University of Szeged

Graduate School of Pharmaceutical Sciences

Department of Pharmaceutical Technology

Programme director: Prof. Dr. Habil. Piroska Szabó-Révész Ph.D., D.Sc.

FEW ASPECTS ON THE IMPORTANCE OF PARTICLE SIZE ENABLING PROPER TABLETTING

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1. INTRODUCTION

Solid dosage forms (powders, tablets, capsules) are the most popular ones among all dosage forms, as they carry many advantages with their therapeutical use, enabling good patent compliance, as well.

According to the meaning of Drug Delivery in Context, it is the method or process of administering a pharmaceutical compound to obtain optimal therapeutic benefit; with its right amount, to the right tissues of the body, as well as in proper, right time.

Powders are encountered in almost every aspect of pharmacy, both in industry and in practice. The smallest items of solid dosage forms are the particles. Although the importance of particle size and its rheological aspects (flowability) has become well-known by today, the newer and newer technological methods and modern pharmaceutical dosage forms make the substantial knowledge of raw materials (ingredients) inevitable. The appearance of mini-tablets has induced the need to study the role of particle size from new aspects.

2. AIMS

The aims of my studies were as follows:

The primary aim of my Ph.D. Thesis is to present the importance of determining the size and shape of solid particles - among the preformulation tests - considering the preparation of mini-tablets, as well.

The findings of the Dissertation and the Thesis can be divided into three parts.

The **first section** of this work describes the need and the selection of proper and quick methods suitable for particle size determination; which are proper to characterize particle size – both in the case of raw materials, and finished products.

Section two deals with the influence of the cohesion coefficient on the flowability of solid particles; and the findings permit the prediction of the smallest orifice diameter, which enables the particles to flow freely into the die cavity during the process of compaction.

Section three studies the role of the particle size during the compression process of common tablets, and thus makes prediction possible for the compression parameters of mini-tablets.

3. MATERIALS AND METHODS

3.1 Materials

Sorbitol was chosen as model material, which is used worldwide as a filling agent for direct compression in the pharmaceutical and food industries. This model material has numerous applications in the pharmaceutical industry, cosmetics and other industrial fields, as well.

Various sorbitol products are available commercially in the food and pharmaceutical industries: two crystalline forms (**Samples 1 and 2** (Ph. Eur.) and one "co-processed" form **(Sample 3**) (Merck, Darmstadt, Germany) were applied.

Magnesium stearate (Ph. Eur.) was used as a lubricant in a quantity of 1 %. The specific surface area of magnesium stearate was 0,69 m^2/g (BET, Brauner-Emett-Teller method).

Arbocel A300 (JRS Pharma, Rosenberg, Germany) is a powdered, microcrystalline cellulose, and according to its function, it was used as a diluent and a binder.

3.2 Methods

3.2.1 Material characterization/Particle Size Analysis

A Laborlux S light microscope (Leitz, Wetzlar, Germany) combined with a colour image analysis system (Leica Quantimet 500MC/Q500 MC/, LEICA Cambridge Ltd., U.K.) proved valuable for particle size analysis.

3.2.2 Morphological study

The morphology of the particles was controlled by scanning electron microscopy (SEM) (Hitachi 2400 S, Hitachi Scientific Instruments Ltd., Tokyo, Japan).

3.2.3 Sieve analysis

Analytic-sieve-machine (Retsch GmbH & Co., Haan, Deutschland) was used with sieve-apertures of 125 µm, 315 µm, 400 µm, 500 µm, 630 µm, 710 µm and 1000 µm. The individual sieving-time was 5 minutes.

3.2.4 Homogenization

Powder mixing was performed with a Turbula mixer (Willy A., Bachofen Maschinenfabrik, Basel, Switzerland), 50 rpm for 10 min.

*3.2.5 Near Infrared Diffuse Reflectance Spectroscopy (NIR***)**

The diffuse reflectance *(R%)* of each fractionated sample was determined in the wavelength range 200-2500 nm by using a 5-mm thin-layered cell in the sample holder of a Hitachi (Japan) U-3501 UV/VIS/NIR spectrophotometer equipped with an integrating sphere (*d*=60 mm) and a PbS detector. Measurements were made at the characteristic wavelengths of 1732 nm, 1584 nm, 1208 nm, 1070.5 nm and 1034 nm.

3.2.6 Flowability - Automated Powder Testing

The PTG powder testing system was used to measure the flow behaviour of granules and powders in compliance with the Ph. Eur. .This instrument is suitable for testing powder flow time, the measurement of the cone angle of the collected powder mound, measuring the weight, calculating the density and the volume of the powder cone as well as the Ph. Eur.

"flowability" results, which measures the flow time of 100 g of sample through a specified pouring nozzle. Using the conical stainless steel funnel and the changeable nozzles of 10, 15 and 25 mm, the cone angle can also be tested.

3.2.7 Compression

Compression was carried out with a Korsch EKO eccentric tablet machine (Korsch Maschinenfabrik, Berlin, Germany) mounted with strain gauges, and a displacement transducer was also applied. The pressure force and displacement were calibrated. Slightly concave punches, 12 mm in diameter were used.

The compression tools were single, flat-faced punches 10 mm in diameter (this was not possible with punches 3 mm in diameter, which easily break) furnished with strain gauges and a displacement transducer. The strain gauges allow the force of compressions on the upper and lower punches to be followed with equipment calibrated with a WAZAU HM-HN-30 kN-D cell (Kaliber, Budapest, Hungary). The displacement transducer was fitted over the upper punch. The transducer distance accuracy was checked by using five measuring pieces of different thicknesses (2.0, 5.0, 7.5, 10.0 and 15.0 mm) under zero loads (Mitutoyo, Tokyo, Japan).

Parameters: Pressure force (upper punch): 15 ± 1 kN, relative air humidity: 45-50%, air temperature: 26° C, rate of pressing: 35 tabl./ min, extent of compression: 3x10 tablets.

Compression procedure

Samples, in a 1 L glass vessel were homogenized at 50rpm in a Turbula mixer (W.A. Bachofen, Basel, Switzerland). After mixing, the powders were compressed into tablets with an instrumented eccentric tablet machine (Korsch EK0, Berlin, Germany). The compression tools were single, flat-faced punches 10 mm in diameter (this was not possible with punches 3 mm in diameter, which easily break) furnished with strain gauges and a displacement transducer. The important compression parameters were calculated.

The crushing strength was investigated with a Heberlein apparatus (Flisa, Le Locle, Switzerland). The geometrical parameters were measured with a screw micrometer (Mitutoyo). The parameters of the tablets were determined 24 h after compression because of the texture change (elastic recovery).

3.2.8 Energy Dispersive X-ray Fluorescence Analyser (XRF)

X-ray analysis was carried out with an energy dispersive X-ray fluorescence analyser (MiniPal, Philips Analytical, Almelo, The Netherlands). The preparation is very simple and the measurement is very rapid. The spectrum was evaluated by non-linear least squares fitting,

based on the AXIL algorithm developed at the University of Antwerp. The measurements were repeated 5 - 10 times.

4. RESULTS AND DISCUSSION

Section I.

4.1 Measurement of particle size and shape

A light microscope combined with an image analysis system has proved valuable proceeding for particle size analysis. 500 particles (average) were measured separately from each unsieved sample, chosen randomly from the bulk of the materials. Among the possible 24 feature parameters, 4 most important ones (with mean, standard deviation, minimum and maximum) were measured; area, length, breadth the shortest of the Feret measurements, convex perimeter, as *Table 1* shows. (These data refer to the unsieved, commercially available "bulk".) Further feature parameters referring to shape – roundness and roughness - could be determined from these "basic" ones by the software of the image analysis system.

Roughness is the ratio of the total length of the boundary of the feature to the length of the polygon circumscribing the feature, formed by 64 tangents to its boundary, revealing the surface irregularities of the particle.

Table 1 Main characteristics of particles

Sample		**Length μm**	**Breadth μm**	**Perimeter μm**	**Convex perimeter μm**	**Roundness**	**Roughness**
Sample 1	Mean	286.41	207.2	889.68	793.4	1.47	1.12
	S.D.	*100.83*	*69.62*	*330.21*	*270.78*	*0.19*	
Sample 2	Mean	344.1	245.17	1048.42	946.36	1.46	1.11
	S.D.	*114.62*	*81.22*	*373.01*	*306.17*	*0.25*	
Sample 3	Mean	657.28	441.5	2101.07	1778.24	1.78	1.18
	S.D.	*205.95*	*134.54*	*719.81*	*542.43*	*0.34*	

The particle size range proved to be a more important characteristic of the size than a mean particle size value, associated with tablet formation.

The differences in particle size can be seen from the data. Sample 1 consists of the smallest crystals, and Sample 3 of somewhat larger particles. It can additionally be seen that the parameters display a rather high deviation. The roundness data reveal that all three samples consist of non-isometric particles; there is no difference in habit between Samples 1 and 2, but the degree of non-isometry of Sample 3 is clearly higher. It can be seen furthermore that the roughness values are higher than 1 in every case. This means that the surface of the particles is uneven. There is a similarity in the cases of Samples 1 and 2, but the value for Sample 3 is a little higher, through the difference is not significant.

From the histograms shown in *Figures 1, 2, and 3* it can be stated, that the distribution of the various Sorbitol samples (unsieved, bulk) follows heterodisperse features.

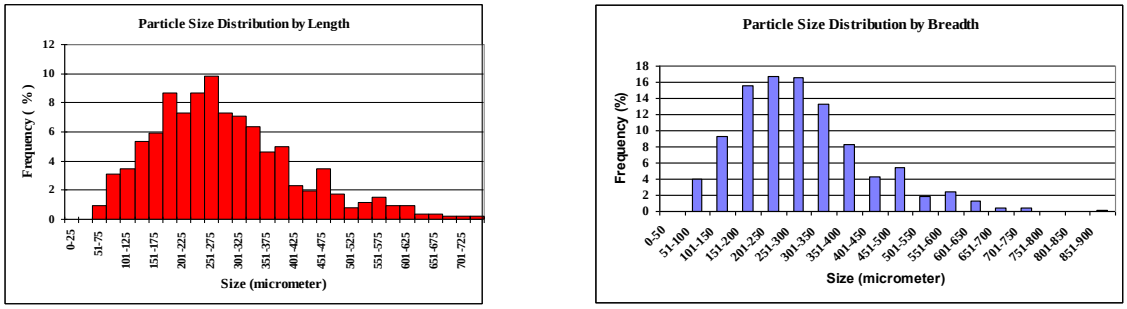

Fig. 1 Sample 1 - Histograms by Length and Breadth

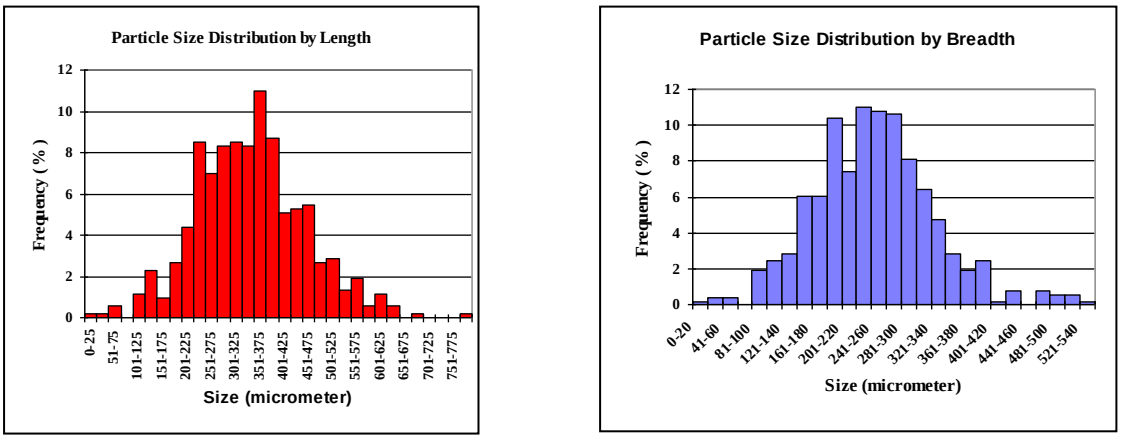

Fig. 2 Sample 2 - Histograms by Length and Breadth

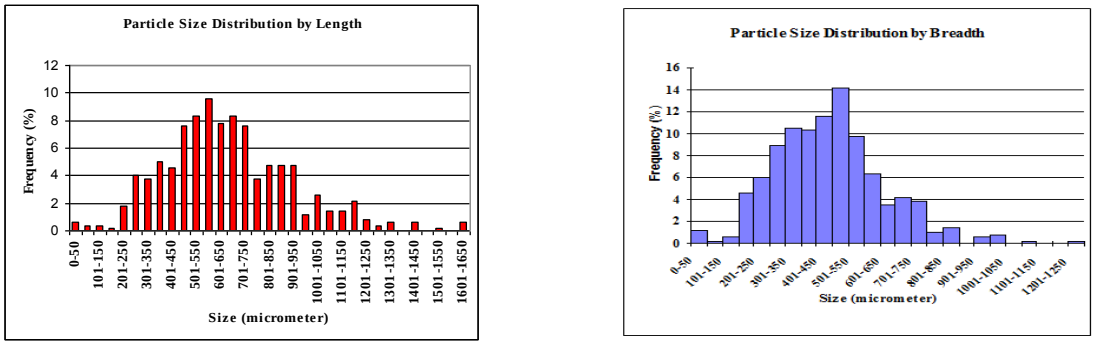

Fig. 3 Sample 3 - Histograms by Length and Breadth

After the examinations of these commercially available "bulks", fractions were also separated with an analytical sieving machine for further tests; with vibration sieve-apertures of 250, 315, 400, 630 and 1000 µm. The individual sieving time was 5 min. In the experiments 315-400, 400-630 and 630-1000 µm fractions were used.

4.2 Morphological study

The application of the proceeding of scanning electron microscopy (SEM) was suitable for the detection of the shape and the surface of the individual particles. The habits of the particles are illustrated in *Figures 4, 5, 6.* It is clear that the shapes of the particles from the shown samples are irregular, and the surface is very uneven. These particles are agglomerates of smaller crystals.

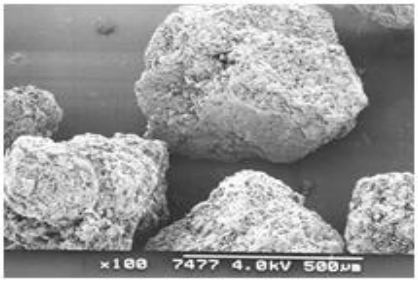

Fig. 4 Sample 1

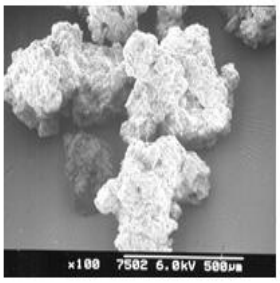

Fig. 5 Sample 2

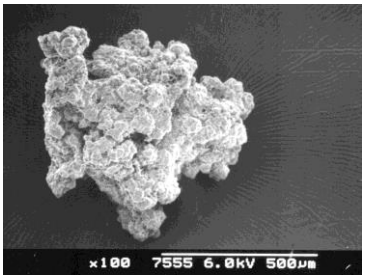

Fig. 6 Sample 3

4.3. Test by NIR Spectroscopy]

Fractions of the Samples were analysed with Near Infrared Spectroscopy.

The spectra at certain, characteristic wavelengths tended to differ from each-other.

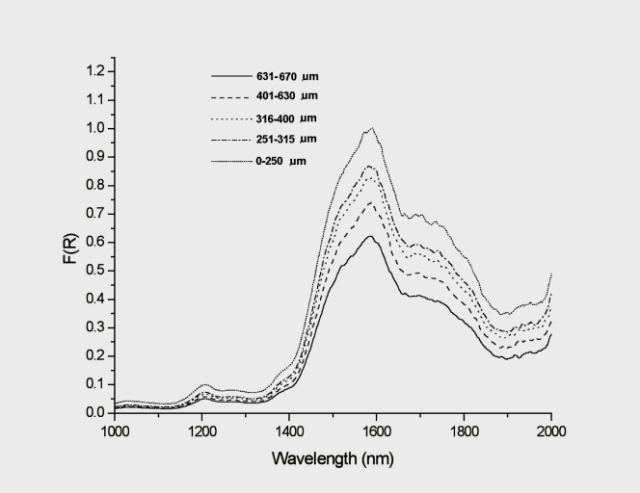

Fig. 7 Near infrared spectra of the sieved sorbitol fractions

Figure 7 above reveals that all the spectra of the fractions ran parallel to each other, which means that the chemical characteristics were constant during the industrial processing of the preparation. Since the sorbitol samples did not contain other excipients, the absorbance must be due to the analyte itself. The differences between the spectra lie in the physical characteristics of the sieved powder fractions, due to the different extents of light reflectance. Smaller particles have a smaller ratio *K/S*, a lower absorbance, and hence a higher *R*.

Figure 8 displays the close relationship between the parameters for each fraction (mean particle size) and the *F(R)* values at 1584 nm. The increase in the baseline with decreasing sample powder particle size was neglected.

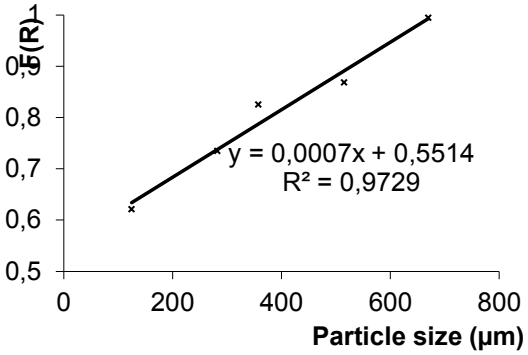

Fig 8 Relationship between particle size and NIR spectral data

A linear relationship was also found between the mean particle size and the bulk density of the sieved fractions (*Figure 9).*

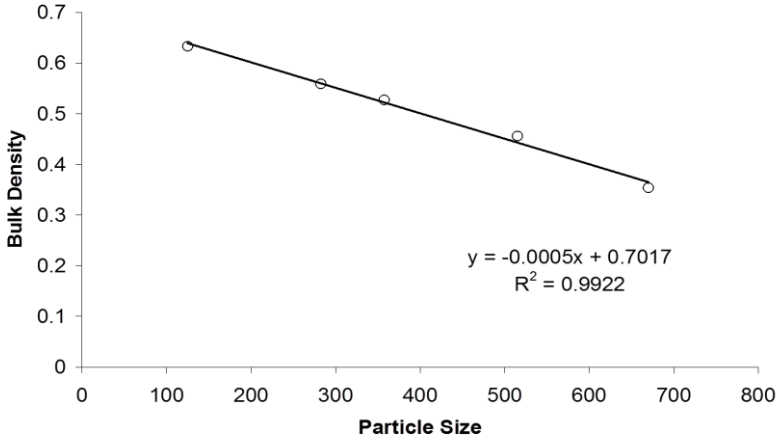

Fig. 9 Relationship between mean particle size and bulk density of sieved sorbitol fractions

Summary

According to the study, the commercially available sorbitol samples represent heterodisperse features. These bulks were unsieved; and due to their heterodispersity, particles were sieved into fractions with an analytical sieving machine in order to be suitable for further tests and analyses.

By comparing the SEM photos of the studied particles with the calculated roughness data, a strong relationship can be seen: the smoother surface has resulted in the smaller roughness data. The sieved fractions were also investigated by the analysis of near infrared spectroscopy; and the findings gave good correlation regarding size determination.

It can be concluded that NIR spectroscopy has now entered a mature stage of development and is currently the most efficient method of performing both qualitative and quantitative analysis; this method can also be used to characterize the particle characteristics, including the sizes of solid samples.

Section II.

4.4 The influence of the cohesion on the flowability characteristics

It is well known that the knowledge of the flow properties of powdered materials is very important in the pharmaceutical industry and the food industry. Good flowability is an essential characteristic of powdered materials during the filling of capsules and in tableting operations.

4.4.1 Calculation of cohesional coefficient (C)

It is also well known that the *flow of powder* in a funnel is influenced by the cohesive forces between the particles, the frictional forces between the wall of the funnel and the particles, and the gravitational force. The *cohesional coefficient* is a function of the internal frictional coefficient, the friction between the particles and the wall of the funnel and the diameter of the particles. Small particles are very cohesive and do not flow well or free. If the particles are very small (<50 μm), the cohesional forces are higher than the gravitational force and outflow is prevented. In the case of larger particles (>300 μm), free flow is expected. Naturally, the diameter of the orifice also influences the flow. In this case, a larger diameter may improve the flow time. In the knowledge of the degree of cohesion, it is possible to choose a suitable orifice size, and punches and dies with suitable diameters during tableting. The degree of friction/cohesion can be expressed in terms of the cohesional coefficient, which can be calculated from the powder rheological parameters:

This gives:
$$D = \frac{4C}{\rho g h} \qquad Eq.(1)$$

The cohesion force between the powder particles can be determined from the angle of repose *(α).* For calculating *C,* the forthcoming equation should be followed*:*

$$C = \frac{1}{2} d \left(\sqrt{\cos^2 \alpha + \frac{4 \sin \alpha}{d}} - \cos \alpha \right) \qquad Eq.(2)$$

The main characteristics of particles are presented in *Table 1* and the shape of the samples can be seen in *Figs 4, 5 and 6*. It was concluded that the shapes of the particles of all the samples are irregular and the surface is very uneven. The *flowability* of the unsieved samples was first tested (*Table 2*). The orifice of the equipment was 10 mm in all cases. The flow properties were tested without stirring.

Table 2. Flowability parameters of unsieved sorbitol

Samples	Flow time (s)	Angle (°)	Volume (ml)	Mass (g/100 ml)	Bulk density (g/ml)
Sample 1	8.2	33.6	87.2	39	0.447
Sample 2	8	33.2	85.6	37.1	0.433
Sample 3	7.8	33.6	87.1	44.8	0.515

The data demonstrate that the differences in particle size and shape between the unsieved commercial products caused practically no appreciable difference in the flow parameters, the flow is mass flow. From the practical aspect of tableting, however, a homodisperse particle size distribution is very important because (together with the other components) it influences the rearrangement in the die cavity.. In this case it is necessary to separate the materials into fractions. After the powder had been sieved, the rheological parameters of the various fractions were determined. The particle sizes were higher than 300 μm and we chose a smaller orifice (diameter 8 mm) in the flowability test accordingly to study the influence of particle size and orifice on the flowing time. A special problem arises during the tableting of small tablets, when the diameter of the punches and die is also smaller. The results are given in *Table 3.*

Table 3 Flowability data on sample fractions

Samples	Fraction (μm)	Flow time(s)	Angle (°)	Volume (ml)	Mass (g/100 ml)	Density (g/ml)
Sample 1*	315-400	12.8 SD±1.62	32.6 SD±0.86	83.8 SD±2.81	41.8 SD±0.74	0.499 SD±0.014
	400-630	14.4 SD±0.82	34.7 SD±0.73	90.7 SD±2.43	38.6 SD±0.68	0.425 SD±0.01
	630-1000	17.1 SD±0.41	36.1 SD±0.2	95.5 SD±0.76	32.3 SD±0.74	0.338 SD±0.006
Sample 2**	315-400	12.4 SD±0.07	33.4 SD±0.45	86.5 SD±1.39	44.3 SD±0.29	0.512 SD±0.005
	400-630	13.5 SD±0.23	35.7 SD±0.57	94.3 SD±1.87	39.2 SD±0.84	0.416 SD±0.012
	630-1000	16.7 SD±0.04	35.8 SD±0.55	94.5 SD±1.89	35.7 SD±0.2	0.378 SD±0.008
Sample 3**	315-400	11.6 SD±0.13	33.2 SD±0.44	85.8 SD±1.53	46.7 SD±0.92	0.545 SD±0.008
	400-630	14.2 SD±0.36	35.3 SD±0.66	92.85 SD±2.27	43.5 SD±0.43	0.470 SD±0.14
	630-1000	16.3 SD±0.13	34.9 SD±0.86	91.7 SD±2.9	38.4 SD±2.76	0.419 SD±0.03

*stirring rate: 10 rpm; ** without stirring

For Sample 1, stirring (10 rpm) was necessary because of the shape of the particles. It is clear from the data in *Table 3*. that increasing particle size was accompanied by an increase in the

flow time. The values of the angle of repose (except for Sample 1, where the angle increased somewhat) were practically the same. The volume steadily increased in the case of Sample 1. In the other two cases, the volume increased between the first two fractions (315-400 and 400-630 μm), but on further increase in particle size, no increase in volume was apparent.

The data also demonstrate that the mass and bulk density of the heap generally correlate negatively with the particle size. This shows that the filling space depends on the particle size, which is very important in tablet making.

The cohesional coefficient and the critical diameter were calculated from the data and are presented in *Table 4*. It is clear that the value of *C* increased with increasing angle of repose. Accordingly, we considered the possibility of a relationship between the cohesional coefficient and the angle of repose in this range of particle size. The angle of repose was found to vary linearly with the cohesional coefficient *(y=ax+b,* where *x*=cohesional coefficient, *a*=slope, *y*=angle of repose and *b*=intercept*)* with good correlation (R^2>=0.972). It is also clear that the angle of repose depends on the particle size and shape, and that the cohesional coefficient therefore characterizes the flow properties of a powder.

Table 4 Relationship between the cohesional coefficient and the angle of repose

Samples	Average diameter of particles in the fraction (μm)	Angle of repose (°)	Cohesional coefficient (*C*)	Minimum orifice diameter (*D*) (mm)
S1	358	32.6	0.01374	1.11
	515	34.7	0.01691	1.62
	815	36.1	0.02159	2.60
S2	358	32.8	0.01377	1.10
	515	33.4	0.01662	1.63
	815	35.7	0.02148	2.32
S3	358	32.4	0.01370	1.03
	515	33.2	0.01657	1.40
	815	34.3	0.02110	2.05

The findings permit the prediction of the smallest orifice diameter (*D*) through which the particles can freely flow into the die cavity. This is very important, especially from the aspect of the preparation of minitablets, which are only 2-3 mm in diameter, and which can be filled in capsules used as multiparticulate dosage forms. Because of the small die diameter, its prediction in preformulation tests is an essential question.

Summary

A new coefficient (*C* = cohesional coefficient) was calculated and a relationship was found between this coefficient and the angle of repose as a function of the particle size (in this range), and the critical minimal orifice diameter could be calculated.

The *influence of cohesion on the flowability characteristic is* especially important in the case of manufacture of minitablets measuring only 2-3 mm in diameter, which open up new possibilities in therapy, e.g. in the treatment of ocular disease or in pediatrics. They can be filled into capsules or further compressed into larger tablets; and the latest developments are the multiparticulate modified release dosage forms.

Section III.

4.5. Compactibility/compressibility study

4.5.1. *Study of the distribution of magnesium stearate*

According to the practice of tabletting and the relevant literature, with the decrease in particle size, not only the parameters of flowability are deteriorating, but the friction between the die wall and the side of the tablet also tends to increase.

One of the types of auxilliaries used to solve this problem are lubricants, which are commonly included in tablet formulations in order to reduce the die wall friction during both the compaction and the ejection of the tablet. Their presence, however, may cause undesirable changes in tablet properties. When a lubricant is added to a tabletting blend, it is distributed either as a free fraction or as a surface film on the carrier material. In tablet making, the most commonly used pharmaceutical lubricant is magnesium stearate. There are several direct and indirect methods by which the distribution of magnesium stearate on the surface of lubricated particles can be examined.

The aim of this experiment was to study the influence of particle size of sorbitol on the distribution of magnesium stearate in a tablet during compaction. A compact table-top energy dispersive X-ray fluorescence analyser was used to measure the elemental range from sodium (Na) to Uranium (U), with a concentration range from ppm to 100%. The magnesium content of magnesium stearate was measured. Lubrication is also considered to be a surface phenomenon. For this reason, the upper and lower surfaces of the tablets were analysed by energy dispersive X-ray fluorimeter. The relevant data can be seen in *Table 5.*

Table 5 Amount of magnesium on the surface of tablets.

Tablet batch	**Particle size (μm)**	**Magnesium (ppm)**	
		Upper surface	**Lower surface**
1	**250-315**	**23.06 (SD=2.45)**	**21.48 (SD=1.28)**
2	**316-400**	**24.58 (SD=0.73)**	**25.46 (SD=4.36)**
3	**401-630**	**25.28 (SD=6.21)**	**22.75 (SD=2.01)**
4	**631-1000**	**22.66 (SD=1.48)**	**22.59 (SD=4.31)**

Practically no difference can be detected in the distribution of magnesium stearate on the upper and lower surfaces of the tablets. It can further be observed that the sorbitol particle size did not influence the distribution of magnesium stearate, and magnesium stearate used with a low specific area exerts a lubricating effect on the surface of the tablets. It was also very interesting to study the distribution of magnesium stearate inside the tablets. Therefore microsections with different thicknesses were prepared from tablets of No. 2 and 4 with the aid of abrasive paper. The thickness was determined with a screw-micrometer (Mitutoyo, Kawasaki, Japan) and the magnesium stearate concentration was measured on the surface of microsections. The results are displayed in *Table 6.*

Table 6: Distribution of magnesium in the tablets

	Tablet batch 2				**Tablet batch 4**			
	Origin	**Microsection**			**Origin**	**Microsection**		
Thickness (mm)	3.944	2.981	2.530	2.114	3.864	2.999	2.228	1.776
Magnesium (ppm)	24.58 SD=0.73	15.4 SD=0.60	13.2 SD=0.90	15.6 SD=1.50	22.66 SD=1.48	9.2 SD=1.20	4.6 SD=2.20	3.3 SD=1.20

It can be seen from the the data that the amount of magnesium stearate decreased progressively towards the middle of the tablets. It can additionally be established that it decreased to a higher degree in the case of tablets No. 4. This means that the particle size influences the distribution of magnesium stearate inside the tablets. Its distribution is better inside tablets prepared from smaller particles. It can be stated that larger particles need more magnesium stearate with a low specific surface area, or another quality of magnesium stearate (e.g. a higher specific surface area).

Summary

It can be concluded, that the X-ray fluorescence analyser is a suitable means of measuring the amount of magnesium stearate on the surface of and inside tablets. The distribution of magnesium stearate with a low specific surface area is uniform on the surface, but it is disturbed by the higher particle size inside the tablets

4.5.2. Role and effect of the particle size (sorbitol) during the compression of common tablets and prediction of mini-tablet compression parameters

The importance of particle size and shape has been shown previously; as they play important roles in particle formation and processing. They influence the intermediate and final products directly, and their effects are especially important in the manufacturing of mini tablets, 2-3 mm in diameter**.** In this section the role of particle size was studied during direct compression. Sorbitol was also chosen as model material and compression was achived with an instrumented tablet machine suitable for measurment of the force of compression, its software allowing calculation of the compression parameters.

Through the extrapolation of the compression parameters, the force of compression required to produce mini-tablets 3 mm in diameter with a mass of 140 mg was predicted.

The compression of sorbitol alone was not possible as it sticks to the punches and the die wall. Powder mixtures were therefore prepared with microfine cellulose (Arbocel) as filler (Arbocel has no tendency to stick) – as shown by *Table 7.*

Table 7. Compositions of samples

Sample	Components	Proportions %
1	Sorbitol 250-315 μm Arbocel	50 50
2	Sorbitol 315-400 μm Arbocel	50 50
3	Sorbitol 400-630 μm Arbocel	50 50
4	Sorbitol 630-1000 μm Arbocel	50 50
5	Sorbitol 250-315 μm Arbocel	70 30
6	Sorbitol 315-400 μm Arbocel	70 30
7	Sorbitol 400-630 μm Arbocel	70 30
8	Sorbitol 630-1000 μm Arbocel Magnesium stearate	70 29 1
9	Sorbitol 250-315 μm Arbocel Magnesium stearate	70 29 1
10	Sorbitol 315-400 μm Arbocel Magnesium stearate	70 29 1
11	Sorbitol 400-630 μm Arbocel Magnesium stearate	70 29 1
12	Sorbitol 630-1000 μm Arbocel Magnesium stearate	70 29 1

Compression procedure (see in section 3.2.7)

The statistical analyses were carried out with Statistica for Windows (Statsoft Inc.).

Compressibility and compactibility behaviour, which is essential during compression, depends on the rearrangement of the particles. If the rate at which a powder rearranges is too low, compression can give rise to brittle fracture and plastic flow in certain regions before a close arrangement has been achieved in other regions;hence, when compression is complete, the tablet formed will have a lower local density in that particular area.

Table 8 Important compression parameters of 10 mm tablets (50% Sorbitol, without lubricant) Force of compression: 15±1 kN

Sample	**Fraction (μm)**	***E_2*** **(Nm)**	***E_3*** **(Nm)**	***Fw*** **(Nm)**	***Pl_{S-M}*** **(%)**	***Pr*** **(Pa/Nmkg^{-1})**	**Tensile strength (MPa)**
1	250-315	6.36 SD:± 0.12	1.08 SD:± 0.34	2.04 SD:± 0.12	86.50 SD:± 2.37	196.26 SD:± 3.71	2.99 SD:± 0.01
2	315-400	6.38 SD:± 0.18	1.09 SD:± 0.12	2.18 SD:± 0.25	85.33 SD:± 1.56	194.71 SD:± 4.06	2.93 SD:± 0.01
3	400-630	6.10 SD:± 0.11	0.80 SD:± 0.13	1.94 SD:± 0.08	86.55 SD:± 0.36	190.32 SD:± 10.11	2.79 SD:± 0.09
4	630-1000	6.32 SD:± 0.18	1.05 SD:± 0.20	2.00 SD:± 0.11	85.76 SD:± 2.45	174.93 SD:± 6.19	2.65 SD:± 0.07

Table 9 Important compression parameters of 10 mm tablets (70% Sorbitol, without lubricant) Force of compression: 15±1 kN

Sample	**Fraction (μm)**	***E_2*** **(Nm)**	***E_3*** **(Nm)**	***Fw*** **(Nm)**	***Pl_{S-M}*** **(%)**	***Pr*** **(Pa/Nmkg^{-1})**	**Tensile strength (MPa)**
5	250-315	5.20 SD:±0.09	0.74 SD:±0.06	1.52 SD:±0.05	86.43 SD:±0.46	250.10 SD:±3.31	3.37 SD:±0.01
6	315-400	5.80 SD:±0.12	1.16 SD:±0.15	1.85 SD:±0.14	87.35 SD:±0.85	226.50 SD:±4.88	3.38 SD:±0.01
7	400-630	5.94 SD:±0.31	0.96 SD:±0.17	1.78 SD:±0.11	85.53 SD:±1.35	220.80 SD:±9.98	3.13 SD:±0.32
8	630-1000	5.54 SD:±0.11	0.97 SD:±0.14	1.49 SD:±0.08	85.57 SD:±1.50	234.70 SD:±6.36	3.47 SD:±0.08

It can be seen from the data *(Tables 8 and 9)* that, on increase of the sorbitol content in the powder mixture, the plasticity of the samples remained the same. This means that the smaller proportion of microfine cellulose (Arbocel) did not influence the deformability of the powder mixture. In spite of this, the deformation energy *(E_2)* and the work of friction *(F_W)* decreased slightly. The compactibility/compressibility *(Pr)* and tensile strength of the powder mixture containing 70% sorbitol *(Table 9)* were higher than those of the mixture containing 50% sorbitol (*Table 8)* because of the formation of stronger solid bridges between the more numerous sorbitol crystals during the compression. This effect appeared in the mechanical (tensile) strength of the tablets. Bonferoni analysis revealed that the Sorbitol particle size

influenced the compressibility behaviour and the mechanical strength of the tablets, but not significantly. Both parameters were lower in the case of 50% sorbitol.

On increasing of the amount of sorbitol without magnesium stearate (*Table 9*), the work of friction was slightly, but not significantly higher for the 315-400 μm and 400-630 μm fractions. *Pr* decreased with the increase of the particle size. In spite of this, the tensile strength was almost the same. The influence of magnesium stearate can be seen in *Table 10.*

Table 10 Important compression parameters of 10 mm tablets (70% Sorbitol, with lubricant) Force of compression: 15±1 kN

Sample	**Fraction (μm)**	***E_2*** **(Nm)**	**E_3 (Nm)**	***Fw*** **(Nm)**	***Pl_{S-M}*** **(%)**	***Pr*** **(Pa/Nmkg^{-1})**	**Tensile strength (MPa)**
9	250-315	5.15 SD:±0.08	1.18 SD:±0.11	1.26 SD:±0.12	81.34 SD:±1.55	207.58 SD:±8.04	2.50 SD:±0.08
10	315-400	4.88 SD:±0.07	1.29 SD:±0.13	1.21 SD:±0.08	79.20 SD:±1.66	192.50 SD:±7.90	2.29 SD:±0.09
11	400-630	4.68 SD:±0.24	1.21 SD:±0.09	1.21 SD:±0.12	79.72 SD:±1.20	195.30 SD:±9.94	2.36 SD:±0.13
12	630-1000	4.78 SD:±0.16	1.33 SD:±0.12	1.22 SD:±0.09	78.12 SD:±1.42	158.50 SD:±6.04	1.95 SD:±0.11

Comparison with the data on the powder mixture without magnesium stearate clearly reveals that the plasticity *(Pl_2)* was lower and the elastic recovery *(E_3)* higher to small extents. The other parameters were generally lower. It is well known from the literature, that magnesium stearate can form a very thin hydrophobic layer on the surface of particles during mixing. This layer hinders the formation of strong solid bridges between the particles. This is the reason why magnesium stearate generally reduced the compression parameters, but this effect was not significant. The smallest particle size fraction produced the best compactibility in every case. Magnesium stearate decreased *Pr.*. According to our findings, in the interior of the tablet, the degree of distribution of magnesium stearate depends on the particle size.

The work of friction was uniform during the compression of sorbitol with 1% magnesium stearate, and this effect appeared in the other parameters as well.

The data in *Tables 8, 9, and 10* indicate that the 250-315 μm fraction at higher sorbitol proportion is the most suitable for the formation of the most compact tablet. Therefore, the data on this fraction were chosen for the extrapolation to mini-tablets.

4.5.3. Extrapolation to mini-tablets

As mentioned above, the force of compression is a very important parameter in tablet compression. In the forthcoming part below, a simple method is given with which to determine a suitable force of compression for mini-tablet formation, and also formulas to determine the energy of making mini-tablets. The initial data are the mass (140 mg) and geometrical dimensions (height: 2 mm, diameter: 3 mm) of the desired mini-tablets. For a

common normal tablet, the height should be a quarter of the diameter, but this is not valid in the case of mini-tablets. They may also be isometric. In the calculation, we assume that the plasticity *($Pl_{S\text{-}M}$)*, compressibility/compactibility factor *($Pr_{(mass)}$)* and the tensile strength *(σ)* are same for normal and mini tablets. We do this if the material parameters are identical in both cases. If these conditions are satisfied, we can write:

$$\frac{2 \cdot F}{\pi \cdot D \cdot h} = \frac{2F^m}{\pi \cdot D^m \cdot h^m} \qquad \textit{Eq.(3)}$$

$$\frac{\sigma_x}{E_2 / m} = \frac{\sigma_x^m}{E_2^m / m^m} \qquad \textit{Eq. (4)}$$

$$\frac{E_2}{E_2 + E_3} = \frac{E_2^m}{E_2^m + E_3^m} \qquad \textit{Eq. (5)}$$

where ^{m} denotes the corresponding values for the mini-tablets. From *equation 3*, the size of the breaking force of the mini-tablet can be calculated as

$$F^m = \frac{D^m \cdot h^m}{D \cdot h} \cdot F \qquad \textit{Eq. (6)}$$

where F and F^m are the forces of breaking of normal tablets and mini-tablets respectively. Then, the force of compression (pressure) for mini-tablets can be obtained from:

$$F^m_{pressure} = \frac{F^m}{F} \cdot F_{pressure} \qquad \textit{Eq. (7)}$$

where $F_{pressure}$ and $F^m_{pressure}$ are the load forces in the cases of normal tablets and mini-tablets respectively.The calculations revealed that for the 250-315 μm fraction the optimum force of compression was 2.5 kN (for Sample 5) and 2.3 kN (for Sample 9).

The energy of plastic deformation (E_2) and the energy of elastic deformation (E_3) of mini-tablets can be obtained from *equations (4) and (5)*, respectively, via the forms

$$E_2^m = \frac{m^m}{m} \cdot E_2 \qquad \textit{Eq. (8)}$$

$$E_3^m = \left(\frac{E_2 + E_3}{E_2} - 1 \right) \cdot E_2^m \qquad \textit{Eq. (9)}$$

The extrapolated values are listed in *Tables 11, 12 and 13* which present the parameters predicted during the compression of mini-tablets. It is clear, that the tendencies are the same as for normal tablets. This justifies the suitability of the calculation specified aboved.

Table 11 Important compression parameters extrapolated to mini-tablets 3 mm in diameter (Samples 1-4)

Sample	**Fraction (μm)**	E_2 **(Nm)**	E_3 **(Nm)**	Fw **(Nm)**
1	250-315	2.23 SD:± 0.04	0.38 SD:± 0.12	0.71 SD:± 0.04
2	315-400	2.23 SD:± 0.06	0.38 SD:± 0.04	0.76 SD:± 0.09
3	400-630	2.14 SD:± 0.04	0.28 SD:± 0.05	0.68 SD:± 0.03
4	630-1000	2.21 SD:± 0.06	0.37 SD:± 0.07	0.70 SD:± 0.04

Table 12 Important compression parameters extrapolated to mini-tablets 3 mm in diameter (Samples 5-8)

Sample	**Fraction (μm)**	E_2 **(Nm)**	E_3 **(Nm)**	Fw **(Nm)**
5	250-315	1.82 SD:± 0.03	0.26 SD:± 0.2	0.53 SD:± 0.02
6	315-400	2.03 SD:± 0.04	0.41 SD:± 0.05	0.65 SD:± 0.05
7	400-630	2.08 SD:± 0.11	0.33 SD:± 0.06	0.62 SD:± 0.04
8	630-1000	1.94 SD:± 0.04	0.34 SD:± 0.05	0.52 SD:± 0.03

Table 13 Important compression parameters extrapolated to mini-tablets 3 mm in diameter (Samples 9-12)

Sample	**Fraction (μm)**	E_2 **(Nm)**	E_3 **(Nm)**	Fw **(Nm)**
9	250-315	1.80 SD:±0.03	0.41 SD:±0.04	0.44 SD:±0.04
10	315-400	1.71 SD:±0.03	0.45 SD:±0.05	0.42 SD:±0.03
11	400-630	1.82 SD:±0.03	0.47 SD:±0.03	0.43 SD:±0.04
12	630-1000	1.82 SD:±0.03	0.51 SD:±0.04	0.43 SD:±0.03

Summary

The influence of various particle size fractions on the compressibility and compactibility of sorbitol revealed that the sorbitol 250-315 μm fraction exhibited the greatest compactibility in the compression experiments when the mass of tablets was 400 mg, the diameter was 10 mm and the force of compression was 15 kN. The proportion of sorbitol increased, whereas the use of lubricant slightly decreased the compressibility factor $(Pr_{(mass)})$ (based on the compression data), but the tendency was the same in each case. On increasing the particle size, the compactibility generally decreased, but not significantly.

The extrapolation of the data on this basis indicated that 2.3-2.5 kN force of compression would be necessary to prepare mini-tablets 3 mm in diameter and 140 mg in mass.

5. FINAL CONCLUSIONS, NOVELTY, PRACTICAL USEFULNESS

During my work, I have aimed to interpret the importance of particle size in tableting from a new point of view.

Determination of particle size, as well as the importance of particle size and homodispersity are already well known; these factors bear special significance during direct compression. However, in practice, obtaining homodispersity by grinding is not always favourable. On the one hand, damages in the crystalline structure during grinding may lead to problems in stability, on the other hand they may induce undesirable interactions. What is more, manufacturers of auxilliaries tend to produce more and more, so-called ”co-processed” products; their milling is not considered to be practical. These ”co-processed” materials contain multicomponent, individual particles, and only ”intact” particles can produce the required effect. Besides these, mini-tablets – forming a special group of tablets, - are considered to be a new trend in modern therapy. During their preparation, the ensuring of appropriate particle size and favourable flowability is of special importance.

Summarizing the final conclusions, novelty, and practical usfulness of my work, it can be stated:

- I have found that the habit of the various, commercially available products is different; and in their heterodispersity diversity can be tracked.
- I have found relationship between the sieved fractions of the samples and near infrared (NIR) spectra.
- Based on the results of the flowability studies, I have determined the value of the cohesion coefficient by a mathematical-statistical method, which enables us to predict the size of the smallest punch diameter (die hole) suitable for particles to fill in via free-flow.
- Nowadays the guidelines of the European Medicine Agency (EMA) suggest the application of a factorial design or an artificial neural network in the development of a dosage form and the new coefficient could be applied to decrease the number of necessary training factors as it combines some of the more important characteristics of the studied materials.
- I have studied the effect of particle size on the distribution of magnesium stearate. Magnesium stearate, as lubricant is mainly responsible for reducing fricton arising between the die wall and the surface of the tablet. This effect could be detected in sorbitol with a smaller particle size, which was considered to be favourable.

- Based on the parameters of compressibility, I have determined the influence of particle size on the compressibilty/compactibilty of tablets.

  By extrapolating the results with mathematical-statistical calculations, the force of compression referring to preparing tablets with 3 mm in diameter, 2 mm in height, and 140 mg in mass, has been determined.

Finally, it can be stated:

1. When receiving raw materials, the study of habit is essential. Furthermore, NIR analysis is suitable for not only the chemical identification of the material, but also for quick particle size determination.
2. By the calculation of the cohesion coefficient (C), the time for development procedure of a dosage form can be shortened; as it can be used as a factor for a factorial design or an artificial neural network.
3. Similarly, by extrapolating the results of the compressibilty parameters, the innovation of mini-tablets can be accelerated.
4. Energy dispersive X-ray fluorescence analyser is a suitable method for carrying out pharmaceutical elemental impurity analysis.

PUBLICATIONS RELATED TO THE THESIS

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III. **Szalay A., K**elemen A., Pintye-Hódi K.: **The influence of the cohesion coefficient (C) on the flowability of different sorbitol types** *Chemical Engineering Research and Design 2015, 93, 349-354* *IF: 2,281*

IV. Kelemen A., **Szalay A**.,Sovány T., Pintye-Hódi K.: **Role of the particle size of sorbitol during the compression of common tablets and prediction of mini-tablet compression parameters** (manuscript is sent for review)

PRESENTATIONS RELATED TO THE THESIS

Verbal presentations:

- **Szalay A.**: **The effect of the particle size and particle size distribution on the flowability of various sugar derivatives**
  Hungarian Society of Pharmaceutical Sciences, V. Ottó Clauder Memorial Competition Budapest, Hungary 21st-23rd September 2000.
- **Szalay A.: Study of the distribution of Magnesium Stearate with an Energy-Dispersive X-ray Fluorescence Analyser**
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Poster presentations:

- **A. Szalay**, K. Pintye-Hódi, P. Szabó-Révész, P. Kása jr. and I. Erös: **Determination of Shape Factors of Particles with an Image Analysis System**
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- **Szalay A.,** Hódi K., Erős I.: **The effect of shape parameters on the compactibility of Sorbitol**

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- **Szalay A.,** Hódi K.: **The effect of particle size on bioavailability**

  Hungarian Society of Pharmaceutical Sciences Symposium on Drug Development - "Challenges and Results" Debrecen, Hungary 24th-25th November 2006.

Forthcoming:

- **Szalay A.**, Kelemen A., Pintye-Hódi K.: **Determination of the cohesion coefficient (C) essential on the particle flowability with different sorbitol types**

  E-poster, Pharmacology 2015 - World Conference on Pharmacology, Brisbane, Australia 20th-22nd July, 2015. ***(invited lecture)***