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Importance of pressure plasticity during compression of probiotic tablet formulations

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ABSTRACT

The usefulness, the high production rate and the cost effectiveness make tablets the dosage form of choice for oral probiotics. Nevertheless, probiotic bacteria undergo a lot of mechanical stress during tableting which causes damage to their cell wall and membrane and other bio-active components. This can lead to an inactivation of the probiotic bacteria and therefore in a failure of the probiotic therapy. To obtain a tablet with a sufficient amount of viable cells, research on the influence of formulation and process parameters on bacterial survival is essential. This study aimed to decipher tableting properties of the probiotic powder blends that have a major impact on survival rates. The powder blends consisted of the prototype probiotic strain *Lactobacillus rhamnosus* GG, a filler-binder and a suitable amount of lubricant. They were manufactured by direct compression at different compression pressures and tableting speeds. The tableting properties were analysed in detail by a 3-D modelling technique, which characterized normalized time, pressure and displacement simultaneously. The results of the 3-D modelling demonstrated the significant effect of the pressure plasticity (e) and the angle of rotation (ω) on the viability of *L. rhamnosus* GG during direct compression.

1. Introduction

It is increasingly documented that specific probiotic bacteria can promote human health, such as by reduction of gastro-intestinal complaints or reducing acute respiratory infections [1,2]. Their activity is generally multifactorial, based on pathogen inhibition, reinforcement of the epithelial barrier function and/or modulation of the immune response. Because of their documented health benefits, the administration of specific probiotic bacteria has been proposed as an alternative strategy in the prevention and treatment of infectious diseases [3,4]. During the last years, there is a growing interest in the respiratory microbiome as a target for acute respiratory prophylaxis and treatment [5–9]. To directly target the oronasopharynx and upper respiratory tract, tablets and more specifically throat lozenges based on *Lactobacillus rhamnosus* GG were produced by direct compression.

According to the definition of an expert panel organized by the Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (WHO) the beneficial effect of the probiotic bacteria can only be conferred if a sufficient number of viable cells are presented at the time of consumption [10–12]. Nevertheless, probiotic bacteria are exposed to various types of stress during production and storage, resulting in a decreased amount of viable cells during shelf life. Consequently, the determination of the ideal compression and formulation conditions is necessary.

For example, it was previously investigated that the bacterial cell wall of *L. acidophilus* ATTC 4356 was already damaged at low pressures [13]. With increasing pressure, the loss of viability increased gradually and not only the cell wall but also the membrane was damaged. The results of other studies have also suggested that the bacterial survival rate is not only influenced by the applied pressure, but also by the type of bacterial strain and excipient to form the tablet matrix [14,15]. More specifically, it has been postulated that the shearing forces caused by interparticulate movement and pore size reduction will be mainly responsible for the initial mortality of the bacterial cells [16]. Moreover, previously research showed the protective role of elastic recovery of the filler-binder during direct compression [17]. More specifically, the

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elastic recovery during decompression lowered the mechanical stress, resulting in less damage to the bacterial cell wall and therefore in a higher survival rate of the model probiotic *Lactobacillus rhamnosus*.

To gain more insight in the relationship between tableting properties of probiotic powder blends and survival rates, the tableting properties were analysed by the 3-dimensional (3-D) modelling technique for the model probiotic strain *Lactobacillus rhamnosus* GG. Tablettose® 100 and Xylisorb® XTAB 240 were chosen as commercially available direct compression filler-binders based on the results of previously investigations where survival rates of Tablettose® 100 tablets were significantly better than within Xylisorb® XTAB 240 tablets, explained by the difference in elastic recovery [17].

This study aimed to relate the essential information of the 3-D modelling technique to the bacterial inactivation during direct compression at different compression pressures and speeds. The 3-D modelling technique uses three main variables to characterize the tableting process, namely time, force and displacement. The time plasticity *d*, the pressure plasticity *e* and the angle of rotation ω are the parameters that are derived by the 3-D modelling. The time plasticity d describes to plastic deformation according to time, which can be influenced by tableting speed. The pressure plasticity *e* describes the relationship between density and pressure and the angle of torsion ω is a measure of the elasticity of the material. Together, these parameters give a rather complete information about the tableting process [18–20].

2. Materials and methods

2.1. Probiotic strain and excipients

The probiotic tablets consisted of freeze-dried *Lactobacillus rhamnosus* GG (ATCC31103, which was provided as THT 030,903 by THT (Gemblaux, Belgium)), a direct compression filler-binder and a suitable amount of lubricant to avoid sticking to punches and die (magnesium stearate; Fagron, Nazareth, Belgium). The used direct compression filler-binders were lactose (Tablettose® 100, Meggle Pharma, Wasserburg, Germany) and xylitol (Xylisorb® XTAB 240, Roquette pharma, Zaventem, Belgium). These filler-binders were selected based on the results of previously investigations [17].

2.2. Compression of probiotic powder

The probiotic tablets were produced by direct compression using a single punch tablet press (MCC Corporation, NJ, US) fitted with a flat-faced bevel-edged punches with diameter of 8 mm. The probiotic powder blends consisted of 10% (w/w) freeze-dried *L. rhamnosus* GG, 85% (w/w) filler-binder and 5% (w/w) magnesium stearate. The effect of compression pressure on bacterial survival was studied by compacting the powder blends at different pressures, from 40 until 120 MPa. At maximum pressure, the tableting speed was increased from 30 until 45 tablets per minute (TPM) to investigate the effect of tableting speed on bacterial viability. More specifically, the dwell time decreased from 66 until 43 ms for lactose and from 64 until 47 ms for xylitol.

2.3. Test of bacterial viability in the probiotic tablets

The bacterial viability was investigated by the plate counting method. Three batches with each filler-binder were made, three powder samples before and three tablets after production were evaluated. The powder blends and tablets were diluted 100 times in purified water. Afterwards, a six fold serial dilution of these suspensions was made in triplicate and spread onto MRS agar plates (Carl Roth, Belgium) in duplicate. The plates ware incubated aerobically at 37 °C for 72 h. After incubation, the colony forming units (CFU) per plate were enumerated. To obtain the bacterial survival rate, the CFU counts of the powder blends before and the tablets after compression were compared.

2.4. Tableting behaviour

2.4.1. Porosity-pressure-time-profile: 3-D model

The tableting properties of lactose and xylitol were evaluated by varying following three important tableting variables: compression force, compression time and displacement of the upper punch. They were recorded and converted to pressure, normalized time and ln(1/1-D_{rel}), respectively. These parameters were presented in a 3-D data plot, which was generated by Advanced Instrumentation monitor software (MCC Corporation, NJ, US). A twisted plane was fitted to this 3-D data by means of a nonlinear least-squares solver according to the Levenberg-Marquardt algorithm [21–23] (Matlab, Mathworks Inc, Unterföhrung, Germany) with the following equation:

$$z = \ln\ 1/1 - Drel = \{[t - tmax] * [d + \omega * (Pmax - P)]\} + (e * P) + (f + d * tmax) \quad (1)$$

where D_{rel} is the relative density, t is the normalized time, t_{max} is the time at maximum pressure, P is the pressure, P_{max} is the maximum pressure, d is the time plasticity, e is the pressure plasticity, f is the intersection and ω is the angle of rotation.

Under each tableting condition (filler-binder, compression pressure and tableting speed), the resulting parameters d, e and ω of the fitted plane of three compaction cycles were averaged and the standard deviations were calculated and presented in a 3-D parameter plot.

2.4.2. Force-displacement profile

The total work exerted on the tablet during compaction ($work_{total}$) can be divided into expansion work ($work_{exp}$) and apparent net work ($work_{net}$). $Work_{exp}$ is the mechanical energy that is stored or recovered during decompression whereas $work_{net}$ represents the energy used in the formation of the compact. Therefore, the consumed mechanical energy could be used to characterize the mechanical properties of the probiotic powder blends.

$Work_{exp}$ and $work_{net}$ were calculated from the force-displacement plot, which demonstrates the relationship between upper punch displacement and upper punch force [24]. The compression force and upper punch movement were measured with strain gauges and linear variable differential transformers (LVDT) respectively and analysed with Advanced Instrumentation monitor software. The resulted force-displacement profiles were studied in absolute values of energy (J) and relative values (%) based on total energy consumption.

2.5. Evaluation of the probiotic tablets

Ten probiotic tablets were weighed and evaluated for their thickness and hardness, which were measured with a tablet hardness tester (PTN-411; Pharmatest, Hainburg, Germany). The tensile strength was calculated according to Fell and Newton's method [25], in which the radial tensile strength (σ) is given by:

$$\sigma = 2F/\pi Dh \quad (2)$$

where σ is the tensile strength (MPa), F is the applied load (N), D is the diameter of the tablet (mm) and h is the thickness of the tablet (mm).

2.6. Statistics

The statistical software GraphPad Prism 7.04 (GraphPad software inc, La Jolla, CA, USA) was used to analyse the data. The two-way analysis of variance (ANOVA) test, Turkey's and Sidak's multiple comparisons test were used to determine the statistical differences in bacterial viability. The statistical tests were performed at a significance level $\alpha = 0.05$.

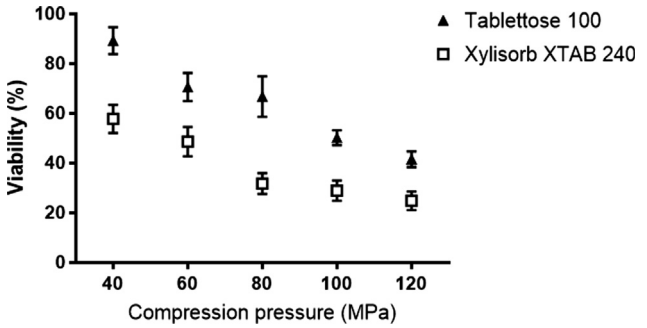

Fig. 1. The evolution of cell viability inside the tablets as function of the applied pressure. The survival rate of *L. rhamnosus* GG decreased significantly with increasing pressure (P-value < 0,0001).

3. Results

3.1. Influence of compression pressure on bacterial viability

The bacterial viability of the freeze-dried probiotic cells was highly affected by the compression pressure (Fig. 1). More specifically, the mortality level increased significantly with increasing pressure (P-value < 0,0001 (two-way ANOVA Turkey's multiple comparisons test; Graphpad software inc, La Jola, CA, USA)). For lactose tablets, the viability significantly decreased with 21% and 25% respectively from 40 to 60 MPa (adjusted P-value 0,0020) and from 80 to 100 MPa (adjusted P-value 0,0063). For the xylitol tablets, a significant decrease of 35% was noticed from 60 to 80 MPa. The results of the two-way ANOVA Sodak's multiple comparisons test showed a significant better survival rate within lactose excipient based tablets than within xylitol (P-value < 0,0001). This difference was observed at each applied compression pressure.

3.2. Influence of tableting speed on bacterial viability

Fig. 2 shows the evolution of cell viability inside the tablets as a function of the tableting speed. Although the tableting speed increased from 30 to 45 TPM at a compression pressure of 120 MPa, no significant differences in bacterial viability were noticeable (P-value 0,6654; two-way ANOVA Turkey's multiple comparisons test). The bacterial viability within tablets of lactose was significantly better than within xylitol (P-value < 0,0001; two-way ANOVA Sodak's multiple comparisons test).

3.3. Tableting behaviour

3.3.1. Tableting properties: 3-D modelling

It was hypothesized that the volume-reduction of the probiotic powder blends were responsible for the significance difference in bacterial survival between the lactose and xylitol tablets. Therefore, the tableting properties of both probiotic powder blends were analysed by the 3-D modelling technique. The resulting parameters d, e and ω are presented in a 3-D parameter plot. Fig. 3 displays the influence of the applied pressure (A) and the tableting speed (B) on the tableting properties. Calculated means and standard deviations for the parameters of the 3-D modelling in function of the applied pressure (MPa) and tableting speed (TPM) are shown in Tables 1 and 2 respectively.

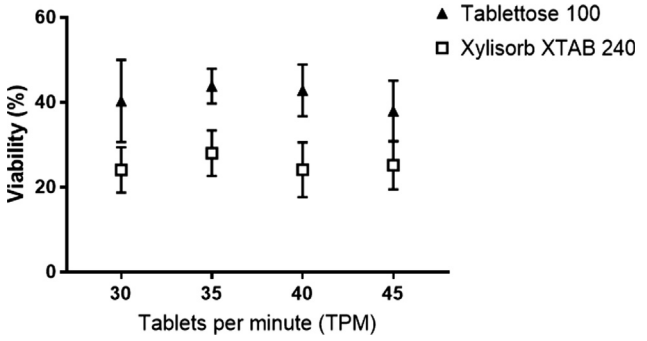

Fig. 2. The evolution of cell viability inside the tablets as a function of the tableting speed. No significant differences in survival rate of *L. rhamnosus* GG was noticeable (P-value 0,6654).

Xylitol exhibited low d values which increased slightly with increasing pressure and declined with increasing speed. The e values were high and diminished sharply with increasing pressure. Therefore, xylitol needed time to deform at low pressure and the deformation is totally plastic. At higher pressures, xylitol exhibited low time and pressure plasticity and required time and pressure to deform. This means that this filler-binder fractured after deformation.

Lactose displayed a similar deformation behaviour. The d values were low and the e values decreased with increasing pressure. It is important to mention that the e values did not decrease as it did with xylitol. The angle of rotation ω of lactose was lower than that of xylitol and decreased slowly with increasing pressure resulting in an increased fast elastic decompression. It is essential to note that the values of ω were in the middle range, illustrating that lactose showed to be more plastic than elastic.

3.3.2. Force-displacement profile

$Work_{net}$ and $work_{exp}$ were determined from the force-displacement plot and the ratio $work_{exp}$ to $work_{net}$ was studied at each compression pressure and speed.

At a minimal pressure of 40 MPa, the ratio $work_{exp}$ to $work_{net}$ was −1,57% for lactose and −0,40% for xylitol. These negative percentages indicate that the mechanical energy was recovered during decompression as expansion work applied to the punches, reflecting elastic recovery. With increasing pressure and speed, the amount of elastic recovery of lactose increased, whereas this of xylitol decreased. Moreover, the ratio $work_{exp}$ to $work_{net}$ was positive from 80 MPa, meaning that the mechanical energy during decompression of xylitol was stored in the compact and therefore there was no more elasticity.

3.4. Evaluation of the probiotic tablets

At the same pressure, xylitol produced the hardest tablets. With increasing pressure, the crushing strength of all the tablets tested increased and the tablet thickness decreased, whereby the tablets of xylitol were most affected. Table 3 shows the crushing strength (N), tablet thickness (mm) and tensile strength (MPa) of the tablets at minimal and maximal tableting conditions. The tensile strength of the tablets were relatively unaffected by the tableting speed, which can be explained by the brittle fragmenting character of both filler-binders. Fragmentation occurs rapidly and is therefore not dependent on the rate of compression.

4. Discussion

In this study, we confirmed that the survival rate of *L. rhamnosus* GG is highly dependent on the applied pressure during tablet production. With increasing pressure, the amount of viable cells showed to decrease significantly. More specifically, at minimal applied pressure of 40 MPa, the bacterial survival rate within lactose tablets was 89% and 58% within xylitol tablets. The survival rate went down to 42% and 25% for the filler-binders respectively at highest tested pressure of 120 MPa (Fig. 1). These results are in agreement with the literature which reports that the mechanical stress experienced by different probiotic bacteria strains increased with increasing pressure. It was shown by Chang and Zhang that this results in more damage to the cell wall and membrane and therefore to a significant loss of bacterial viability [13,15,16,26].

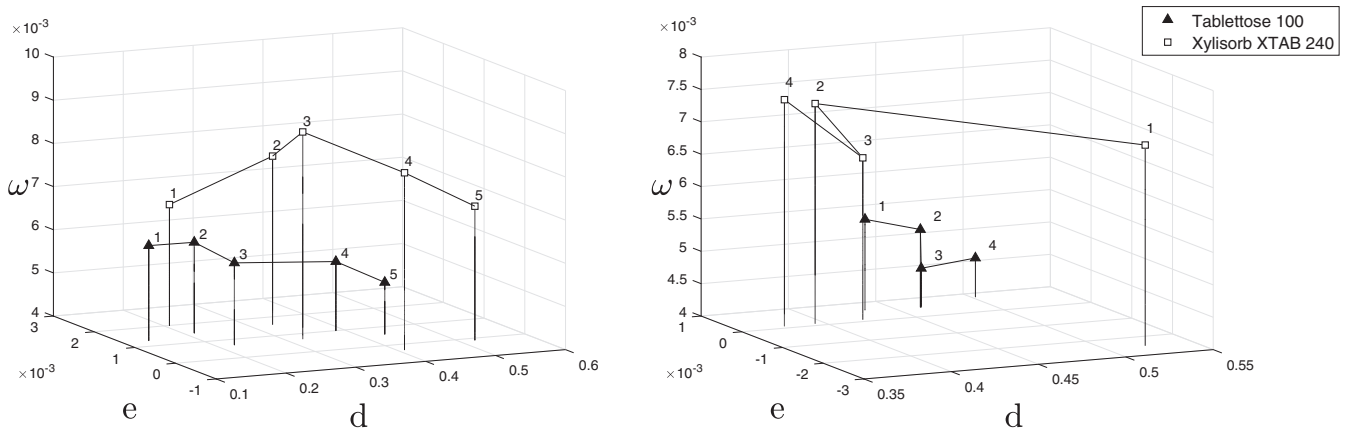

Fig. 3. 3-D parameter plot of Tablettose 100 and Xylisorb XTAB 240 at (A) different compression pressures (1) 40 MPa – 2) 60 MPa – 3) 80 MPa – 4) 100 MPa – 5) 120 MPa) and (B) different tableting speeds (1) 30 TPM – 2) 35 TPM – 3) 40 TPM – 4) 45 TPM).

Table 1
Calculated means and standard deviations for the parameters of 3D modeling in function of the applied compression pressure (MPa).

	Lactose			**Xylitol**		
Pressure (MPa)	*d*	*e* (MPa^{-1})	*ω*	*d*	*e* (MPa^{-1})	*ω*
40	0,1374 ± 0,0235	0,0013 ± 0,0005	0,0062 ± 0,0017	0,2078 ± 0,0506	0,0020 ± 0,0016	0,0068 ± 0,0031
60	0,2142 ± 0,0101	0,0015 ± 0,0009	0,0061 ± 0,0010	0,3322 ± 0,0210	0,0016 ± 0,0012	0,0079 ± 0,0003
80	0,2250 ± 0,0303	0,0007 ± 0,0002	0,0059 ± 0,0002	0,3229 ± 0,0138	0,0007 ± 0,0004	0,0088 ± 0,0004
100	0,3878 ± 0,0533	0,0010 ± 0,0002	0,0056 ± 0,0005	0,4103 ± 0,0351	−0,0003 ± 0,0005	0,0081 ± 0,0009
120	0,4345 ± 0,0169	0,0006 ± 0,0002	0,2199 ± 0,0009	0,5227 ± 0,1316	−0,0001 ± 0,0007	0,0071 ± 0,0017

Table 2
Calculated means and standard deviations for the parameters of the 3D modeling in function of the tableting speed (TPM).

	Lactose			**Xylitol**		
Speed (TPM)	*d*	*e* (MPa^{-1})	*ω*	*d*	*e* (MPa^{-1})	*ω*
30	0,4345 ± 0,0169	0,0006 ± 0,0002	0,0054 ± 0,0009	0,5227 ± 0,1316	−0,0025 ± 0,0048	0,0071 ± 0,0017
35	0,4639 ± 0,0174	0,0005 ± 0,0002	0,0052 ± 0,0009	0,3943 ± 0,1316	0,0001 ± 0,0002	0,0074 ± 0,0017
40	0,4644 ± 0,0177	0,0005 ± 0,0002	0,0045 ± 0,0009	0,4216 ± 0,1294	0,0001 ± 0,0004	0,0065 ± 0,0017
45	0,5024 ± 0,0190	0,0008 ± 0,0002	0,0044 ± 0,0009	0,3767 ± 0,1294	0,0001 ± 0,0004	0,0075 ± 0,0017

Table 3
Crushing strength, tablet thickness and tensile strength of the probiotic tablets.

Filler-binder	Tableting conditions	Crushing strength (N)	Thickness (mm)	Tensile strength (MPa)
Lactose	40 MPa–30 TPM	13,50	5,06	0,0315
	40 MPa–45 TPM	14,58	5,27	0,0302
	120 MPa–30 TPM	41,15	4,56	0,1047
	120 MPa–45 TPM	43,23	4,62	0,1033
Xylitol	40 MPa–30 TPM	22,55	5,20	0,0306
	40 MPa–45 TPM	22,65	5,31	0,0300
	120 MPa–30 TPM	63,10	4,68	0,1020
	120 MPa–45 TPM	68,83	4,89	0,0976

In our study with *L. rhamnusus* GG, the survival rate within lactose tablets was significantly better than within xylitol tablets. It was previously reported that the compression behaviour of the used filler-binder, namely plastic deformation and – or brittle fracturing, has an effect on bacterial survival rate. More in detail, Blair et al. indicated that, especially at low pressure, plastically deforming materials cause more bacterial inactivation than fracturing materials because of their greater surface disruption [14]. In our study, at low pressure, both filler-binders required time for densification and mainly deformed plastically. Because of the higher pressure plasticity *e*, xylitol deformed easier than lactose. The survival rate within xylitol tablets was lower. These results are in agreement with the investigation of Blair et al. Furthermore, it must be noticed that the ratio $work_{net}$ to $work_{exp}$ and the angle of rotation *ω* of lactose were lower than these of xylitol, meaning that this filler-binder undergo more fast elastic decompression. This protective effect of the elastic recovery during decompression is in agreement with our previous work. The elasticity of the filler-binder lowers the mechanical stress during tableting, resulting in less damage to the probiotic membrane and therefore in a higher survival rate [17].

Here, we further showed that with increasing pressure, the fast elastic decompression of lactose increased, indicating by lower *ω* values. In contrast, the *ω* values of xylitol increased and therefore the elastic recovery decreased, resulting less protection of *L. rhamnosus* GG. In addition, the *e* values of both filler-binders strongly decreased. Therefore the tableting properties changed, namely from plastic deformation to fracture. It is important to notice that the pressure plasticity of xylitol dropped sharper, resulting in lower *e* values. Consequently, xylitol deforms more difficult and therefore it fractured more. Nevertheless, the bacterial viability was significantly lower than within lactose tablets, which contradicts the investigations of Blair et al. The results of this study indicate the importance of the simultaneous evaluation of pressure, normalized time and density. Moreover, it shows that pressure plasticity *e* plays a key factor in the protection of *L. rhamnosus* GG during tablet production, which is not previously

reported.

The effect of the tableting speed on bacterial viability of *L. rhamnosus* was investigated at maximal pressure, whereby the tableting speed increased from 30 to 45 TPM. At a pressure of 120 MPa, both filler-binders fractured. Fragmentation occurs rapidly and is therefore not influenced by the tableting speed. Consequently, the effect of the tableting speed was insignificant. Additionally, the difference in dwell time between minimal and maximal tableting speed was just 23,04 ms for lactose and 17,41 ms for xylitol.

In conclusion, the deformation behaviour of probiotic powder blends could be described by the 3-D modelling technique. This unique characterization makes it possible to explain the significant differences in viability between different probiotic formulations. The studied formulations showed similar tableting properties. However, a difference in pressure plasticity e and angle of rotation ω was noticed. This indicates that the survival rate of *L. rhamnosus* GG during direct compression is dependent on these tableting parameters.

Declaration of Competing Interest

The authors declared that there is no Conflict of Interest.

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