5 wt.-% MgSt. Data points show mean value and standard deviation ($n = 10$).

As observed in previous studies (Plumpton et al., 1986a; Plumpton et al., 1986b; Fassihi and Parker, 1987; Blair et al., 1991; Stadler and Viernstein, 2001; Chan and Zhang, 2002; Ayorinde et al., 2011; Poulin et al., 2011; e Silva et al., 2013; Nagashima et al., 2013; Muller et al., 2014; Vorländer et al., 2020; Vorländer et al., 2023a; Vorländer et al., 2023b; Vorländer et al., 2023c; Vorländer et al., 2023d; Byl et al., 2018; Byl et al., 2020), the survival of microorganisms decreases with increasing compression stress regardless of the formulation (Fig. 3). However, the decrease in survival is again dependent on the formulation. Within a certain range, changes in the tablet mass cause different survival rates. However, a global systematic effect cannot be recognized and slightly different curves appear to be random. A steady decrease in survival with decreasing tablet mass is only recognizable in the case of MCC and the lowest compression stress. With the lowest compression

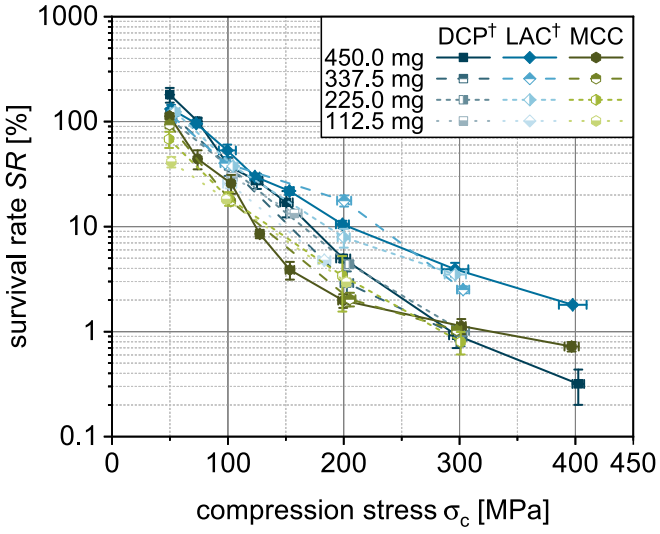

Fig. 3. Influence of compression stress on survival of yeast cells during tableting of yeast-loaded granules based on DCP, LAC and MCC. Tablets with a mass of 112.5 to 450 mg were produced. (†) Lubrication with 0.5 wt.-% MgSt. Data points show mean value and standard deviation ($n = 10$).

stress, survival rates may exceed 100 %. This is not an experimental error, but a reproducible result that has been reported in previous studies and was attributed to the change in reconstitution speed (Plumpton et al., 1986b; Vorländer et al., 2023b; Vorländer et al., 2023c). Compared to the loose reference granules, the microorganisms are wetted more slowly when the tablets disintegrate. A fast wetting of dried cells can be linked to packing defects of the cell membrane and loss of integrity and viability. Nevertheless, in the case of high compression stresses, the mechanical damage to the cells outweighs the potential benefits of slower reconstitution.

Previous studies have shown that yeast cell survival is largely determined by tablet porosity and changes in porosity during compaction (Fassihi and Parker, 1987; Vorländer et al., 2023b). The decrease in porosity was associated with increased compressive and shear stresses on the microorganisms. Lower porosities are generally associated with lower survival rates (Fig. 4a). However, there is a clear influence of the formulation, i.e., the carrier material used. The variation in initial porosities is the reason why previous studies by the same authors focused on porosity changes, which demonstrated a correlation with survival across different formulations (Vorländer et al., 2023b). Nevertheless, the survival plotted as a function of absolute porosity indicates that both the formulation and tablet mass have an impact. Irrespective of the formulation, lower tablet mass is linked to lower survival at the same tablet porosity. To examine the influence of tablet mass in more detail, the porosity reduction was calculated analogously to (Vorländer et al., 2023b) as

$$\varepsilon_{\text{reduction}} = \varepsilon_{\text{t,50 MPa}} - \varepsilon_{\text{t},i} \tag{9}$$

with $\varepsilon_{\text{t,50 MPa}}$ as out-die porosity of the tablets obtained at the lowest compression stress of 50 MPa and $\varepsilon_{\text{t},i}$ as porosity for tablets produced with a compression stress i greater than or equal to 50 MPa. The survival as a function of porosity reduction shows a significantly better correlation for the different formulations and the different tablet masses (Fig. 4b). However, it is important to note that for all three materials, survival rates decrease as mass decreases, even with the same porosity reduction. Therefore, porosity reduction alone cannot fully explain the observed survival rates. This is especially evident in the case of MCC, where different survival rates can already be clearly recognized at the lowest compression stress and thus a porosity reduction of 0.

In order to better understand the influence of tablet mass on survival, it is therefore necessary to take a more detailed look at the effects of tablet mass on the compaction process and tablet properties. The different porosities resulting from the same compression stress (see Figs. 3 and 4) indicate a change in compressibility as a function of tablet mass. Compressibility describes the densification of a material, i.e., the porosity as a function of the applied compression stress (United States Pharmacopoeia, 2023). For the three formulations investigated, it is clear that compressibility increases with increasing tablet mass (Fig. 5). This effect is particularly pronounced with MCC and applies not only to the yeast granules shown here, but also to tablets produced from the ungranulated carrier materials (Figure S2). The overall different compressibilities depending on the carrier material used correspond to the expectations based on the compressibility of the ungranulated carrier materials (Vorländer et al., 2023b). Particularly high porosities in the case of DCP are due to its brittle deformation character. The material has a high resistance to deformation and tends to fragment instead of undergoing plastic deformation (Garr and Rubinstein, 1991). Cavities between the particles are filled more poorly than the ductile deformation of MCC and LAC allows, which is why a high porosity remains. The effect is less pronounced here than with the tableting of the ungranulated carrier material, as the yeast cells and protective substances introduced into the formulation are plastically deformable components that can partially fill the pores between the DCP particles (Vorländer et al., 2023b; Garr and Rubinstein, 1991). The dependence of the

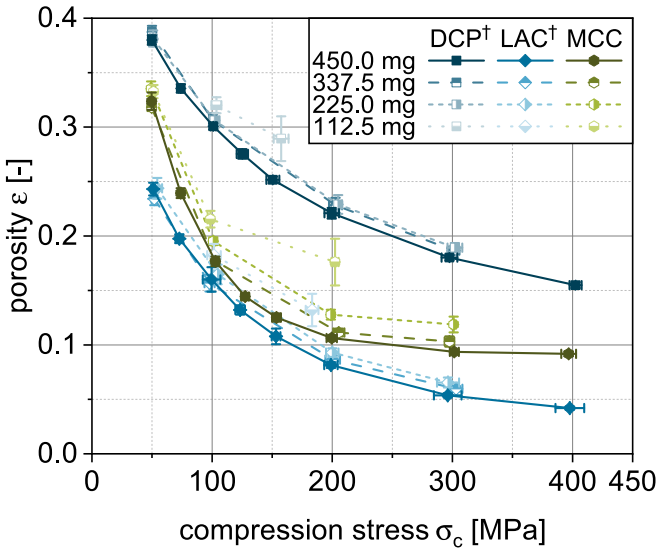

Fig. 5. Compressibility of different formulations (yeast granules based on DCP, LAC and MCC) and tablet masses (112.5 to 450 mg). (†) Lubrication with 0.5 wt.-% MgSt. Data points show mean value and standard deviation ($n = 10$).

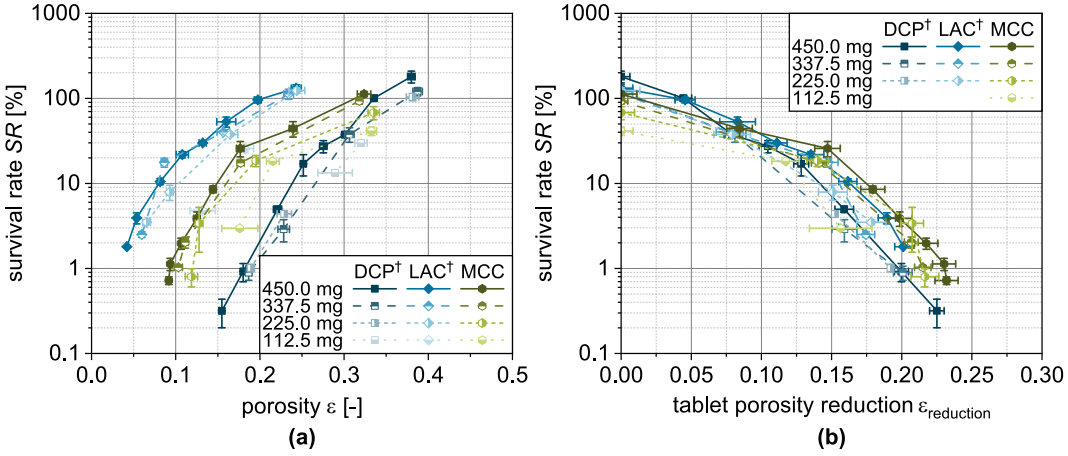

Fig. 4. Dependency of survival on (a) tablet porosity and (b) tablet porosity reduction for different formulations (yeast granules based on DCP, LAC and MCC) and tablet masses (112.5 to 450 mg). (†) Lubrication with 0.5 wt.-% MgSt. Data points show mean value and standard deviation ($n = 10$). Tablet porosity reduction for DCP and LAC for 112.5 mg could not be calculated since no intact tablets were obtained at 50 MPa compression stress.

compressibility on the tablet mass, on the other hand, does not necessarily correspond to expectations and should therefore be examined in more detail.

In order to evaluate the extent to which the deformability of the materials depends on the tablet mass, the apparent minimum tablet porosity is first calculated (Fig. 6). This is calculated based on in-die data, whereby the projection area of the die and the distance between the upper and lower punches are used to calculate the tablet volume and thus the porosity analogous to Eq. (3). It becomes clear that the in-die compressibility is significantly less influenced by the tablet mass. With the same compression stress, almost identical porosities are observed regardless of the tablet mass. The same applies to the in-die compressibility profiles of the tableting of the ungranulated carrier materials (Figure S3). The porosities are only slightly higher in the case of DCP and LAC granules for the lowest tablet mass, but are also characterized by a greater uncertainty here, as mass fluctuations during filling of the die have a greater effect here. For high compression stresses, negative apparent minimum porosities are observed in the case of LAC and MCC. These are the consequence of the change in solid density of these materials under pressure, which can be taken into account by corresponding mathematical models (Wünsch et al., 2019). Since this correction of the porosity does not change the basic statement for the present study, the corresponding models are not shown here for the sake of clarity.

Considering the almost unaffected in-die porosity, the dependence of the out-die porosity on the tablet mass must result from the decompression phase. During the decompression phase, the energy elastically stored during the deformation is released again and leads to an elastic recovery (Armstrong and Haines-Nutt, 1972). This is accompanied by an increase in volume – particularly in the axial direction – and thus an increase in porosity and is thus usually calculated as (Adolfsson and Nyström, 1996):

$$ER_{\text{axial}} = \frac{h_{\text{out-die}} - h_{\text{min,in-die}}}{h_{\text{min,in-die}}} \tag{10}$$

In addition, the radial elastic recovery is considered:

$$ER_{\text{radial}} = \frac{d_{\text{out-die}} - d_{\text{die}}}{d_{\text{die}}} \tag{11}$$

The elastic recovery depends on the tableted formulation (Fig. 7). The lowest axial elastic recovery occurs when the LAC-based granules are tableted, the highest in the case of the MCC-based granules (Fig. 7a). This basically corresponds to the expectations and published results, according to which tablets made of fragmenting materials such as DCP and LAC show lower elastic recovery than predominantly plastically deforming materials such as MCC (Haware et al., 2010). For all granules, it is clear that the lower the tablet mass, the higher the axial elastic recovery. The same also applies to the tableting of non-granulated carrier materials (Figure S4). The low tablet mass is accompanied by significantly lower tablet heights, some of which are <1 mm. The reduction in tablet height seems to be accompanied by a reduced possibility of bond formation and disadvantageous stress distributions, resulting in greater elastic recovery. This could be due to reduced particle rearrangement. In purely statistical terms, the possibilities for particle rearrangement are reduced in thinner tablets. Particle rearrangement to fill interparticle pores is limited, resulting in less favorable packing. As a result, the particles themselves deform more, whereby the elastic part of the deformation increases and thus also the axial elastic recovery. In addition, the number of contact points can be reduced due to the poorer packing, which further promotes axial elastic recovery. The radial elastic recovery is considerably lower than the axial one (Fig. 7), which corresponds to the expectations and published observations in view of the direction of force during compression (Haware et al., 2010). In contrast to the axial elastic recovery, the radial elastic recovery shows a decrease in elastic recovery with increasing compression stress for all formulations and almost all tablet masses as reported earlier (Cabiscol et al., 2018). In the case of MCC granules in particular, this leads to negative values even at low compression stresses, i.e. the diameter of the tablets is smaller than the diameter of the die. The compact contracts in the radial direction during relaxation. In view of the comparatively low radial elastic recovery compared to the axial elastic recovery, this is considered negligible here.

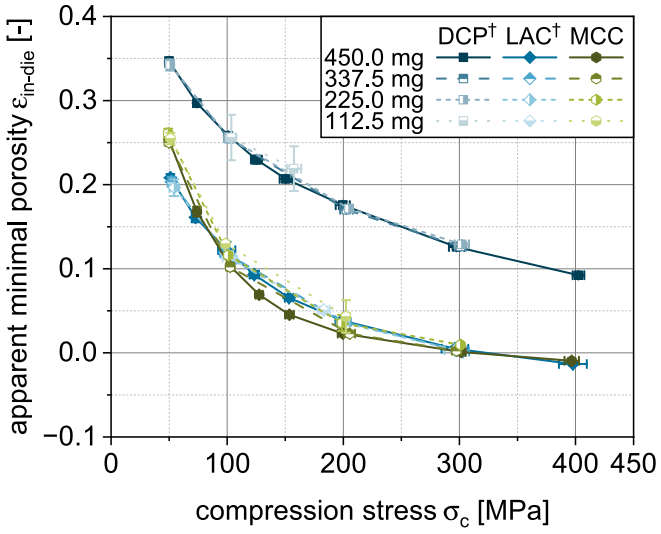

Fig. 6. Compressibility (in-die) of different formulations (yeast granules based on DCP, LAC and MCC) and tablet masses (112.5 to 450 mg). (†) Lubrication with 0.5 wt.-% MgSt. Data points show mean value and standard deviation (n = 10).

The state of the minimum in-die porosity should be decisive for the survival of the microorganisms, as this is the state of the highest densification, even though for a short time, which is assumed to be associated with the highest pressure and shear stress of the microorganisms. The survival as a function of the applied minimum in-die porosity (Fig. 8a) shows the same dependence of the formulation that was previously shown for the out-die porosity. However, the curves are now closer together for both the different formulations and tablet masses. The same applies to the survival as a function of the change in minimum in-die porosity (Fig. 8b), which was calculated analogously to Eq. (9) with the respective apparent minimum in-die porosity data. However, a certain scatter of the data points remains. Nevertheless, it is clear that the consideration of the change in porosity is an important variable for the cross-formulation correlation of survival. It is also possible that the state of the apparent minimum in-die porosity alone is not yet sufficient to describe the damage to the microorganisms, as the elastic recovery of the tablets themselves could lead to further shear stress on the microorganisms.

In addition to the survival of the microorganisms, the strength of the tablets is also an important parameter. The compactibility, i.e., the tensile strength of the tablets as a function of the tablet porosity (United States Pharmacopoeia, 2023), is considered first (Fig. 9). Here, once again, the formulation has an influence, with the lowest compactibility occurring in the LAC-based granules. With the same porosity, lower tensile strengths are always achieved here. The same applies to the compaction of the ungranulated carrier materials (Figure S5) and corresponds to expectations (Vorländer et al., 2023b). The differences in compactibility between the ungranulated carrier materials and yeast granules were discussed in detail in earlier studies by the same authors. The reason for this are, in particular, the material-specific interparticle attraction forces as well as the different deformation mechanisms and the associated susceptibility of the carrier materials to the coating of the particle surface with yeast cells and protective additive molecules shown earlier via scanning electron microscopy (Vorländer et al., 2023b). The tablet mass has a systematic influence on the compactibility. Low tablet

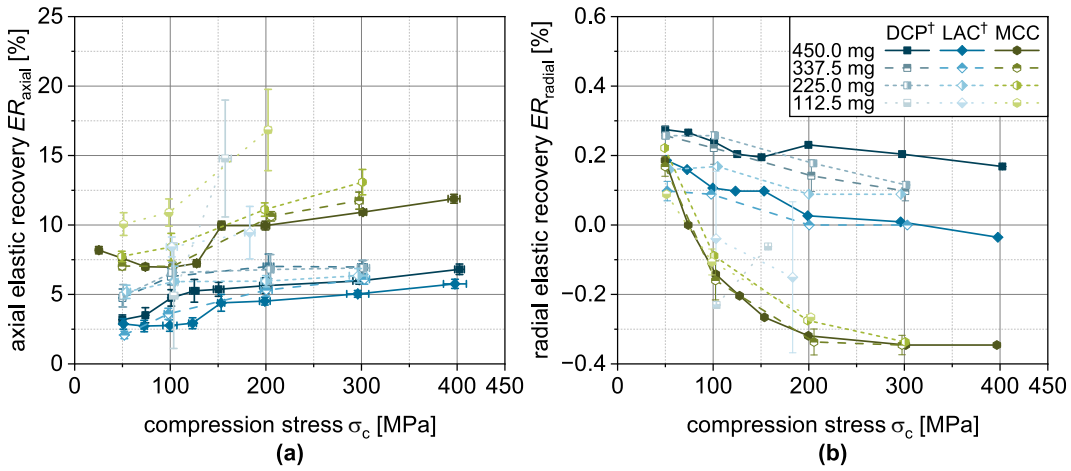

Fig. 7. Axial elastic recovery (a) and radial elastic recovery (b) of different formulations (yeast granules based on DCP, LAC and MCC) and tablet masses (112.5 to 450 mg). (†) Lubrication with 0.5 wt.-% MgSt. Data points show mean value and standard deviation ($n = 10$).

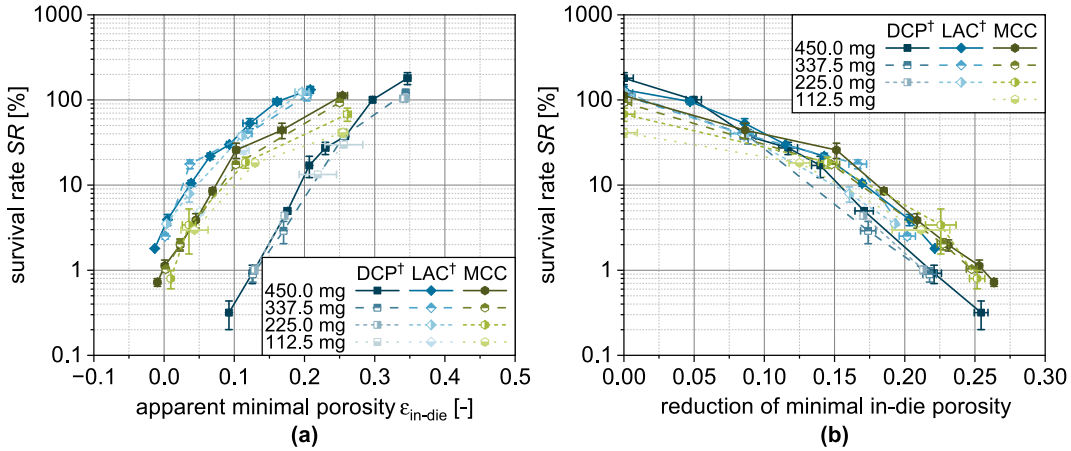

Fig. 8. Dependency of survival on (a) apparent minimal in-die tablet porosity and (b) reduction of minimal in-die porosity for different formulations (yeast granules based on DCP, LAC and MCC) and tablet masses (112.5 to 450 mg). (†) Lubrication with 0.5 wt.-% MgSt. Data points show mean value and standard deviation ($n = 10$). Reduction of minimal in-die porosity for DCP and LAC for 112.5 mg could not be calculated since no intact tablets were obtained at 50 MPa compression stress.

masses are associated with lower tensile strengths with the same porosity. This is particularly noticeable in the case of DCP where significantly reduced tensile strengths are achieved for the two lowest tablet porosities and the lowest weight. The elastic recovery of these tablets differs only slightly overall (Fig. 7), but in case of the lowest weight, pores are created which are significantly larger than in the case of the thicker or heavier tablets (pore size distribution shown in Figure S6). This, together with the lower tablet height, results in the reduced strength of the tablets, as these pores are particularly noticeable as imperfections in the material structure.

The tabletability, i.e., the tensile strength of the tablets as a function of the compression stress (United States Pharmacopoeia, 2023), again shows different profiles depending on the formulation, but also a clear effect of the tablet mass (Fig. 10). The lower tablet masses in particular are characterized by lower tensile strengths. The same dependence has also been reported for aspirin tablets of various thicknesses (Sinka et al., 2009) and is the result of the previously considered compactibility and compressibility. While the compactibility was only slightly influenced, the compressibility showed a stronger dependence on the tablet mass. This could be attributed to the elastic recovery and also offers an explanation here. Due to the higher elastic recovery with lower tablet mass, more porous tablets were obtained here. Due to the higher porosity, the structure of the tablets is weakened and the strength is reduced.

Probiotic tablets should show the highest possible survival of the microorganisms and a sufficient tablet tensile strength, typically at least 1.0 to 1.7 MPa (Pitt and Heasley, 2013). Much higher strengths can be associated with disadvantageous disintegration and release kinetics. For the final evaluation of formulation and tablet mass, the two quality attributes of interest are plotted against each other (Fig. 11). On the one hand, this shows a clear advantage of MCC, which was also observed in earlier studies by the same authors (Vorländer et al., 2023b) and is a consequence of the very good tabletability. This means that only low compression stresses have to be applied to produce sufficiently strong tablets. The porosity is correspondingly high, porosity change low and, accordingly, the stress on the microorganisms is low. On the other hand, high tablet masses (heights) are advantageous, which can also be attributed to the improved tabletability due to the lower elastic recovery and the associated structural weakening. The production of tablets with a higher mass also has the advantage that the total number of microorganisms and thus also the number of viable microorganisms is higher, which has a multiplying positive effect in conjunction with a higher survival rate.

3.2. *Variation of tablet shape*

When investigating the influence of tablet mass on the survival of microorganisms during tableting, the MCC-based granules proved to be

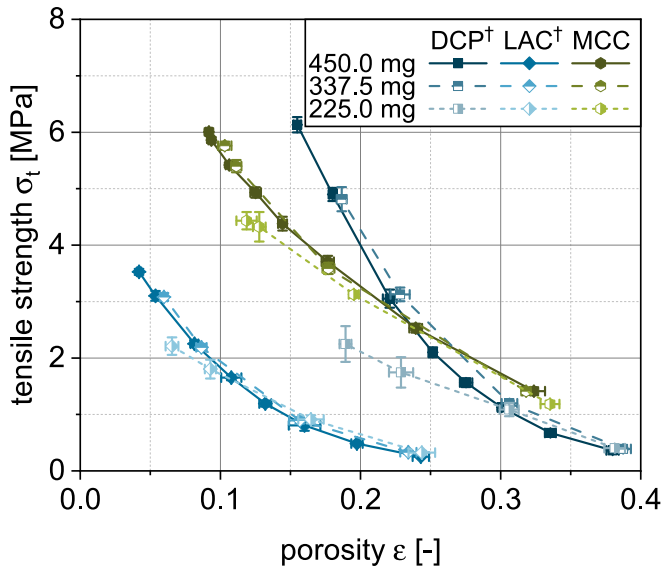

Fig. 9. Compactibility profiles of different formulations (yeast granules based on DCP, LAC and MCC) and tablet masses (225.0 to 450 mg). (†) Lubrication with 0.5 wt.-% MgSt. Data points show mean value and standard deviation (n = 10). Data points for 112.5 mg are missing, since no intact tablets were obtained or no breaking force could be determined during diameteral compression test.

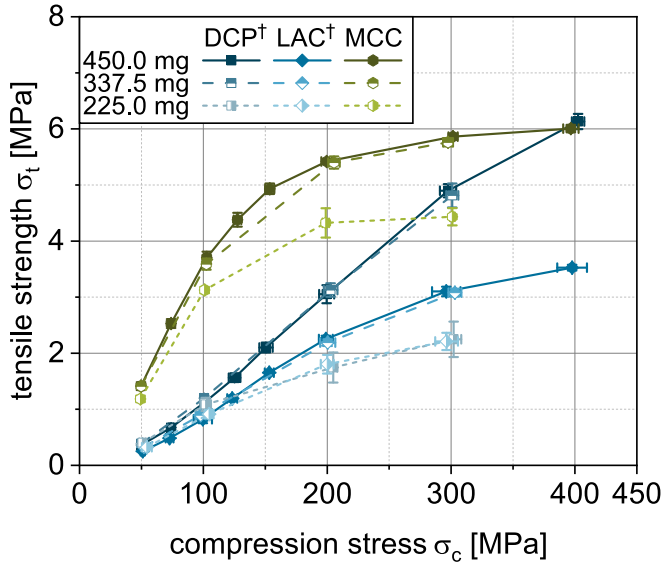

Fig. 10. Tabletability profiles of different formulations (yeast granules based on DCP, LAC and MCC) and tablet masses (225.0 to 450 mg). (†) Lubrication with 0.5 wt.-% MgSt. Data points show mean value and standard deviation (n = 10). Data points for 112.5 mg are missing, since no intact tablets were obtained or no breaking force could be determined during diametral compression test.

particularly suitable. In order to limit the scope of the experiment when investigating the influence of different tablet geometries on the survival of microorganisms during tableting, only MCC-based granules were tableted. The survival of the microorganisms shows no clear effect as function of the tablet shape depending on the applied compression stress (Fig. 12). All of the data points form the same trend that has already become clear previously (Fig. 3, (Vorländer et al., 2023b)). However, the experimental data also show a certain scatter and a higher relative deviation of the survival rates can be observed in the high compression stress range than was the case in the low compression stress range. It appears that the round tablets allow higher survival rates, regardless of diameter and curvature. An influence of the tablet height can be largely

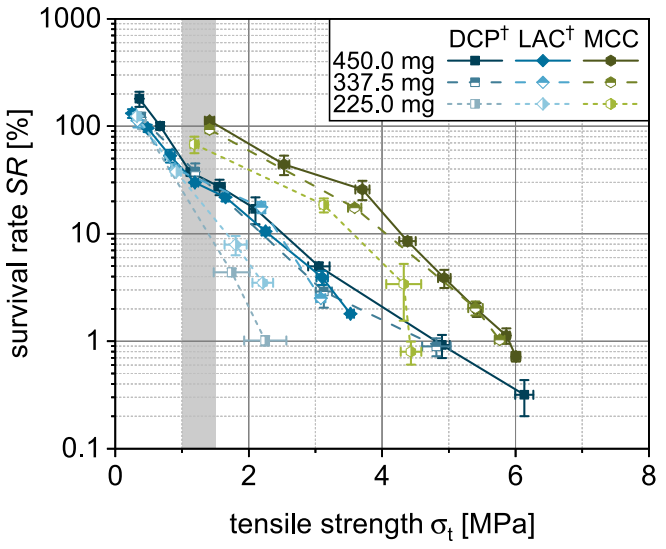

Fig. 11. Survival related to tablet tensile strength for different formulations (yeast granules based on DCP, LAC and MCC) and tablet masses (225.0 to 450 mg). The target tensile strength range is highlighted gray. (†) Lubrication with 0.5 wt.-% MgSt. Data points show mean value and standard deviation (n = 10). Data points for 112.5 mg are missing, since no intact tablets were obtained or no breaking force could be determined during diametral compression test.

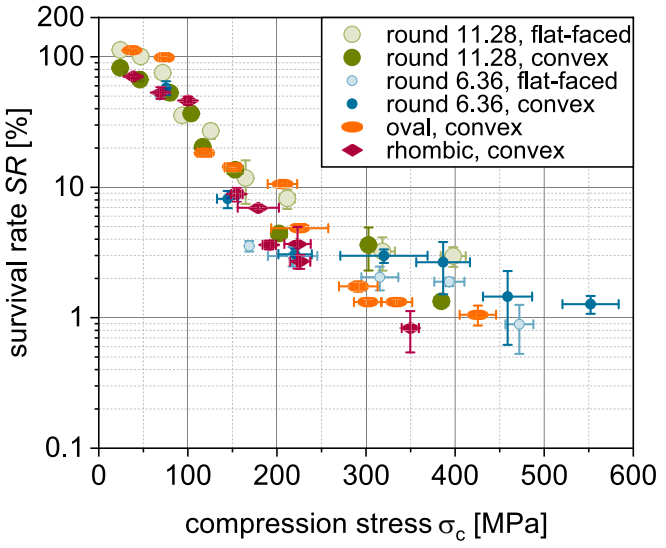

Fig. 12. Influence of compression stress on survival of yeast cells during tableting of MCC-based yeast granules. Data are shown for different tablet geometries. Data points represent mean value and standard deviation (n = 10).

excluded here because tablets with the same projection area-specific weight and thus similar tablet height were produced (deviations arise due to different calotte volumes and heights). In addition, the absolute differences in the survival rate at high compression stresses are small and the uncertainty of the values is higher compared to low compression stresses. In order to check whether there is an unrecognized systematic behind the fluctuation of the data points, the diagrams relating survival to different tablet properties already shown in the first part of this publication are used.

First, the survival is again considered as a function of tablet porosity (Fig. 13). It is noticeable that the decrease in survival rate becomes faster with decreasing porosity. This is mainly due to the increasing elastic deformation and the associated elastic recovery of the tablets. However, once again, there is hardly any separation of the data points according to

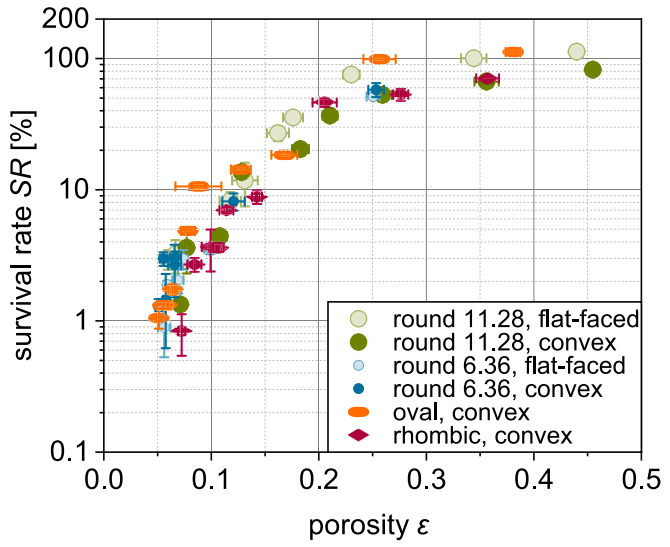

Fig. 13. Dependency of survival of yeast cells during tableting of MCC-based yeast granules on tablet porosity. Data are shown for different tablet geometries. Data points represent mean value and standard deviation ($n = 10$).

tablet shape. Only in the case of oval and flat, round tablets with a diameter of 11.28 mm, slightly higher survival rates can be seen with high porosities. Nevertheless, the effect is comparatively small and possibly random. This is supported by the essentially unchanged compressibility when varying the tablet geometry (Fig. 14). This is consistent with observations reported when MCC and DCP were compressed into cylindrical, square and hexagonal flat-faced tablets (Davies et al., 2007). Certain differences are probably the result of the calculation of porosity under the simplifying assumption of constant tablet cap volumes rather than actual effects on compressibility. At the macroscopic scale, the various shaped tablets therefore have approximately the same structure (Davies et al., 2007). It is therefore assumed that the different density distributions, which result from the use of different punch geometries (Sinka et al., 2004a; Eiliazadeh et al., 2003), are largely negligible, as the same densification occurs on average (Fig. 14). Local areas with higher density and thus higher stress on the microorganisms are compensated by areas with lower density and thus lower stress on the microorganisms. The density distribution is accompanied

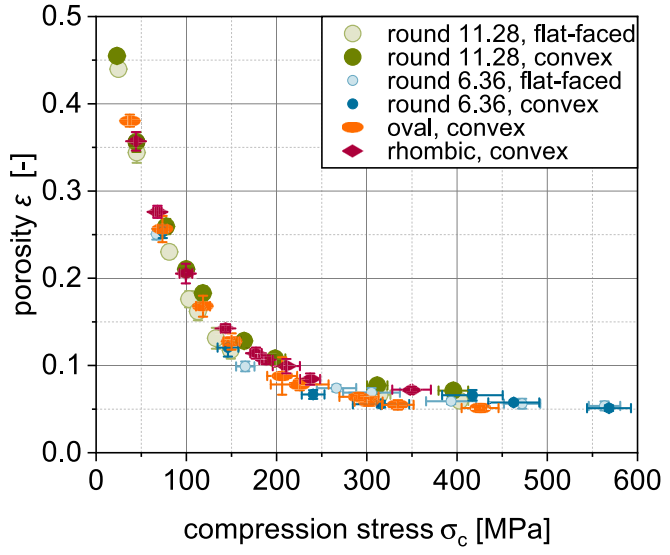

Fig. 14. Compressibility of MCC-based yeast granules for different tablet geometries. Data points represent mean value and standard deviation (n = 10).

by temperature gradients during compression. Higher densification states are associated with higher temperatures (Klinzing et al., 2010), but these do not appear to have a critical effect here either.

Different distributions of the densification depending on the shape of the tablets should lead to different elastic recoveries. As before, the axial and radial elastic recovery are considered (Fig. 15), whereby the radial recovery in the case of non-round tablets is related to the length of the tablet in the test direction of the diametral test. Here, too, the radial elastic recovery is negligibly small compared to the axial elastic recovery and tends to decrease with increasing compression stress (Fig. 15b). Interestingly, the ranking of tablet shapes shows a largely contrary picture: tablet shapes with high axial recovery, e.g. oval and rhombic, are characterized by low or more strongly negative radial elastic recovery. A stronger recovery in the direction of compaction is therefore accompanied by a stronger contraction in the lateral direction. However, a correlation with the shape-dependent survival of microorganisms is not evident.

Even if the tablet shape does not significantly determine the survival (in terms of compression stress and tablet porosity), one tablet geometry can still prove to be particularly suitable if the specific stress distributions enable high tablet strengths. This may be due to differences in the microstructure despite the similarity at the macroscopic level (Davies et al., 2007). For this purpose, the compactibility is considered first. In addition to the typical plot of tensile strength as a function of tablet porosity (Fig. 16a), the breaking strength is also considered (Fig. 16b), as no suitable formula for calculating the tensile strength of oval and rhombic tablets has been published to date. Furthermore, in view of the separation of the data into a group with flat tablets and a group with convex tablets, it is questionable whether such different strength conditions actually exist here or whether the assumptions made for the calculation of the tensile strength are not justified. The calculation of the breaking strength is a pragmatic approach, which merely represents a standardization of the experimentally determined breaking force to the theoretical breaking surface. In principle, this makes it possible to calculate strengths for any tablet shape, in this case oval and rhombic tablets. However, a group separation can also be observed here, which is not as pronounced as with the tensile strength. It is noticeable, however, that the shapes that led to the lowest compactibility when considering the tensile strength show the highest compactibility when calculating the breaking strength. Overall, it can nevertheless be stated that the compactibility (breaking strength) is also mainly unaffected by the tablet shape – especially in the area of high porosity, which is particularly relevant for the tableting of living microorganisms.

When considering the tabletability, two groups are formed for both the tensile strength and the breaking strength (Fig. 17). Here, the distance between the groups is greater compared to the compactibility, as slight differences in compressibility have an amplifying effect. Here, the effect that the tablet shapes with the lowest tensile strength-related tabletability show the highest breaking strength-related tabletability, which can be attributed to the different calculation approaches, is observed again. In earlier studies, however, it was found that the tablet shape has no influence on the tabletability when compacting MCC, LAC and DCP (Davies et al., 2007). In contrast to the present study, however, cylindrical, square and hexagonal flat-faced tablets were produced in this case, which had cross-sectional areas (fracture areas) of the same size, and the diametral test was modified with regard to the use of platens fitted with 3.0 mm radius semi-circular rods instead of flat platens (Davies et al., 2007).

Finally, it is again necessary to consider tablet strength and survival together for a comparative evaluation of the different tablet formats (Fig. 18). This results in a separation of the curves both when looking at the tensile strength and when looking at the breaking strength in the high strength range. In the relevant strength range, this is only low and the oval tablet shape and flat-round tablet with a large diameter in particular are characterized by very high survival rates. Due to the easier swallowing of the convex oval tablets, this tablet shape is to be favored

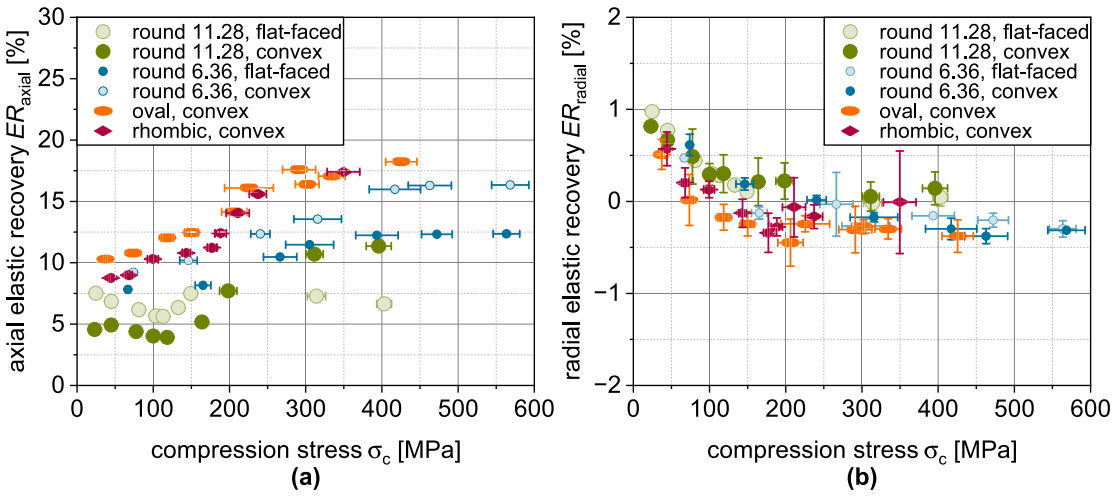

Fig. 15. Axial elastic recovery (a) and radial elastic recovery (b) of MCC-based yeast granules for different tablet geometries. Data points represent mean value and standard deviation (n = 10).

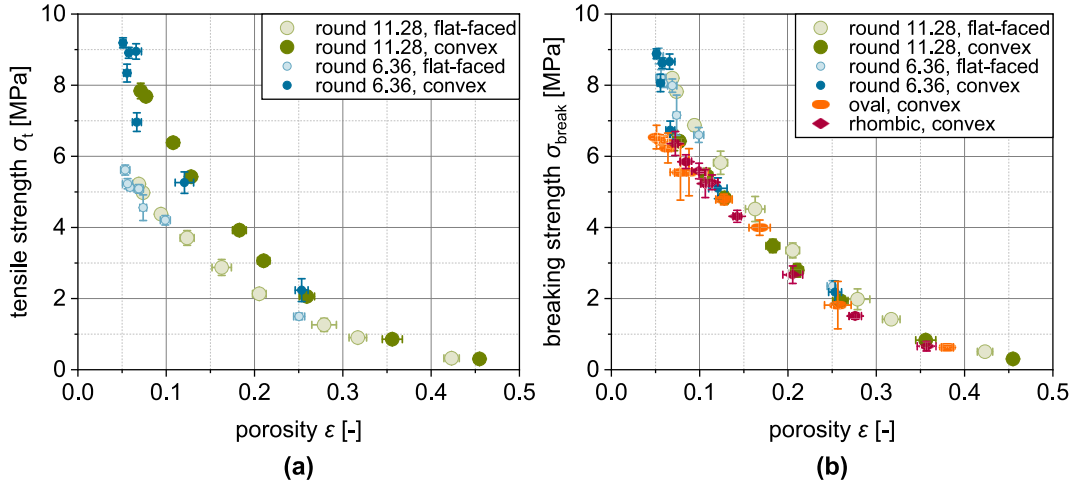

Fig. 16. Compactibility of MCC-based yeast granules for different tablet geometries. Tablet strength is calculated as tensile strength (a) and breaking strength (b). Data points represent mean value and standard deviation (n = 10).

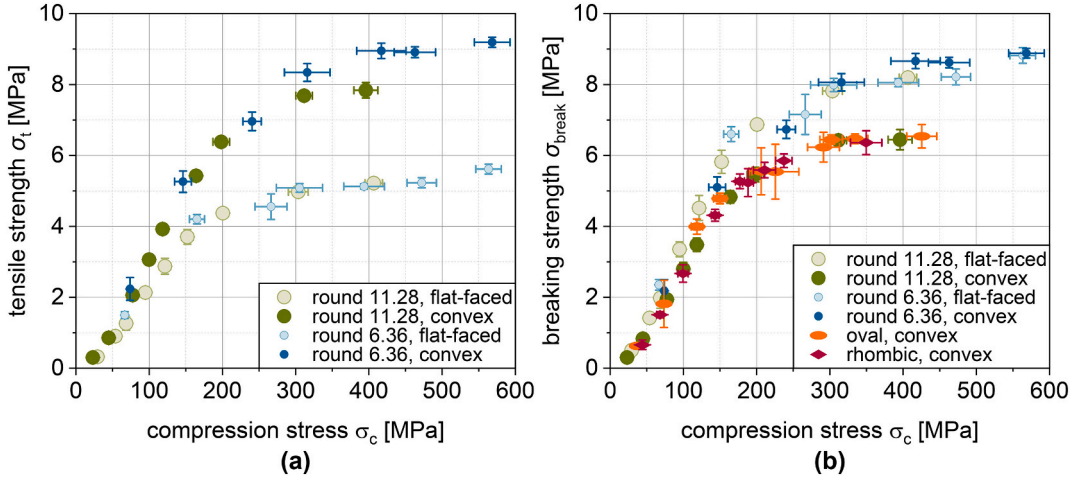

Fig. 17. Tabletability of MCC-based yeast granules for different tablet geometries. Tablet strength is calculated as tensile strength (a) and breaking strength (b). Data points represent mean value and standard deviation (n = 10).

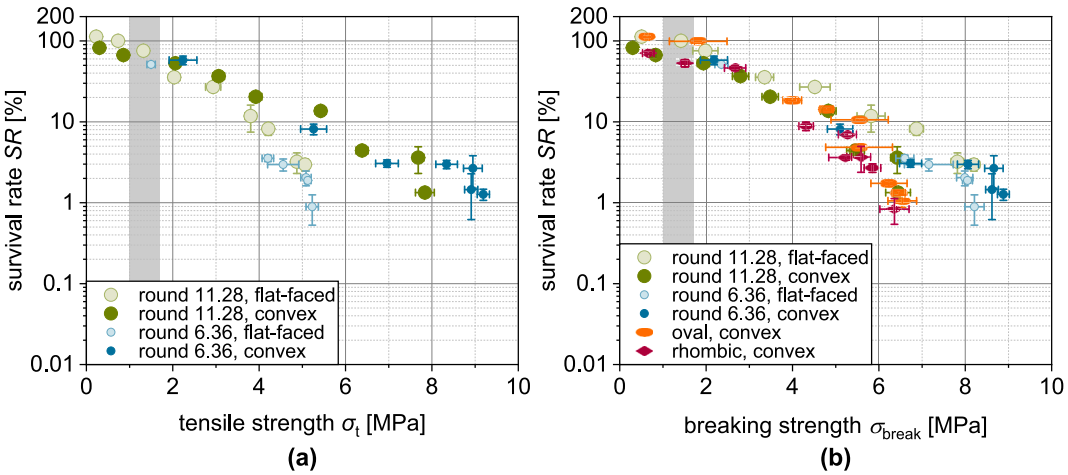

Fig. 18. Survival related to tensile strength (a) and breaking strength (b) of tablets during compaction of MCC-based yeast granules for different tablet geometries. The target tensile strength range is highlighted gray. Data points represent mean value and standard deviation (n = 10).

for the production of probiotic dosages. At the same time, it seems uncritical to use flat, round tablet punches during the development phase or formulation studies. At this point, it must be emphasized once again that this consideration was only made for the MCC-based granules. However, in view of the fact that the effects are always the same when the tablet mass is varied, regardless of whether MCC, DCP or LAC granules were tableted, it can be assumed that there is no major formulation specificity when the tablet shape is varied and that the findings can be transferred to other formulations.

4. Conclusions

As in previous studies, the survival of the microorganisms in fluidized bed granules compressed to tablets was found to be dependent on the applied compression stress and the formulation or, more precisely, the carrier material used. The higher the compression stress, the lower the survival. This is directly linked to the porosity of the tablets, although there are formulation-specific differences. If not the absolute tablet porosity is considered, but rather the change during compression, a cross-formulation correlation becomes apparent. Differences that arise during the production of tablets with different masses and therefore tablet heights, as well as the variation of the punch shape, can also be attributed to precisely these correlations. For example, the reduction in tablet mass (height) is accompanied by greater axial elastic recovery of the tablets and thus poorer compressibility and compactibility. Higher compression stresses are therefore required to produce sufficiently strong tablets, which has a detrimental effect on survival. At the same time, higher tablet masses (heights) allow higher doses, as the absolute number of microorganisms is higher, which is why higher tablet masses are to be preferred. The larger a tablet, the more important its shape is to ensure comfortable swallowing.

The tablet shape showed less influence than the tablet mass, mainly due to the largely unaffected compressibility. Although the compactibility differed when the tablet shape was varied, this is essentially attributed to the calculation of the tensile strength. The breaking strength introduced as an alternative measure of the mechanical strength showed a more homogeneous picture and the same strength for all tablet shapes, particularly in the relevant porosity range. If tablet strength and survival are evaluated together, convex, oval tablets appear to be particularly suitable, as they are easy to ingest and enable high survival with sufficient strength. At the same time, however, it can also be stated that the influence is small and formulation studies can be carried out with flat-faced round punches without having to expect problems with transferability to other tablet formats.

CRediT authorship contribution statement

Karl Vorländer: Writing – original draft, Visualization, Validation, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Lukas Bahlmann:** Writing – review & editing, Validation, Methodology, Investigation, Formal analysis, Data curation. **Arno Kwade:** Writing – review & editing, Supervision, Resources, Project administration, Funding acquisition, Conceptualization. **Jan Henrik Finke:** Writing – review & editing, Supervision, Resources, Project administration, Funding acquisition, Conceptualization. **Ingo Kampen:** Writing – review & editing, Supervision, Resources, Project administration, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this publication.

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Karl Vorländer reports financial support was provided by German Research Foundation. Jan Henrik Finke reports financial support was provided by German Research Foundation. Arno Kwade reports financial support was provided by German Research Foundation. Ingo Kampen reports financial support was provided by German Research Foundation. Lukas Bahlmann reports financial support was provided by German Research Foundation. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

The authors acknowledge the funding of this research by the German Research Foundation (grant no. 457022725). The authors thank Budenheim KG, J. Rettenmaier & Söhne GmbH + Co KG and MEGGLE GmbH & Co. KG for providing DCP, MCC and LAC, respectively. The

authors also thank Sebastian Hilmes for his experimental support of this work and Oliver Luhn from BENEO GmbH for the mercury intrusion tests.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijpx.2025.100332.

Data availability

Data will be made available on request.

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