European Journal of Pharmaceutics and Biopharmaceutics 73 (2009) 424–431

Contents lists available at ScienceDirect

European Journal of Pharmaceutics and Biopharmaceutics

journal homepage: www.elsevier.com/locate/ejpb

Research paper

Multivariate analysis of relationships between material properties, process parameters and tablet tensile strength for α-lactose monohydrates

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ARTICLE INFO

Article history:
Received 17 April 2009
Accepted in revised form 13 August 2009
Available online 19 August 2009

Keywords:
Compression
Heckel equation
Kawakita equation
Multivariate methods
α-Lactose monohydrate
PAT
Prediction

ABSTRACT

The present work describes an approach to quantify relationships between the material properties of various α-lactose monohydrate grades (αLM), process parameters (punch velocity, lubricant fraction) and the tablet tensile strength (TS). Milled, sieved, agglomerated and spray-dried αLMs were studied. Each material was tableted (11 mm flat punches, constant true volume of 0.2833 cm^3) on a compaction simulator at a pressure of 104.4 ± 0.1 MPa. The force–displacement data was analyzed by applying a combination of compression descriptors (derived from Kawakita and Heckel equations, work-related parameters). The relationships were evaluated and quantified by principal component analysis (PCA) and partial least square regression (PLS-1). PCA verified fundamental relationships between different powder and compression properties of studied materials. It was found that the compression descriptors Kawakita '1/*b*' and WoC were sufficient to distinguish the tested αLM-grades, even in combination with different lubricant fraction or by utilizing different punch velocities; the identified descriptors correlated with TS. These relationships were quantified by PLS-1. Finally, TS were successfully predicted for all αLM with the help of separate optimized PLS-1 models. The present study shows an approach how to extract relevant information about tableting behavior from a limited amount of material.

1. Introduction

Understanding of the relationships between material properties, process parameters and resulting tablet properties is beneficial in early drug development stages and essential in tablet production. In early stages of development, even prior to phase I clinical trials, with a limited amount of drug available (few grams only) rational tablet formulation leads to optimization without unnecessary delay with advantages for both cost and time-to-market. Additionally, the introduction of Process Analytical Technology (PAT) guidelines by FDA [1] focuses on quality by design rather than end-product control for pharmaceuticals. This requires a good understanding of the process and thorough control of critical formulation and process parameters. Thus, to fulfill the expectations of both successful tablet formulation in an early stage and the PAT concept in tablet production, it is necessary to establish a meaningful quantitative relationship between material properties and process parameters with regard to resulting tablet properties e.g. tablet tensile strength (TS). However, this is a challenging task due to the complexity of interactions between material properties, process parameters and the mechanism of compression itself.

It is possible to improve our understanding of the complex relationships by application of a compaction simulator to obtain the most accurate time resolved force–displacement data possible, and by subsequent data evaluation using a combination of global compression equations, such as the Heckel equation and work descriptors [2]. However, large data matrices are generated, and careful identification of the important information is needed in order to avoid over-determinations of correlations using multivariate analysis. To test the applicability of this concept, chemically identical substances with rather small, though relevant, material property differences (i.e. various grades of α-lactose monohydrates (αLMs)) were selected in the present study as an example.

The aim of present work was to find the set of most descriptive parameters derived from time-resolved compression data for the tensile strength of tablets. Therefore, as a first step to describe quantitative relationships between material properties of αLMs (crystalline, agglomerated, spray-dried) and process parameters (punch velocity, lubricant added, compression descriptors) with tablet TS, principal component analysis (PCA) and partial least square regressions (PLS) were used. Furthermore, limiting the number of parameters to the most descriptive ones was done to avoid over-determinations. Subsequently, the optimized PLS-1 models were challenged by evaluating their ability to predict mechanical strength of tablets from all tested grades of αLM.

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doi:10.1016/j.ejpb.2009.08.005

2. Materials

Different types of αLMs were all donated by Meggle Pharma, Germany: Granulac®70 (Lot no. L0711/A4152), Granulac®140 (Lot no. L0702/A4142), Granulac®200 (Lot no. L0701/A4172), Granulac®230 (Lot no. L0703/A4202), Spherolac®100 (Bach L.9909 A4132), Tablettose®70 (Lot no.9837), Tablettose®80 (Lot no. 9917), Tablettose®100 (Lot no. 9939) and Flowlac®100 (Lot no. L0704/A4950. Magnesium stearate (Batch MF19/70089) was purchased from NMD, Norway.

3. Methods

3.1. Basic powder properties of αLMs

3.1.1. Particle size distribution

A mechanical sieve shaker (Retsch VE 1000, Retsch GmbH and Co. Kg, Hann, Germany) was used to perform analytical sieving as described in Ph. Eur. 2008 [3].

3.1.2. Powder densities

The bulk and tap density of the αLMs was determined according to Ph. Eur. 2008 with three repetitions [4] (Erweka® Tapped Volumeter, Typ Svm, Heusenstamm, Germany). Hausner ratio (HR), which is a ratio of tapped to bulk density of powder [5] was calculated to determine the powder flowability.

The particle (pycnometric) density of the powder particles was measured by using Helium gas pycnometer (Micromeritics AccuPyc™1330 Pycnometer, Micromeritics GmbH, Neuss, Germany). Each sample was tested in triplicates; ten repetitive purge cycles were performed before recording each result. Also, the pycnometric density of the lubricated excipients was calculated according to the volume fraction [6]:

$$\rho_{tlm} = \left(\frac{\alpha_1}{\rho_{t_1}} + \frac{\alpha_2}{1.03}\right)^{-1} \quad (1)$$

where ρ_{tlm} represents the pycnometric density of lubricated excipient (g/cm^3), α_1 the % mass fraction of excipient, ρ_{t_1} the pycnometric density of excipient (g/cm^3), α_2 the % mass fraction of Magnesium stearate and 1.03 g/cm^3 the pycnometric density of magnesium stearate [7].

3.2. Experimental design for evaluation of compression behavior

The effects of process parameter, punch velocity (saw tooth profiles; 10.0 mm/s, 50.0 mm/s and 150.0 mm/s) and formulation parameter, lubricant level (0% and 1.0%) were investigated for the nine qualities of αLMs listed in Table 1. A total of 54 experiments were performed, i.e. six experiments with different combinations of the design variables (formulation and process variables) for each of the selected materials. All experiments were characterized with respect to the following compression responses: Kawakita '*a*' parameter [*KwA*], Kawakita '1/*b*' parameter [*Kw*1/*b*], mean yield pressure value of plastic deformation (YPpl), mean YP of immediate elastic recovery ($YPel_I$), work of compression (WoC), work of immediate elastic recovery (WoE_I) as well as the tablet tensile strength (TS).

3.3. Tablet preparation

Prior to compaction, the experiments containing lubrication agent, 200 g of material was lubricated with 1% magnesium stearate using a Turbula mixer (Turbula® System Schatz, Basel, Switzerland) for 3 min at 23 rpm.

Cylindrical 11-mm tablets of theoretically constant volume of 0.2833 ± 0.0127 cm^3 were prepared on a calibrated and validated compaction simulator (ServoPress 450, Schmidt Technology, St. Georgen, Germany; IBR, Waldkirch, Germany). The constant true volume (calculated from pycnometric density) was employed since the response to punch movement (i.e. punch force) is a function of volume of solid in a die and not its mass. Before every compression, the punch tips and die wall were pre-lubricated with a suspension of magnesium stearate in acetone. The weighed amount of powder mass was poured manually into the die and compressed at a pressure of 104.4 ± 0.1 MPa and at above-mentioned punch velocities. Tablet mass was measured right after production (CP225D, Sartorius AG, Goettingen, Germany). Tablets were stored for 24 h in desiccators at 24.7 ± 1.2 °C and at a relative humidity of 26 ± 7%. Tablet dimensions, such as diameter and thickness, and tablet tensile strength (TS) were measured after 24 h using a micrometer (0.01 mm micrometer IP54, Wilson Wolpert, Netherlands) and crushing force tester (model TBH20, Erweka® GmbH, Heusenstamm, Germany), respectively. Tensile strength was calculated using the following equation [8]:

$$TS = \frac{2F}{\pi Dt} \quad (2)$$

where F is the crushing force in N, D the diameter, and t the thickness of tablet, both in mm.

3.4. Determination of compression parameters

The compression behavior in the low pressure range (0–20 MPa) was studied using the Kawakita equation [9–11].

Table 1
Investigated α-lactose monohydrates (αLMs) with manufacturer's and measured particle size values.

Brand name	Chemical name[a]	Method of preparation[a]	Particle size (μm)							
			Manufacturer's values[a]				Experimental values[b]			
			d10	d50	d75	d75–10	d10	d50	d75	d75-d10
Granulac®70	α-LM	Milling	37	98	197	160	68	118	163	95
Granulac®140			19	46	68	49	75	108	122	47
Granulac®200			18	38	58	40	95	145	200	105
Granulac®230			7	22	33	26	102	205	249	147
Spherolac®100		Sieving	71	117	148	77	69	118	161	92
Tablettose®70		Agglomeration	104	186	266	162	107	182	241	134
Tablettose®80			45	158	248	203	73	175	240	167
Tablettose®100			54	166	243	189	73	149	220	147
Flowlac®100		Spray-drying	43	132	174	131	72	150	197	125

[a] Derived from Manufacturer's data [29].
[b] Determined according to Ph. Eur. [3].

$$\frac{P}{C} = \frac{P}{a} + \frac{1}{ab} \quad (3)$$

$$C = \left[\frac{V_0 - V}{V_0}\right] \quad (4)$$

where P is applied pressure, a the maximum volume available for reduction under pressure which is considered to describe compressibility of the powder, b the constant inversely related to the yield strength of the particles, C the degree of volume reduction, V the volume of compact at pressure P, and V_0 the initial apparent volume of powder. The Kawakita parameters 'a' [KwA] and '$1/b$' [$Kw1/b$] were used as descriptors in further evaluation.

In addition, the compression behavior was also studied using the "*in-die*" method for Heckel equation [12].

$$\ln\left[\frac{1}{1-D}\right] = kP + A \quad (5)$$

where D is the relative density of compact at pressure P, and A is the y-intercept.

In order to determine the constants of the Heckel equation [the mean yield pressure value of plastic (YPpl) and elastic deformation ($YPel_l$)], linear regression analysis was performed in the compression (20–80 MPa) and in the decompression phases (20–90 MPa). From the reciprocal of the slope (k) of the compression and decompression phase, YPpl and $YPel_l$ were calculated, respectively. Also, the apparent work of compression (WoC) and immediate elastic recovery (WoE_l) values were determined from the force–displacement data recorded during each compression cycle [13] and used as descriptors in the evaluation.

3.5. Multivariate analysis

Principal component analysis (PCA) followed by partial least squares regressions (PLS-1) was performed to identify the most important factors, to quantify their influences, to select descriptors that best describes the behavior and finally to predict the tablet TS (Unscrambler®9.7, CAMO AS, Norway). In the data matrix used for these investigations, the quality of lactoses was defined as a category variable, and the category variable was coded 1 or 0 and split in order to single out the effect of each of the qualities. This leads to an over dimensioning of the size of X-matrix, resulting in an underestimation of the true amount of variance used for explaining the variance on the different components. This is typically seen as a very low explained variance of the X-variables. Prior to modeling, the variables were weighted by autoscaling (1/S.D.). The models were calculated by using systematic cross-validation and Jackknifing [14] in order to explore quantified relationships between a set of variables and a set of measured responses for the prediction of TS. Further information regarding the PCA and PLS methods and interpretation of the typical plots can be found elsewhere [15,16]. Different PLS-1 models were optimized searching for the best model for prediction of tablet tensile strength based on the optimum number of PLS components and root mean square of prediction (RMSEP) values (regardless of punch velocity and lubrication level) employing as few compression descriptors as possible.

As a final step, the ability of the optimized models to predict tablet tensile strength from different materials was tested by systematically leaving one of the materials out (creating a sample set) and performing the predictions for this material (regarded the test

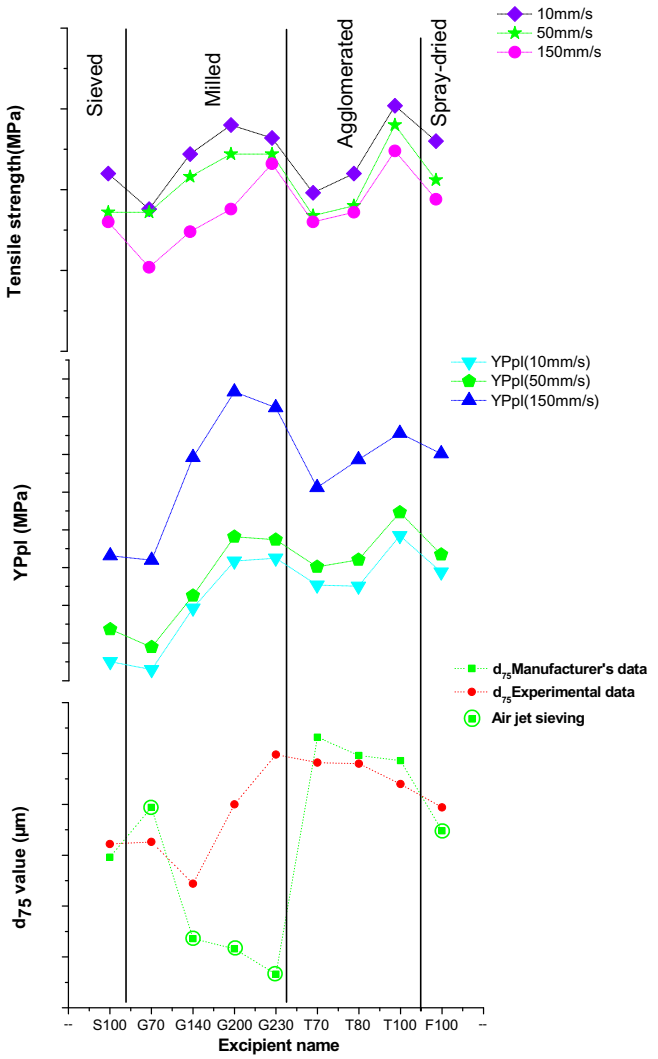

Fig. 1. Experimental and manufacturer's d_{75} values of plain α-lactose monohydrates and corresponding Heckel YPpl deformation values and tablet tensile strengths. Abbreviations G70 = Granulac®70, G140 = Granulac®140, G230 = Granulac®230, etc., S100 = Spherolac®100, T70 = Tablettose®70, T80 = Tablettose®80, T100 = Tablettose®100, F100 = Flowlac®100.

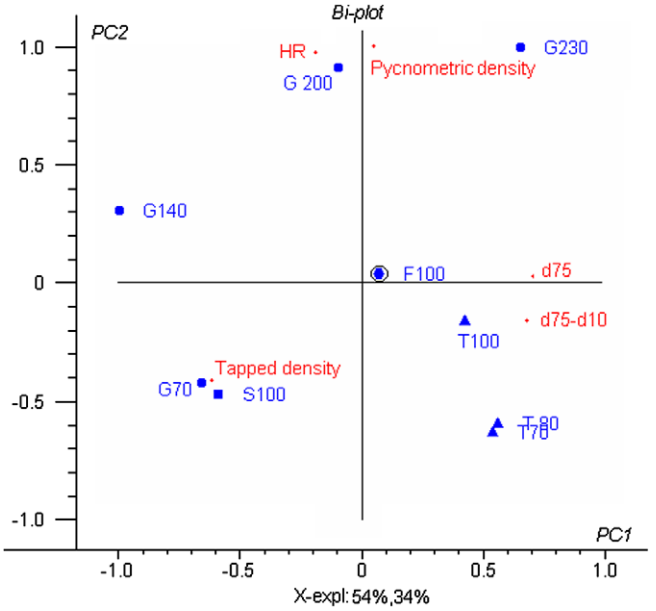

Fig. 2. Bi-plot from a PCA showing that the selected plain α-lactose monohydrate qualities spanning out the design space with respect to basic powder characteristics. ■ milled, ■ sieved, ▲ agglomerated, and ◉ spray-dried.

set) at different levels of the design variables (punch velocity and lubrication).

4. Results and discussion

The results of particle size distribution studies of αLMs from both manufacturer [17] and our experimental data are given in Table 1 and Fig. 1. The values for the two datasets for the sieved, the agglomerated and the spray-dried lactoses are analogous within experimental error. However, for the milled αLMs (Granulac® types 140, 200, 230), smaller values were reported by the manufacturer [17]. This is probably due to the use of different particle size analysis methods: manufacturer's data were obtained by air -jet sieving for milled and spray-dried αLMs, whereas the present data were obtained by mechanical sieving only. Probably, the fine particles of the milled αLMs develop cohesion forces which are not overcome by mechanical sieving even after continuing for longer time (3 h, data not shown). Thus, the method is not able to separate the fines to the same degree as air jet sieving. However, no clear relationship between particle size obtained by any of the analytical sieving methods and the powder compression properties (expressed as YPpl) or tensile strength of the tablets was found (Fig. 1). The samples differ not only in particle size, but also in manufacturing methods, densities (particle density, bulk density and tapped density) as well as flowability (Hausner ratio). Fig. 2 shows a PCA bi-plot containing both scores and loadings of powder

Table 2
Experimental matrix and some responses [A = type of αLM, B = punch velocity (mm/s), C = lubricant fraction (%)]. (Results are given as means of three measurements.)

No.	A	B	C	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Particle density (measured) (g/cm^3)	Particle density (calculated) (g/cm^3)	Hausner ratio	YPpl (MPa)	$YPel_I$ (MPa)	*KwA* (%)	*Kw*1/*b*(MPa)	WoC (Nm)	WoE_I (Nm)	TS (MPa)
1	Granulac®70	10	0	0.717	0.924	1.5401	–	1.289	81.48	228.83	37.55	1.8658	3.48	0.64	0.94
2	Granulac®70	50	0	0.717	0.924	1.5401	–	1.289	84.46	241.16	36.51	1.7825	3.57	0.66	0.93
3	Granulac®70	150	0	0.717	0.924	1.5401	–	1.289	95.97	310.56	35.17	1.8578	3.57	0.64	0.76
4	Granulac®70	10	1	0.851	0.966	1.5326	1.5325	1.135	73.67	177.05	30.15	3.6923	3.00	0.63	0.55
5	Granulac®70	50	1	0.851	0.966	1.5326	1.5325	1.135	75.20	182.27	29.22	3.7432	3.17	0.71	0.51
6	Granulac®70	150	1	0.851	0.966	1.5326	1.5325	1.135	89.96	266.47	27.41	4.6259	3.21	0.66	0.43
7	Granulac®140	10	0	0.592	0.824	1.5415	–	1.392	89.63	239.62	48.58	0.6513	2.96	0.65	1.11
8	Granulac®140	50	0	0.592	0.824	1.5415	–	1.392	91.27	244.17	48.25	0.6249	3.01	0.66	1.04
9	Granulac®140	150	0	0.592	0.824	1.5415	–	1.392	109.6	329.73	46.68	0.6299	3.12	0.67	0.87
10	Granulac®140	10	1	0.606	0.795	1.5348	1.5339	1.317	84.26	212.62	47.81	0.6803	2.94	0.68	0.99
11	Granulac®140	50	1	0.606	0.795	1.5348	1.5339	1.317	85.96	221.9	47.27	0.6342	2.98	0.69	0.89
12	Granulac®140	150	1	0.606	0.795	1.5348	1.5339	1.317	105.00	309.29	45.82	0.6478	3.00	0.67	0.84
13	Granulac®200	10	0	0.508	0.726	1.5453	–	1.429	95.85	255.54	55.92	0.4170	2.88	0.66	1.20
14	Granulac®200	50	0	0.508	0.726	1.5453	–	1.429	99.08	267.48	55.42	0.4076	2.96	0.70	1.11
15	Granulac®200	150	0	0.508	0.726	1.5453	–	1.429	118.30	335.95	54.78	0.4047	3.00	0.72	0.94
16	Granulac®200	10	1	0.507	0.679	1.5363	1.5376	1.341	91.49	239.05	56.35	0.4141	2.86	0.64	1.19
17	Granulac®200	50	1	0.507	0.679	1.5363	1.5376	1.341	93.69	243.90	56.04	0.3872	2.91	0.69	1.08
18	Granulac®200	150	1	0.507	0.679	1.5363	1.5376	1.341	115.30	337.10	54.88	0.4177	2.94	0.69	0.74
19	Granulac®230	10	0	0.443	0.613	1.5468	–	1.384	96.25	255.11	61.03	0.3219	2.96	0.69	1.16
20	Granulac®230	50	0	0.443	0.613	1.5468	–	1.384	98.68	265.73	60.73	0.3100	3.02	0.72	1.11
21	Granulac®230	150	0	0.443	0.613	1.5468	–	1.384	116.20	353.80	59.33	0.3685	3.21	0.69	1.08
22	Granulac®230	10	1	0.429	0.595	1.5424	1.5391	1.384	91.24	240.59	62.43	0.3158	2.93	0.68	1.14
23	Granulac®230	50	1	0.429	0.595	1.5424	1.5391	1.384	93.87	251.68	62.12	0.3058	2.99	0.71	1.07
24	Granulac®230	150	1	0.429	0.595	1.5424	1.5391	1.384	112.40	348.96	60.62	0.3564	3.20	0.68	1.00
25	Spherolac®100	10	0	0.683	0.836	1.5410	–	1.223	82.53	215.28	40.55	3.8519	3.77	0.58	1.05
26	Spherolac®100	50	0	0.683	0.836	1.5410	–	1.223	86.83	272.74	38.08	3.3325	3.80	0.62	0.93
27	Spherolac®100	150	0	0.683	0.836	1.5410	–	1.223	96.56	331.50	36.66	3.4690	4.02	0.63	0.90
28	Spherolac®100	10	1	0.745	0.868	1.5288	1.5334	1.165	73.23	193.68	38.03	4.8019	3.42	0.64	0.51
29	Spherolac®100	50	1	0.745	0.868	1.5288	1.5214	1.165	75.67	199.96	36.39	4.3098	3.51	0.66	0.44
30	Spherolac®100	150	1	0.745	0.868	1.5288	1.5214	1.165	86.94	265.06	35.13	4.7923	3.56	0.65	0.44
31	Tablettose®70	10	0	0.542	0.664	1.5371	–	1.226	92.68	294.70	51.79	1.4728	4.06	0.65	0.99
32	Tablettose®70	50	0	0.542	0.664	1.5371	–	1.226	95.09	316.13	51.31	1.6337	4.17	0.66	0.92
33	Tablettose®70	150	0	0.542	0.664	1.5371	–	1.226	105.60	384.63	50.28	1.6546	4.26	0.65	0.90
34	Tablettose®70	10	1	0.596	0.642	1.5326	1.5296	1.077	81.35	214.91	49.01	1.4271	3.56	0.69	0.63
35	Tablettose®70	50	1	0.596	0.642	1.5326	1.5296	1.077	82.62	226.08	48.61	1.6632	3.84	0.70	0.55
36	Tablettose®70	150	1	0.596	0.642	1.5326	1.5296	1.077	101.30	339.76	47.94	2.1582	3.98	0.70	0.51
37	Tablettose®80	10	0	0.588	0.730	1.5383	–	1.241	92.54	292.97	47.79	1.7133	3.97	0.63	1.05
38	Tablettose®80	50	0	0.588	0.730	1.5383	–	1.241	96.03	316.47	47.01	1.7797	4.09	0.66	0.95
39	Tablettose®80	150	0	0.588	0.730	1.5383	–	1.241	109.30	386.13	46.45	1.9928	4.11	0.67	0.93
40	Tablettose®80	10	1	0.653	0.740	1.5330	1.5307	1.135	80.39	211.72	45.14	2.0145	3.52	0.69	0.68
41	Tablettose®80	50	1	0.653	0.740	1.5330	1.5307	1.135	82.30	226.50	43.96	2.0597	3.68	0.69	0.59
42	Tablettose®80	150	1	0.653	0.740	1.5330	1.5307	1.135	102.30	338.65	43.07	2.6142	3.75	0.70	0.49
43	Tablettose®100	10	0	0.552	0.692	1.5414	–	1.254	99.24	338.60	49.12	1.6408	4.43	0.66	1.26
44	Tablettose®100	50	0	0.552	0.692	1.5414	–	1.254	102.30	365.41	48.72	1.7725	4.54	0.69	1.20
45	Tablettose®100	150	0	0.552	0.692	1.5414	–	1.254	112.80	421.45	47.67	1.6731	5.59	0.69	1.12
46	Tablettose®100	10	1	0.606	0.703	1.5335	1.5338	1.160	91.46	291.83	46.13	2.2592	4.19	0.68	0.94
47	Tablettose®100	50	1	0.606	0.703	1.5335	1.5338	1.160	93.40	302.74	45.80	2.3346	4.29	0.69	0.88
48	Tablettose®100	150	1	0.606	0.703	1.5335	1.5338	1.160	108.90	391.16	44.84	2.4665	4.33	0.69	0.84
49	Flowlac®100	10	0	0.608	0.748	1.5448	–	1.230	94.40	325.14	45.68	2.2010	4.13	0.65	1.15
50	Flowlac®100	50	0	0.608	0.748	1.5448	–	1.230	96.72	352.58	44.73	2.5038	4.52	0.66	1.03
51	Flowlac®100	150	0	0.608	0.748	1.5448	–	1.230	110.10	416.67	44.21	2.7847	5.43	0.67	0.97
52	Flowlac®100	10	1	0.670	0.760	1.5369	1.5371	1.134	85.77	279.40	45.58	4.7706	4.12	0.68	0.82
53	Flowlac®100	50	1	0.670	0.760	1.5369	1.5371	1.134	88.79	302.72	44.79	5.2654	4.45	0.67	0.71
54	Flowlac®100	150	1	0.670	0.760	1.5369	1.5371	1.134	101.90	375.07	46.87	7.3811	4.48	0.68	0.70

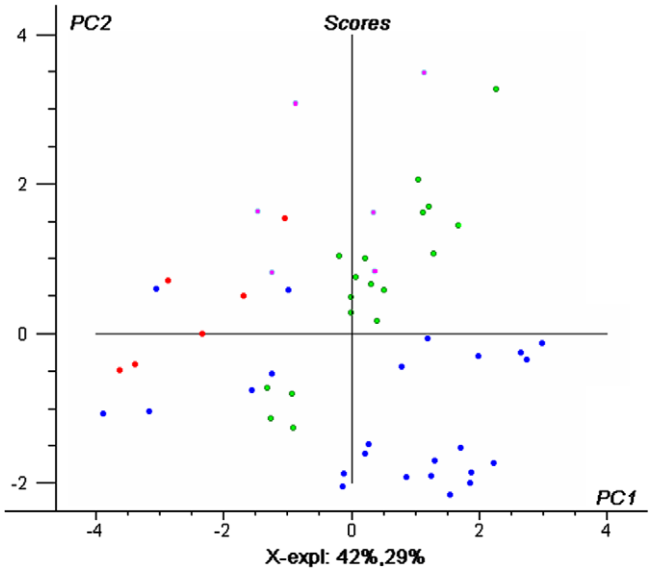

Fig. 3A. PCA of the selected α-lactose monohydrate qualities with respect to compression characteristics. Score plot: the two displayed PCs explain totally 71% of the variation in the data (42% on PC1 and 29% on PC2). Blue color represents milled; green – agglomerated; red – sieved; pink – spray-dried αLMs.

characteristics of the unlubricated materials. The loading plot shows the contribution of individual powder characteristics to the distribution of tested materials in the score plot when projected along the principal component vectors. In this PCA, the first two components explained 88% of the variation in the data and clearly indicate the spread of the powder properties of the studied lactose grades. As expected, the pycnometric densities of plain αLMs decrease upon lubrication (Table 2) due to lower density of magnesium stearate compared to lactose, as can be verified by calculation.

In order to study, compression behavior of the materials, porosity pressure profiles were measured and evaluated. Due to the speed and ease of data collection, the *'in-die'* methods were chosen in the present study. It is well known from literature that the αLMs show predominantly fragmentation at low compression pressure [18]. The Kawakita equation has been recommended for characterization of compression properties at (such) low pressures and high porosities [19] and therefore has been used in addition to the well-known Heckel equation. Fig. 3 shows results from a PCA of the compression descriptors from Kawakita (*KwA, Kw*1/*b*), Heckel (YPpl, $YPel_I$) and work-related parameters (WoC, WoE_I) in addition to mechanical properties of the tablets (TS) for all the experiments. The PCA would use five principal components to describe 97% of the variation in the total data; the first two components that are displayed in Fig. 3 explain 71% of the variation (42% and 29% on PC1 and PC2, respectively). The score plot (Fig. 3A) shows the grouping related to the αLM qualities according to their manufacturing method. The corresponding loading plot (Fig. 3B) suggests that there are strong correlations in between the compression descriptors from work-related, Heckel and Kawakita equations, which means that employing all descriptors overestimates their significance and would not add extra information to the interpretation of compression behavior. Employing all descriptor may therefore not be necessary in order to achieve acceptable predictions of tablet tensile strength (TS). Thus, in order to identify the most important (informative) descriptors or combinations of such, separate PCA models of different combinations of descriptors were calculated and compared.

The combination of WoC, *Kw*1/*b* and TS was found to be the best combination of descriptors with as few descriptors as possible for the tested αLMs, and Fig. 4 presents the respective bi-plot of the PCA. Using two principal components, which explain 92% of the variance in the data, *Kw*1/*b* was identified as the most important descriptor for the present system with a high impact on the first principal component, whereas WoC and TS have higher impact on the second PC. All three descriptors have approximately the same quantitative effect on the first two PCs, as by their relative distance to origin. Thus, it was concluded that the combination of WoC, *Kw*1/*b* and TS is sufficient to qualitatively separate the different materials of αLMs.

Four different strategies for the optimization of PLS-1 models in order to quantify the effect of the design variables on tablet TS were compared (Table 3, columns A–D). The alterations were using

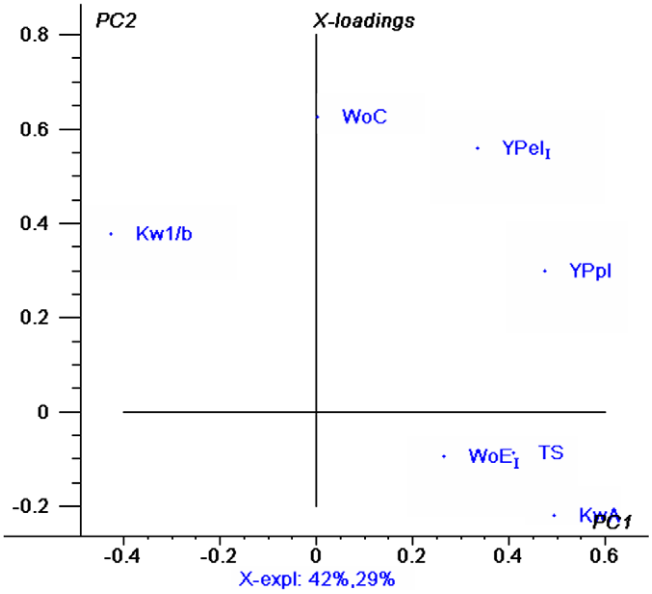

Fig. 3B. Loading plot: the PCA uses five PC's to describe 97% of the variation in the data matrix. The two displayed PCs explain totally 71% of the variation in the data (42% on PC1 and 29% on PC2).

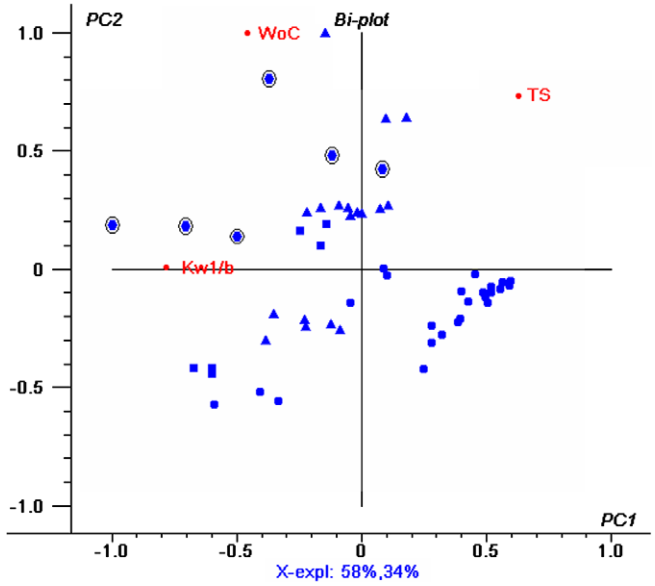

Fig. 4. PCA Bi-plot of crystalline α-lactose monohydrate using compression parameters *Kw*1/*b*, WoC and TS. The two PCs (PC1 and PC2) explain 92% of variance in the data. ■ milled, ■ sieved, ▲ agglomerated, and ◉ spray-dried.

Table 3
Regression coefficients of the design variables, their interaction and square effects on the response variable 'tablet tensile strength' obtained in separate PLS-1 models. The significance of regression has been determined by cross-validation and Jack-Knifing [14] and corresponds to approx. $p < 0.05$. RMSEP – root means square error of prediction; RMSEC – root means square error of calibration (A – without splitting of material as category variables and using punch velocity and lubricant fraction as *X*-variables, B – without splitting of material as category variables and using punch velocity, lubricant fraction, WoC and *Kw*1/*b* as *X*-variables, C – all materials split as category variables and using punch velocity and lubricant fraction as *X*-variables, D – all materials split as category variables and using punch velocity, lubricant fraction, WoC and *Kw*1/*b* as *X*-variables).

Design variables (*X*)	Effect on response variable 'tablet tensile strength' (*Y*)												
	A	B	C	D	Without S100	Without G70	Without G140	Without G200	Without G230	Without T70	Without T80	Without T100	Without F100
Materials													
Materials split													
Granulac®70			−0.271	−0.218	−0.272		−0.193	−0.199	−0.193	−0.238	−0.250	−0.221	−0.164
Granulac®140			–	–	–	–			0.079	–	–	0.048	–
Granulac®200			–	0.137	–	–	0.159	–	0.192	–	–	0.159	0.137
Granulac®230			0.287	0.199	0.209	0.197	0.217	0.240		0.190	0.193	0.232	0.195
Tablettose®70			−0.184	−0.194	−0.235	−0.244	−0.226	−0.198	−0.190		−0.221	−0.166	−0.222
Tablettose®80			−0.141	–	−0.172	−0.183	−0.150	–	−0.123	−0.195		−0.108	−0.137
Tablettose®100			0.213	0.202	0.213	0.211	0.173	–	0.218	–	0.196		0.198
Spherolac®100			−0.237	−0.133		−0.201	−0.098	–	−0.109	–	−0.162	−0.120	–
Flowlac®100			–	–	–	0.090	0.118	–	0.127	–	–	0.176	
Punch velocity	−0.224	−0.217	−0.280	−0.233	−0.257	−0.245	−0.247	−0.199	−0.254	−0.286	−0.234	−0.235	−0.270
Lubricant fraction	−0.618	−0.468	−0.602	−0.481	−0.462	−0.511	−0.499	−0.509	−0.523	−0.455	−0.448	−0.499	−0.484
*Kw*1/*b*		−0.461		−0.328	−0.311	−0.295	−0.308	−0.312	−0.294	−0.351	−0.339	−0.326	−0.361
WoC		–		0.116	0.104	0.076	0.109	0.157	0.161	0.124	0.114	0.045	0.098
Punch velocity∗lubricant fraction	–	–	–	–	–	–	–	–	–	–	–	–	–
Punch velocity**2	–	–	–	–	–	–	–	–	–	–	–	–	–
Lubricant fraction**2	–	–	–	–	–	–	–	–	–	–	–	–	–
Optimum no. of PCs used	2	1	2	3	2	2	3	2	2	2	2	2	3
Explained *X*-variance (%)	87	71	20	40	32	32	44	29	29	32	31	32	43
Explained *Y*-variance (%)	43	62	85	88	88	85	89	89	88	86	86	85	89
RMSEP (MPa)	0.18	0.15	0.11	0.11	0.10	0.11	0.11	0.10	0.10	0.11	0.10	0.11	0.10
RMSEC(MPa)	0.17	0.14	0.08	0.08	0.07	0.08	0.08	0.07	0.08	0.08	0.08	0.08	0.08

materials as split category variables or not and including WoC and *Kw*/*b* as *x* variables or not. Out of these, the PLS-1 model calculated by employing tablet TS as the *Y*-variable and the individual αLMs, WoC and *Kw*1/*b* as *X*-variables was selected on the basis of explained *X*- and *Y*-variance and root means square error values of prediction (column D).

For evaluation of the prediction abilities of the models, each material was once kept out of the data matrix, and the respective optimized model used to predict the tensile strength of the tablets made from this particular material. The last nine columns in Table 3 give the details of these models with respect to number of PCs used, regression coefficients and error of prediction.

As an example, the model used for prediction of Tablettose®80 (Table 3, third-last column) is discussed in more detail in the following: the PLS-1 model of all αLMs except Tablettose®80 was significant according to cross-validation and displayed that the first two components accounted for 86% of the variance in the *Y*-data. It only employs 31% of variance in the *X*-data, which is extraordinary low due to the chosen structuring of the *X*-matrix by the split category variable approach. The other agglomerated αLMs (Tablettose®70 and 100) show, respectively, negative and positive correlation to TS. Tablettose® qualities are specially designed for direct compression (i.e. better flowability and compressibility) [20–22] and thus contain a balance of coarse and fine agglomerated particles. Tablettose®100 contains higher amounts of fines than Tablettose®70, which attributes to better compressibility (as can be seen from *KwA* parameter), resulting in higher tensile strength. The other lactose grades (Granulac®70, Spherolac®100 and Granulac®230) show negative or positive correlations to TS, respectively. In all models, *Kw*1/*b* parameter shows a negative correlation to TS. As suggested by Nicklasson et al. [23] and others [18,24,25], higher *Kw*1/*b* indicates poor fragmentation tendency by high yield strength of the particles and would thus result in tablets of higher porosity (i.e. lower tensile strength). Furthermore, WoC of all studied materials shows a positive correlation to TS as expected. The investigated design variables 'punch velocity' and 'lubricant fraction' show negative correlations to TS: the αLMs are supposed to be sensitive to non-uniform transition of applied pressure at high punch velocities and consequently formation of less interparticulate interaction, as described by other researchers [26,27]. In addition, as expected, the presence of MgSt as a lubricant weakens inter-particle bonding [28]. Therefore, both design variables show reduction in tablet TS. Neither interaction effect between punch velocity and lubricant fraction nor their square effects were found to have significant influence on the models (Table 3).

Fig. 5 individually compares the predicted and measured TS values for all the materials. For all models (I–IX), the predicted tablet TS and measured tablet TS values were found to be quite close for plain materials, the deviation being less than 0.2 MPa. Relationships between compression speed and tablet TS are predicted correctly: at low compression speed, higher tablet TS is reached. However, for two of the models, Granulac®70, Tablettose®100, the predicted values deviate systematically and substantially from the measured values. Furthermore, the models are not able to predict the compression behavior in lubricated samples of any of the materials: there is deviation between measured and predicted tensile strength in the range of ±0.5 MPa. This difficulty can already be suspected from the raw data: lubrication affects the TS of the materials to a different degree. This fact may be attributed to increased complexity of the particle surface properties upon lubrication. Based on these observations, it is assumed that models optimized with *Kw*1/*b* and WoC are well suitable for prediction of TS of plain lactose tablets with different punch velocities, but less suitable for the lubricated materials.

5. Conclusions

In the present study, it was shown that powder properties, tableting process parameters and tablet properties can be quantified for several grades of alpha lactose. Based on these data, partial least

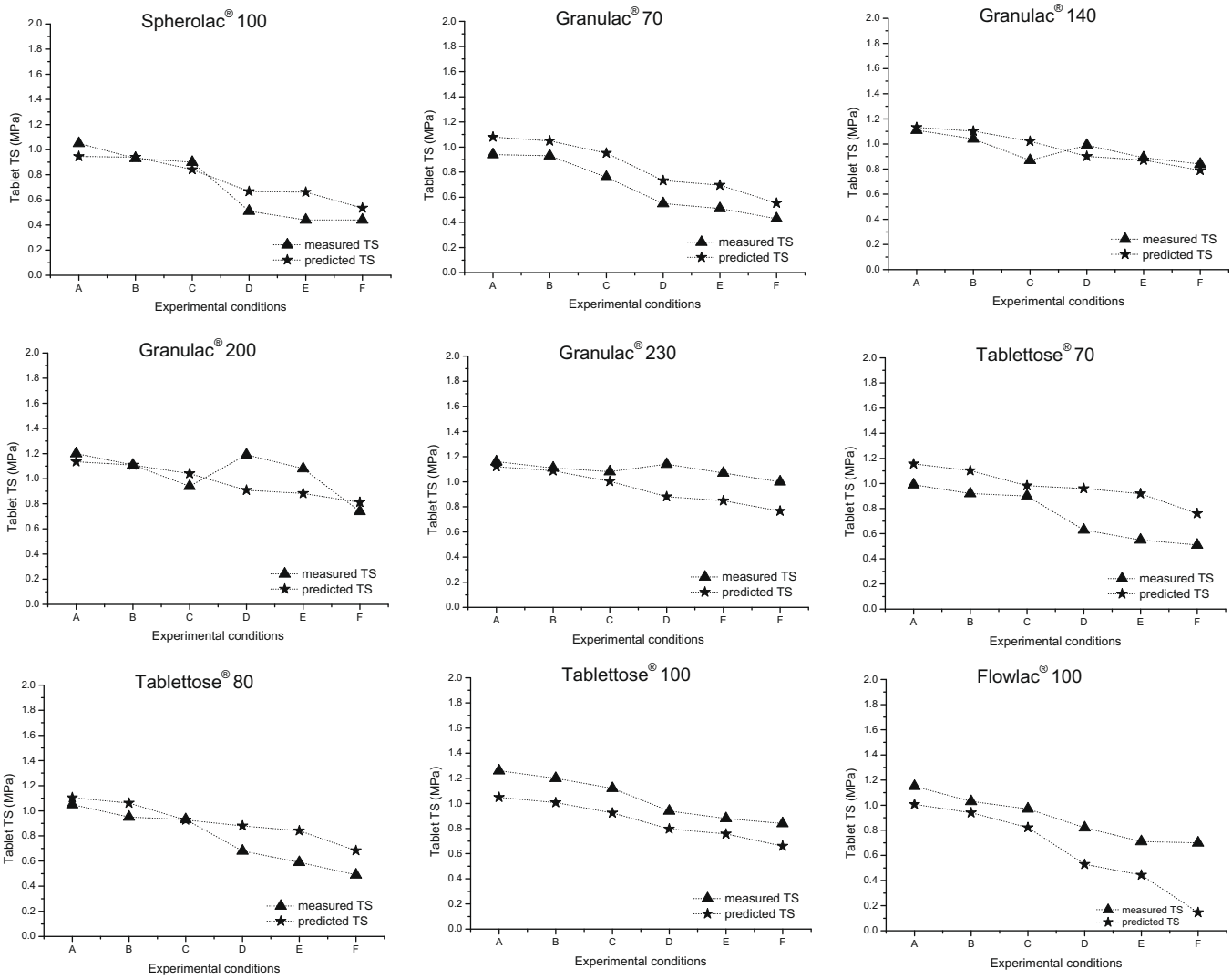

Fig. 5. Predicted and measured TS values for I: Spherolac®100 II: Granulac®70 III: Granulac®140 IV: Granulac®200 V: Granulac®230 VI: Tablettose®70 VII: Tablettose®80 VIII: Tablettose®100 IX: Flowlac®100 Experimental conditions (Punch velocity, Lubricant fractions) – A: 10 mm/s; B: 50 mm/s; C: 150 mm/s; D: 10 mm/s, 1%; E.50 mm/s, 1%, F: 150 mm/s, 1%. Measured TS values are means of three measurements.

square models (PLS-1) were optimized to study the predictability of tablet tensile strength. Out of all studied compression parameters (derived from Kawakita, Heckel equation and work descriptors), two, namely $Kw1/b$ and WoC, were found sufficient for the predictions. However, measured and predicted values for lubricant-containing materials deviated more than for different compression speeds. It can be concluded that for the plain materials, such prediction may be sufficiently accurate, but for lubricated materials, the effects are too complex as to comply with the simple models. This fact is in agreement with practical experience.

Acknowledgement

Authors are thankful to Ritter Pharma-Technik GmbH, Hamburg (Germany) for donating the punches and the Norwegian Research Council for financial support.

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