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A few aspects on the importance of particle size enabling proper tabletting

Ph.D. Thesis

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Szeged

2015

Publications related to the thesis

I. **Szalay A.,** Pintye-Hódi, K., Joó K., Erős, I.: **Study of distribution of magnesium stearate with an energy dispersive X-ray fluorescence analyser**
Pharmazeutische Industrie 2004, 66, 221-223 *IF: 0,190*

II. **Szalay, A.,** Antal, I., Zsigmond, Zs., Marton, S., Erős, I., Regdon, G. jr., Pintye-Hódi, K.: **Study on the Relationship between Particle Size and Near Infrared Diffuse Reflectance Spectroscopic Data**
Particle and Particle System Characterisation 2005, 22, 1-4 *IF: 0,619*

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

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**
Ph.D. Forum and Conference Szeged, Hungary 5th September 2002.

- **Szalay A.,** Pintye-Hódi K., Antal I., Erős I., Marton S.: **Is Near Infrared Spectroscopy (NIR) suitable for particle size determination?** *XIVth National Conference on Pharmaceutical Technology Hévíz, Hungary 8th-10th November 2002.*

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** *The 6th EUFEPS Congress Budapest, Hungary 16th-19th. September 2000.*

- **Szalay A.,** Hódi K.: **The effect of particle size and particle size distribution on the flowability** *PORANAL 2001. 8th Symposium on Particle Size Analysis, Environment and Powder Technology Eger, Hungary 13th-14th September 2001.*

- **Szalay A., Pintye-**Hódi K., Antal I., Szabó-Révész P., Kása P., Erős I.**: A new aspect in particle size determination: Near Infrared Spectroscopy** *Syntapharm Workshop Budapest, Hungary 23rd April 2002.*

- **Szalay A.,** Kelemen A., Pintye-Hódi K., Erős I.: **The Influence of Particle Size and Shape Parameters on the Flowability of Various Sugar Derivatives** *6th Central-European Symposium on Pharmaceutical Technology and Biotechnology Siófok, Hungary 25th-27th May 2005.*

- **Szalay A.,** Hódi K., Erős I.: **The effect of shape parameters on the compactibility of Sorbitol** *Congressus Pharmaceuticus Hungaricus XIII.th Budapest, Hungary 25th-27th May 2006.*

- **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)***

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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 [1-5].

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 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. LITERATURE SURVEY

Particle size is now widely accepted as being a critical parameter with a significant impact on the performance of pharmaceutical materials at all stages of their production and also on the finished product. The U.S. Food and Drug Administration (FDA), - as well as the European Medicine Agency (EMA) - is becoming stricter with regard to particle size analysis as a quality procedure [1-6].

The following aspects justify the particle size determination and the repeated study of flowability parameters:

1. By the preparation of solid dosage forms, it is essential to support their monodispersity; especially in the case of direct compression. However, ingredients and products commercially available show heterodispersity, as their feature.

In order to obtain proper particle size, comminution and milling process can be carried out. Consequently, the structure of the original crystals might be damaged, thus creating new and more „active” crystalline surfaces, resulting in the increase of the speed of dissolution, or other undesired interactions. Therefore, during preformulation tests, it is inevitable to check the suitability of the procedure.

2. In case of the preliminary milling process, the use of the so-called ”co-processed” materials, which seems to be favourable nowadays, should also be taken into consideration.

These auxillaries (e.g. Ludiflash, PharmaBurst 500, Prosolv ODT, F-melt type C, Parteck ODT, etc.) consist of individual particles with multiple components. The unique feature of these particles should not be destroyed.

3. Nowadays the so-called ”mini-tablets” are also commercially available; the size of their diameter tends to be between 2-3 mm. In the course of their preparation, during the compressional phase, the material should fill out properly the die hole with a diameter of 2-3 mm. This problem is considered to be a big challenge for pharmaceutical technologists; how to plan and how to predict optimal circumstances with any of the ”usual”, every-day-methods.

3.1 Particle Size Measurement and Classification

Particle size determination is essential in the following aspects:

- Safety of drug utilisation,
- Quality of drugs,
- Stability of drugs,
- Standardisation and validation of the various dosage forms [7-9],
- The preparation‘s optimal bioavailability, or other pharmacological effects; as powder characteristics may also influence the rate of absorption [4-5].

3.1.1. Statistical Parameters

Monodisperse systems of particles of regular shape, such as perfect cubes or spheres, can be completely described by a single parameter, e.g. a length of a side or diameter. However, when either nonuniform size distributions or anisometric shapes exist, any single parameter is incapable of totally defining the powder.

For irregular particles the assigned size will be strongly dependent on the method of measurement.

Mean particle diameter is the most important single statistical parameter since, if the proper diameter is chosen, the various other parameters of interest such as specific surface area, number, mean particle weight etc., may often be calculated.

For spherical particles the size is defined by the measurement of the diameter. However, for other-shaped particles some other single size designation is generally used, e.g. the diameter of a sphere with the same projected area as the nonspheroidal particle being measured. An irregularly shaped particle has a number of different dimensions, e.g.: Feret’s diameter, Martin’s diameter, projected area diameter, maximum horizontal intercept, maximum projected area, inscribed circle (d_{min}), circumscribed circle (d_{max}). Depending on the method of measurement, various diameters are obtained [10-13].

In measuring particle size it is important first to select the parameter that is related to the ultimate use of the product, and then to select the method that will measure this parameter.

Methods for particle size measurement can be either direct or indirect ones. Direct methods measure the actual dimensions of the particle by use of a calibration scale as in microscopy and sieving. Indirect measurements make use of some characteristic of the particle, which can be related to particle size; e.g. sedimentation rates, permeability, and optical properties [14].

The simpliest method among all is the sieving analysis, and the use of microscopy is considered to be one of the most accurate direct methods.

A variety of semiautomated and automated procedures have been developed in order to reduce any error in connection with the manual counting of particles, e.g. image analysis with various softwares.

Besides these ones, numerous methods suitable for particle size measurement exist, e.g. scanning and transmission electron microscopy (SEM, TEM), laser diffraction and spectroscopic proceedings (Near Infrared Spectroscopy - NIR).

3.1.2. Microscope and image analysis

Referring to Turbitt-Daoust et al., one of the most widely used and well-known methods is the microscope combined with an image analysis system, as it is considered to be principal among the other ones, gives a general study about the statistical dimensions of the analysis, and the method provides excellent reproducibility [11]. Podczeck has pointed out, that the results of the measured particles (size, shape, morphology) are considered to be standard data in comparison with any other sizing methods or techniques, enables the measurements on images from any source, provides rapid and accurate data, replacing the traditional, and rather subjective methods [13, 15].

Image analysis involves several separate stages: the image is acquired by the hardware, and converted into an electrical form, which is stored in the computer memory, or on a mass storage system such as a hard disc [12].

The results of the measured particles (size, shape and morphology) are considered to be standard data for comparison with other sizing methods or techniques.

In my work, the most important size and feature parameters of the model materials were determined by using the Leica Q500 MC image processing and analysis system (applying the principles of light microscope equipped with an image analysis system).

The software of the image analysis system derives roughness and other shape parameters from the measured data.

3.2 Flowability test

Particle size and shape have an impact on the powder rheological parameters, especially on flowability.

In flowability studies, the angle of repose is considered to be a parameter that can be measured well. An inverse relationship has been reported between the particle size and the angle of repose [16].

Besides the angle of repose, powder flow can be described by the flow time, the Carr index and the Hausner ratio. Powder flow can be characterized in two ways: as *mass flow*, when the particles can flow comparatively easily, as the cohesion between the particles is very low; and as *funnel flow*, when the particles flow much more poorly as the frictional forces acting at the funnel wall and the cohesion between the particles are much higher [17] (*Fig. 1*). In the case of mass flow, all of the powder particles in the funnel are in motion [18, 19]. In the case of funnel flow, the central core of powder flows from the funnel first, followed by the remaining powder from closer to the walls of the funnel.

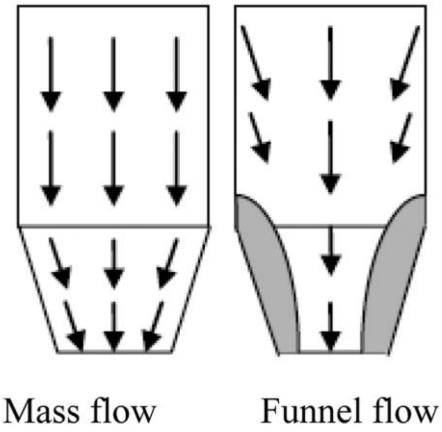


Fig. 1 Types of flow through a funnel [17]

Good flowability requires mass flow as in funnel flow the powder particles are held together more strongly by cohesion forces. Funnel flow leads to unevenness in filling during capsulation or compression, and high deviations can occur in the average mass of capsules of tablets. Accordingly, flowability testing is official in the Pharmacopoeias, and it is necessary to investigate flowability in the preformulation tests in the process of development of a solid dosage form. The multiparticulate dosage forms that are currently at the focus of therapy include hard capsules filled with mini-tablets, which are very small tablets (2–3 mm in diameter). This means that good flowability is especially important during the manufacturing of these tablets, where the diameter of the dies is very small and the filling time is also very short [16-19].

3.3 Near-infrared Spectroscopy (NIR)

Among the numerous techniques for the measurement of particle features, *near-infrared (NIR) spectroscopy is an alternative method,* which plays an increasing role in manufacturing as industry strives to improve the quality and process efficiency while reducing the costs. The wavelength range that constitutes the NIR region of the electromagnetic spectrum, and the demarcation of that range from other spectral regions, are somewhat indistinct. NIR is interpreted by BL-Analytics as the area between the visible and the infrared regions, thus covering the range from around 800 nm to 2500 nm.

The absorption bands observed in NIR spectra originate from overtones of hydrogen-stretching vibrations or from combinations of stretching and bending modes of vibration [20]. Since the absorption in the NIR region is much weaker than in the middle-IR region, NIR spectra can be obtained by direct measurement on samples without dilution, an integrating sphere being used to measure the diffuse reflection [21].

As the reflectance of solid samples varies with the concentration, the absorptivity and the scattering coefficient according to the Kubelka–Munk theory [22], the NIR spectrum of a solid material depends both on its chemical composition and on its physical properties, such as the particle size and surface characteristics [23-26].

Reflection spectroscopy is the study of light reflected from the surface of a sample, rather than the light transmitted through the sample. Light reflection can be either specular or diffuse. Diffuse reflection is reflection that occurs in all directions from the surface as a result of absorption and scattering processes.

The reflectance *(R%)* can be introduced on the analogy of transmittance:

$$\mathbf{R\% = \left(\frac{I_R}{I_O}\right) * 100} \qquad \textit{Eq. (1)}$$

where I_R is the intensity of the diffusely reflected light collected by the integrating sphere, and I_0 is the intensity of the incident light.

The absorbance can be interpreted as the logarithm of the reciprocal reflectance: $A=log(1/R)$.

The relationship between diffusively reflected spectral values involving the scattering of solid particles can be evaluated by means of the Kubelka-Munk mathematical transformation [27, 28]:

$$\mathbf{F(R) = \frac{(1-R)^2}{2R} = \frac{K}{S}} \qquad \textit{Eq. (2)}$$

where K is the absorption coefficient and S is the scattering coefficient. S depends on the number, size, shape, and refractivity of particles, while K depends on the absorbing species and the wavelength. It may be stated that R, the diffuse reflectance, is a function of the ratio K/S [29].

The relationship is a limiting equation, like Beer's Law, and can be applied with the following most important assumptions [30]:

- the distribution of the scattered light is uniform and specular reflection is ignored,
- the randomly distributed particles are smaller than the sample layer,
- the particles are much larger than the wavelength of the illuminated light (to ensure the independence of S from wavelength) [30].

Thus, the diffuse reflectance of solid samples can be measured at several wavelengths to obtain spectra and both chemical and physical information can be gathered on various properties, including material identity, concentrations of chemical constituents, physical characteristics and complex evaluation criteria. The universal capabilities of this method are based on statistical algorithms, through which it is possible to establish a correlation between spectral information and the foregoing parameters [31, 32].

3.4 Energy Dispersive X-ray Fluorescence Analyser (XRF)

This proceeding examines the elemental range from sodium (Na) to Uranium (U), with a concentration range from ppm to 100%.

An XRF instrument is typically comprised of an excitation source and a detection system. The principle is that an X-ray tube creates an incident X-ray, which excites the sample. Each element in the sample will fluoresce (or emit) a secondary X-ray at a characteristic energy. With its detection system, the amount and energy of fluoresced X-rays can be measured. In case the instrument is equipped by a software, it translates this information into the type and amount of each element present in the sample. A typical X-ray spectrum from an irradiated sample will display multiple peaks of different intensities. This proceeding is a fast and non-destructive method to the sample, it can be used for analysis and in the industry for control of materials. Depending on the application, XRF can be produced by using not only X-rays but also other primary excitation sources like alpha particles, protons or high energy electron beams [33].

3.5 Mini-tablets

Mini-tablets are considered to be a new innovative technological and therapeutical way within the solid dosage forms, with advantages. Their preparation is a new challenge in the technology of solid dosage forms, because of the small dimensions (suitable for multiparticulate dosage forms e.g. in chronotherapy, as they provide- right drugs, at right time; and effective healing; also in paediatrics).

According to its definition, mini-tablets are compacts with diameters between 2 and 3mm [34]; they are a multiple unit dosage form with a low risk of dose dumping and a high degree of dispersion in the gastrointestinal tract (GI tract) and reproducible bioavailability. One of the most important issues in the global development of medicines for children is the suitability and acceptability of the dosage form in relation to age [35-37].

In my work, mini-tablets came to focus, as flowability could be studied from new aspects. As the diameter of the die cavity is very small, good flowability - a factor influenced by the particle size - is especially important. The questions may arise as to whether the particle size influences the compactibility of the tablets and, if so, what is the optimum particle size. Both the force of compression and the particle size are very important since the volume of the die cavity and the diameter of the punches are very small, and the multiple-tip slim punches (resembling a number of needles side by side) can easily break under a higher force of compression [34].

In the relevant literature [34-49], numerous advantages of mini-tablets can be found; among the advantages we can mention:

- mini-tablets present many benefits over orally administered liquids,
- delivery of accurate dose,
- require fewer or less problematic excipients,
- dry product formulation would improve drug stability,
- maintaining steady plasma levels,
- from the industrial point of view the product is cost-effective,
- defined sizes and strengths can be easily produced ,
- convenience of administration and accurate dosing as compared to liquids, as they are easy to swallow (a positive aspect in paediatrics),
- rapid dissolution of drug and absorption which may produce a rapid onset of action,
- they tend to act as a good alternative to granules and pellets,
- their direct compression is possible (this is important in the case of water-sensitive drugs),
- their coating is possible (in a perforated coating pan or a fluid bed apparatus),
- complex release profiles are possible (e.g. the. initial and maintenance doses in one capsule),
- several chemically incompatible drugs can be compressed into mini-tablets, coated and combined in a single capsule,
- they may offer a solution in paediatrics (the guidelines of the European Medicine Agency (EMA) suggest the improvement of the health of children in the European Union (EU Paediatric Regulation, Regulation (EC) No 1901/2006 of the European Parliament and of the Council on medicinal products for paediatric use, amended by Regulation (EC) No 1902/2006)).

As a disadvantage it should be borne in mind, that high dose drugs could not be transformed into mini-tablets, and due to their small size the powder of these tablets tends to stick to the die or punch to a greater extent or the powder flow may get affected [47, 49].

4. MATERIALS AND METHODS

4.1 Materials

Sorbitol was chosen as model material, which is used worldwide as a filling agent for direct compression in the pharmaceutical and food industries. It is named after the sorbus tree or rowan, in whose berries it was first discovered. It has been found in a number of other fruits, in all of which it acts as a natural anti-freeze and sweetener. First synthesized in 1925, it is today produced commercially in the form of D-sorbitol by the catalytic hydrogenation of D-glucose [50].

Sorbitol is able to crystallise in different forms. This polymorphism is monotropic, i.e. some crystalline forms are unstable thermodynamically but stable in their molecular configuration.

Among applications, we may use it as:

- a humectant and a stabiliser, a cryoprotective agent,
- a non-fermentable extract,
- an aroma carrier,
- for lowering the freezing point,
- a non-cariogenic bulk sweetener suitable for diabetics,
- a sweetener approved for food use in the majority of countries,
- applications in animal-feed: feed for monogastrics, ruminants,
- applications in pharmaceutical and cosmetic applications: in liquid forms, solid forms, injectable forms,cosmetics, toothpastes,
- a humectant and a plasticiser for tobacco, papermaking, glues and adhesives, textile industry, leather industry, cream polishes, cellulose films,
- a complexing agent,
- miscellaneous properties: biological applications, casting, mortars and concrete,continuous liquid coolants, plastics industry,
- chemical aspects: chemical intermediate for the synthesis of Vitamin C [50-54].

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.

It is chemically inert excipient, is not metabolized by the human body; and can be used as an alternative to lactose, its natural fiber structure provides stable tablets with low friability [55, 56].

4.2 Methods

4.2.1 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.

Altogether 24 feature parameters were measured: area, length, breadth, convex perimeter, equivalent diameter, Feret-diameters (0;112,5;135;157,5;22,5;45;67,5;90), orthoFeret (Feret diameters, sometimes known as calliper diameters, may be defined as the orthogonal distance between a pair of parallel tangents to the feature at the specified angle to the scan), perimeter, roundness, as well as X Max (F0), X Min (F0), Y Max (F90) and Y Min (F90).

4.2.2 Morphological study

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

A Polaron sputter coating apparatus (Polaron Equipment, Greenhill, UK) was applied to induce electric conductivity on the surfaces of the samples. The air pressure was 1.3-13 mPa. The surfaces of the crystals were treated with gold for 60 s (coating thickness: 18 nm).

4.2.3 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.

4.2.4 Homogenization

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

4.2.5 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.

4.2.6 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.

Fig. 2 Pharma Test PTG-1 powder testing equipment

The PTG analysis provides:

- powder flow time of a pre-defined mass,
- powder cone volume,
- powder cone density,
- cone angle (angle of repose),
- flowability of 100 mg of product (Ph. Eur.),
- amount of sample (mg in a preset time),
- flow chart of sample (mg/time).

4.2.7 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: 48-50%
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 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). The rate of compression was 36 tablets/min at 15 kN, an air temperature of 24 °C and a relative humidity of 45%. The tablet mass was 400 mg.
The relationship between the upper punch force and the upper punch displacement during compression is represented as a force-displacement profile *(Fig. 3).*

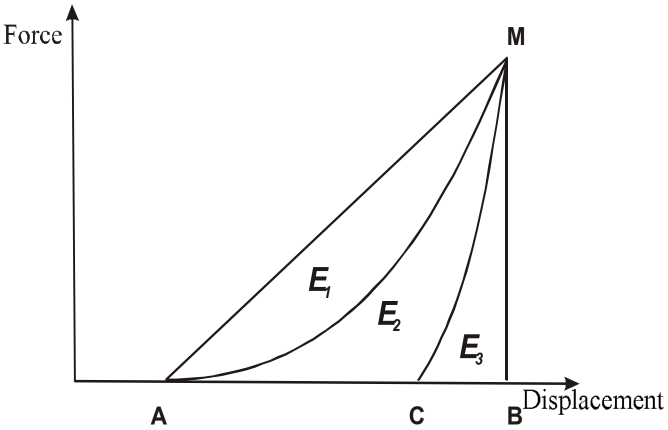


Fig. 3 Force-displacement diagram [57]

Figure 3 (above) depicts three regions. E_1 is the lost energy, corresponding to the rearrangement and packing in the die, E_2 is the energy of compaction and E_3 is the energy of elastic recovery [58].

The plastic behaviour of materials is very important in tablettability. Plasticity was described by the Stamm-Mathis relationship [58]:

$$Pl_{SM} = \frac{E_2}{E_2 + E_3} 100\% \qquad Eq.\ (3)$$

The compressibility factor ($Pr_{(mass)}$) (based on the compression data) was calculated via the following equation [57]:

$$Pr_{(mass)} = \frac{\sigma_x}{W_{spec}} = \frac{\sigma_x}{E_2 / m} \left(\frac{Pa}{Nmkg^{-1}} \right) \qquad Eq.\ (4)$$

where σ_x is the tensile strength and W_{spec} is the specific work. W_{spec} expresses the effective work *(E_2)* invested into the compression of unit mass *(m)* of the substance at a given compression. The tensile strength of the tablets was calculated according to Fell and Newton [59]:

$$\sigma_x = \frac{2 \cdot F}{\pi \cdot D \cdot h} \qquad Eq.\ (5)$$

where D is the diameter, F is the force and h is the thickness of the tablet.

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).

4.2.8 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).

Fig. 4 Dispersive X-ray fluorescence analyser
(MiniPal, Philips Analytical, Almelo, The Netherlands)

The advantage of this apparatus is that other equipment (e.g. TEM, SEM) is not necessary for determination of the elements. 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.

Characteristics of the measurements:

- Sample handling: Types of samples: powder, pressed; sample size: solids, 12 mm in diameter and< 40 mm in height; sample changer: 12 positions with removable tray.
- X-ray tube: Type: low-powered with side window; anode material: Rh; software controlled tube setting; voltage: 4-30 kV; current: 1-1000 μA, max. tube power: 9 W; tube filters: 5 filters selected by software.
- Detector: High-resolution Si-PIN diode (< 250eV at 5,9keV).
- He purge: to improve identification of low atomic number elements such as Na, Mg and Al.
- Inlet pressure: 1 bar
- Gas purity: 99.996 %
- Operating ambient temperature: 5-35 °C.

Measurement:

- Channel code: Mg; compound name: Mg
- Unit: ppm
- Line name: KA
- Measuring time: 600 s
- Condition set: 4 kV, 1000 μA, He purge, without filter
- Induced deep of Mg K_α : 20 μm

The measurements were repeated 5 - 10 times.

Some powder mixtures with different magnesium stearate contents were prepared for the calibration. The magnesium stearate contents were 2.1, 4.3, 8.5, 12.8 and 17.0 ppm.

The calibration demonstrated a linear model (k = 0.000667; r = 0.9533).

5. RESULTS AND DISCUSSION

Section I.

5.1 Measurement of particle size and shape

A light microscope combined with an image analysis system has proved valuable proceeding for particle size analysis.

White light itself can resolve particles within the range of 0.2 to 100 μm. This lower limit can be decreased to about 0.1 μm by the use of ultraviolet light and to about 0.01 μm by the use of the ultramicroscope [1].

According to the Leica Users' Manual, image analysis involves several separate stages: the image is acquired by the hardware, and converted into electrical form which is stored in the computer memory, or on a mass storage system such as a hard disc. Most cameras provide an analogue signal, which must be converted to digital format before it can be processed by the computer. A frame grabber - a small piece of hardware which consists of an analogue to digital converter and some memory to store the picture, - can also be used; possibly with local processor for control purposes. The image can be stored in the computer memory as an array of numbers, each particular number representing a particular shade of grey [12].

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 (this is the length of the longest Feret measurements), 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, as follows:

$$Roundness = (perimeter)^2/(4\pi\, area\ 1.064) \qquad Eq.\ (6)$$

$$Roughness = perimeter/convex\ perimeter \qquad Eq.\ (7)$$

Referring to Podczeck and co-authors [7, 8, 13]; and followers, Rashid, Heinamaki et al. [60], roundness as a shape factor gives a minimum value of unity for a circle in terms of the perimeter and area. (A perfectly round pellet gives a roundness factor of 1.0; the value increases as a function of the irregularity of the particle.)

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.

A roughness value of 1.0 indicates that a particle (sphere) has a smooth surface; the value increases as a function of the irregularity of particle [7, 8, 12, 13, 60].

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 [7].

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 5, 6, and 7* it can be stated, that the distribution of the various Sorbitol samples follows heterodisperse features.

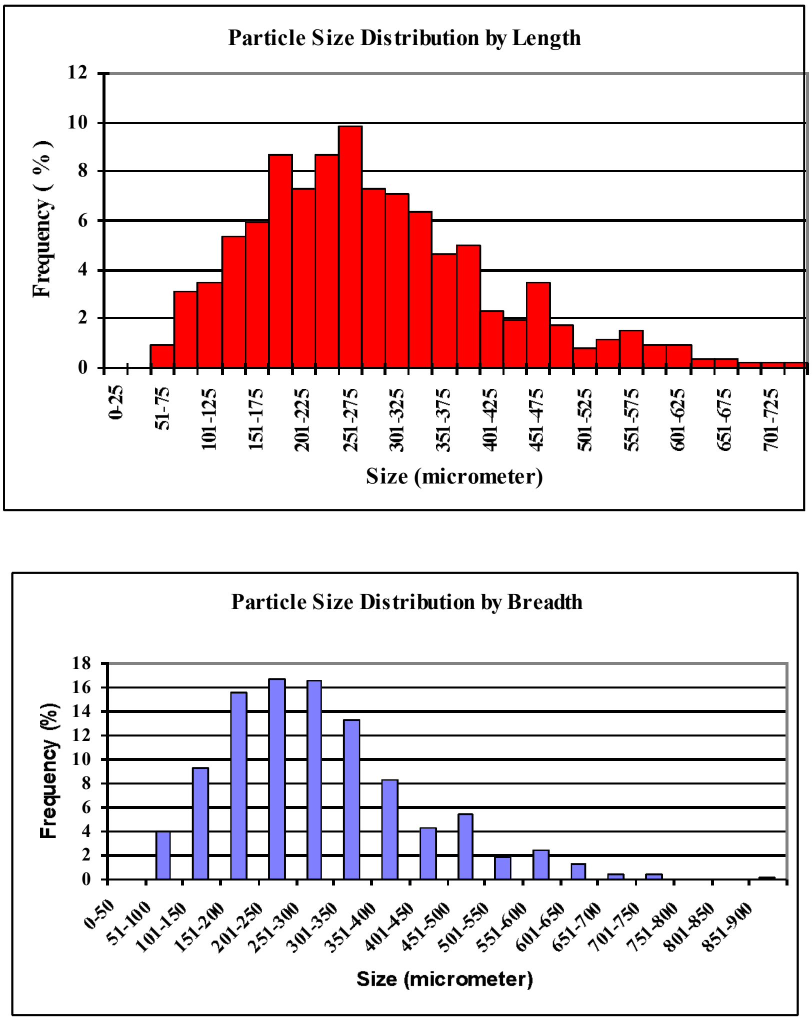
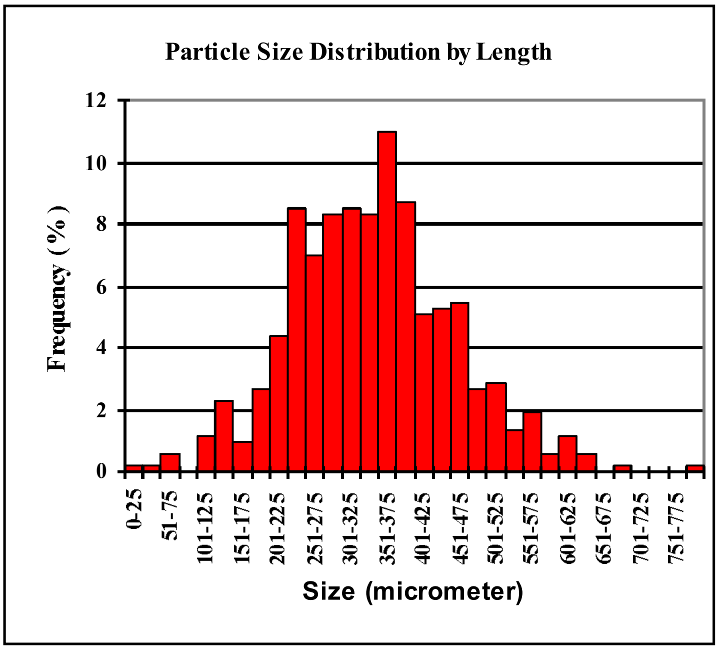


Fig. 5 Sample 1 - Histograms by Length and Breadth



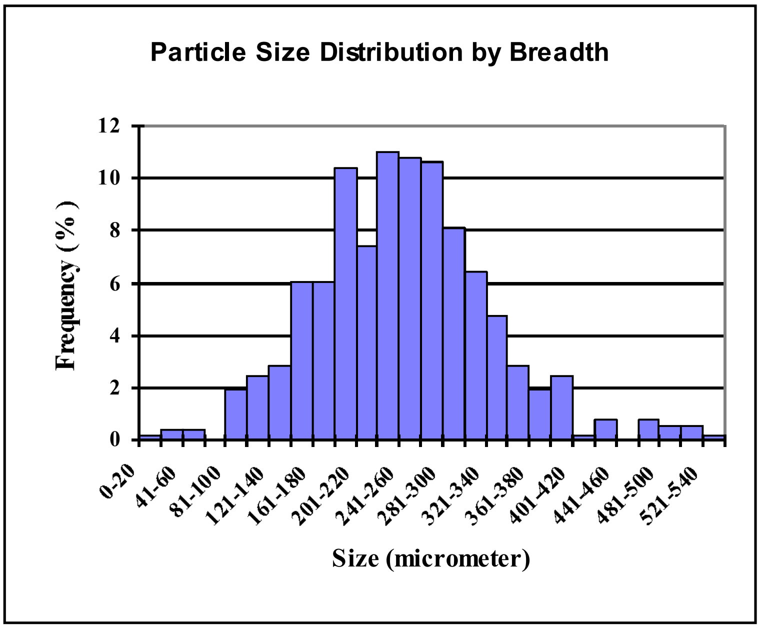


Fig. 6 Sample 2 - Histograms by Length and Breadth

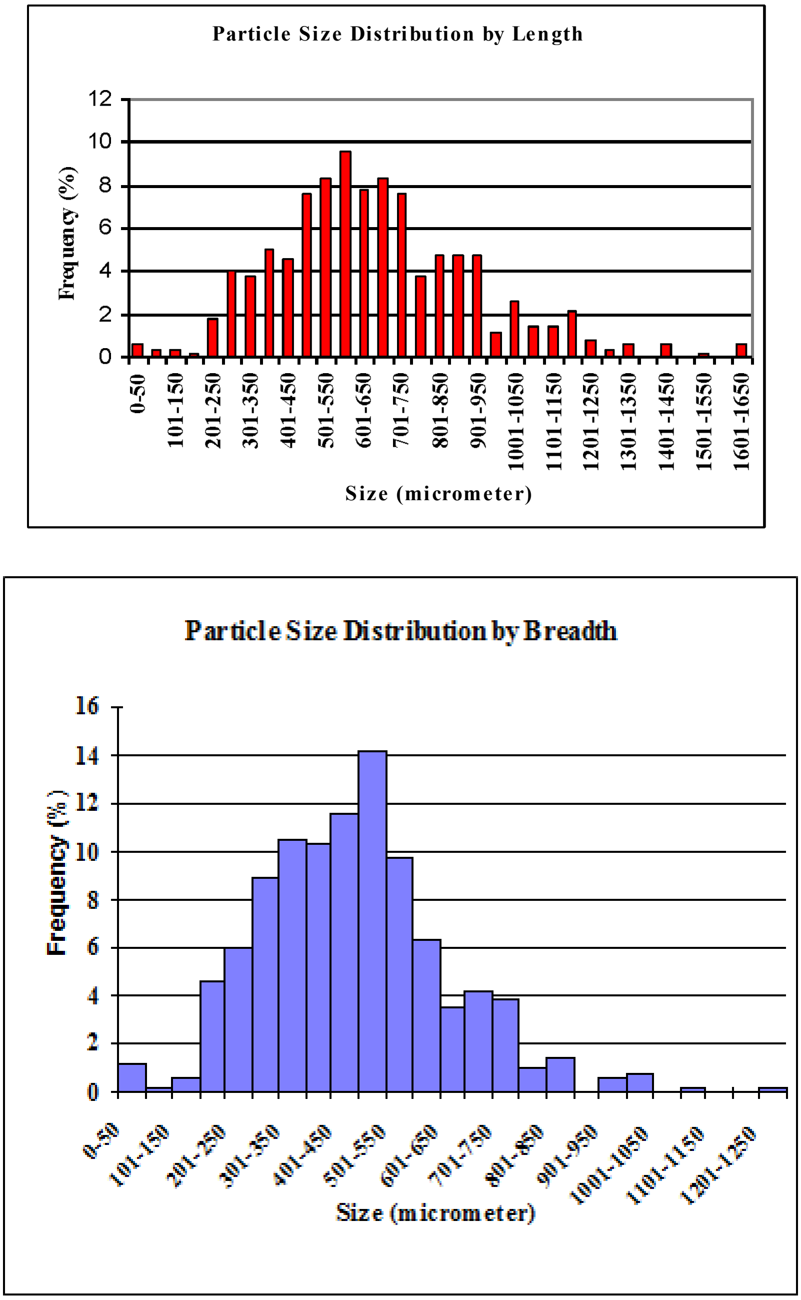


Fig. 7 Sample 3 - Histograms by Length and Breadth

Regarding the histogramms (by length and breadth) of the commercially available sorbitol samples (unsieved, bulk), it can be seen that particles form a heterodisperse system.

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.

Table 2 *Size ranges sieved from the samples*

Samples	**Fraction (µm)**
Sample 1*	315-400
	400-630
	630-1000
Sample 2**	315-400
	400-630
	630-1000
Sample 3**	315-400
	400-630
	630-1000

*stirring rate: 10 rpm; ** without stirring

5.2 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 8, 9, 10.* 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.

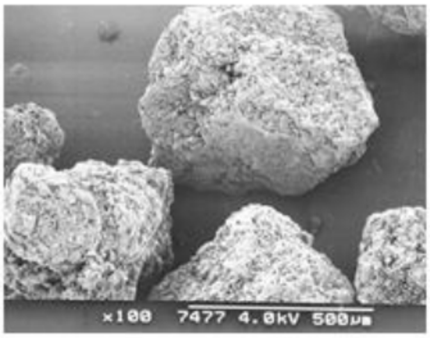


Fig 8 Sample 1

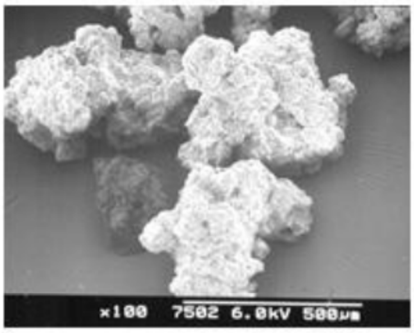


Fig 9 Sample 2

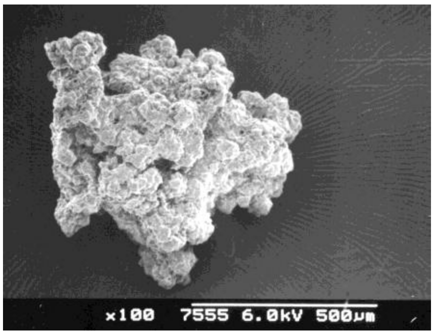


Fig. 10 Sample 3

By comparing the SEM photos of the rather irregular particles with the calculated roughness data, a strong relationship can be seen: the smoother surface has resulted in the smaller roughness data (see in *Table 1*).

5.3. Test by NIR Spectroscopy [61]

Fractions of the Samples were analysed with Near Infrared Spectroscopy.

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

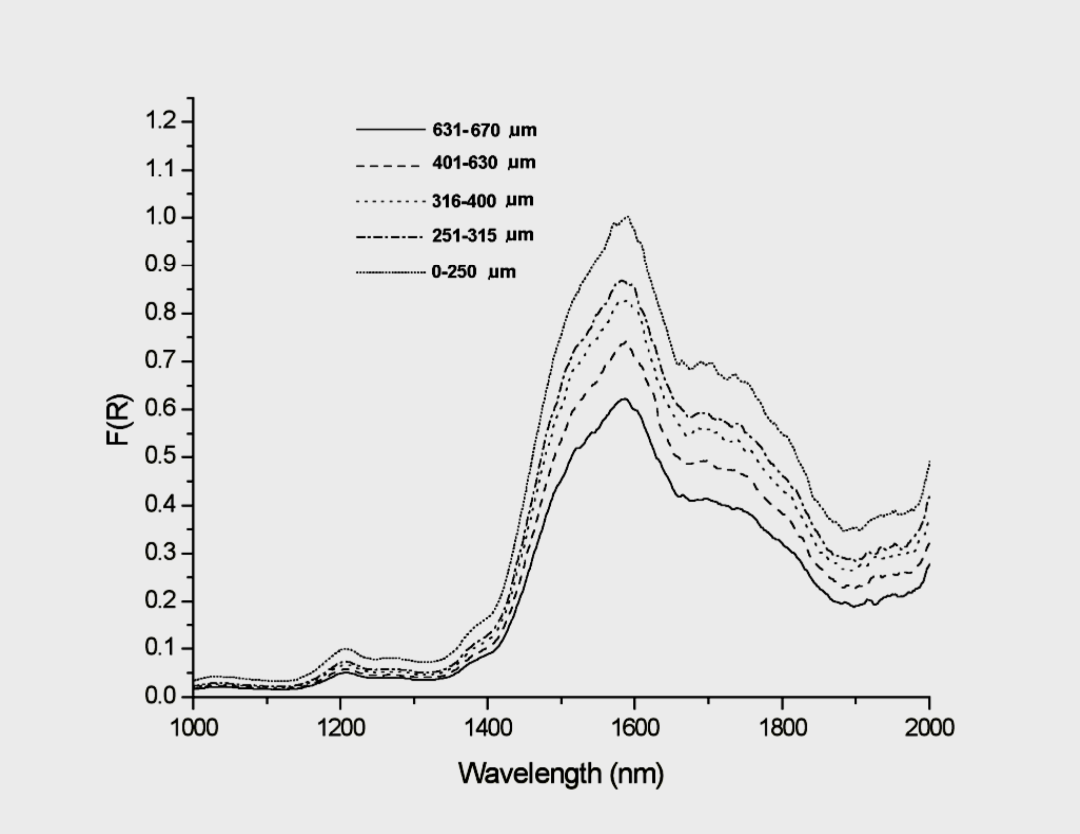


Fig. 11 Near infrared spectra of the sieved sorbitol fractions

Figure 11 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 12 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.

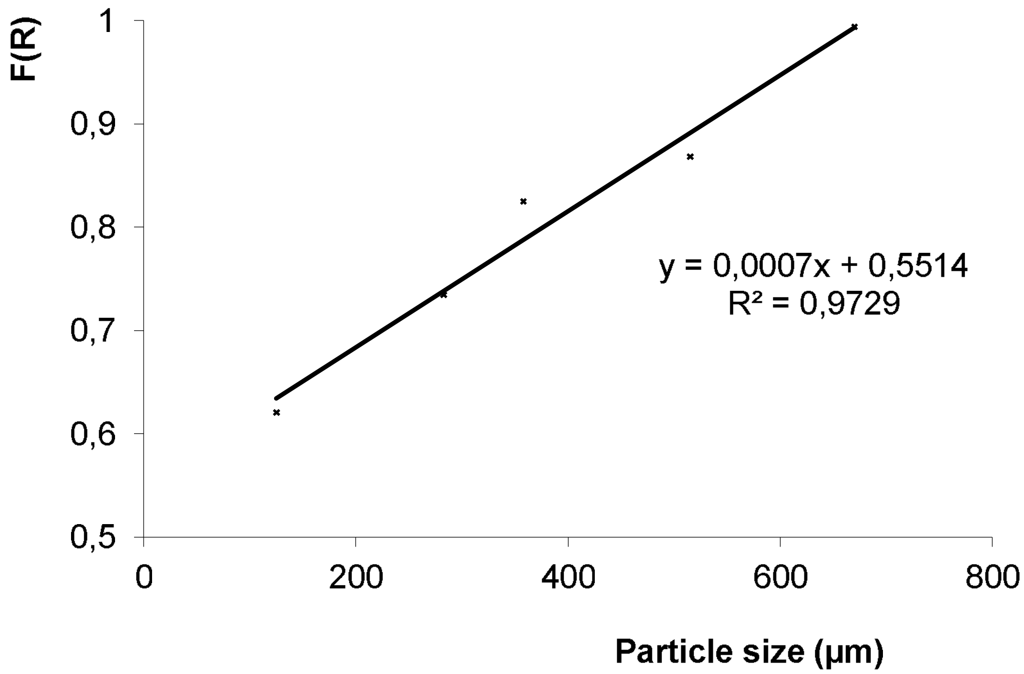


Fig 12 Relationship between particle size and NIR spectral data

In the early days of NIR spectrophotometric analysis, the results were usually interpreted as a function of log *1/R* rather than via the Kubelka-Munk relationship [30]; quantitative spectrometric analysis relies upon a linear relationship between the absorption or reflectance intensity and concentration [62].

However, our results indicate that, in the evaluation of the physical characteristics of solid sorbitol samples, the transformation of the spectral data in accordance with the Kubelka-Munk relationship can appropriately be used to find a good correlation between the particle characteristics and the diffuse reflectance data even at the single wavelength for the sorbitol samples tested. A linear relationship was also found between the mean particle size and the bulk density of the sieved fractions (*Figure 13).*

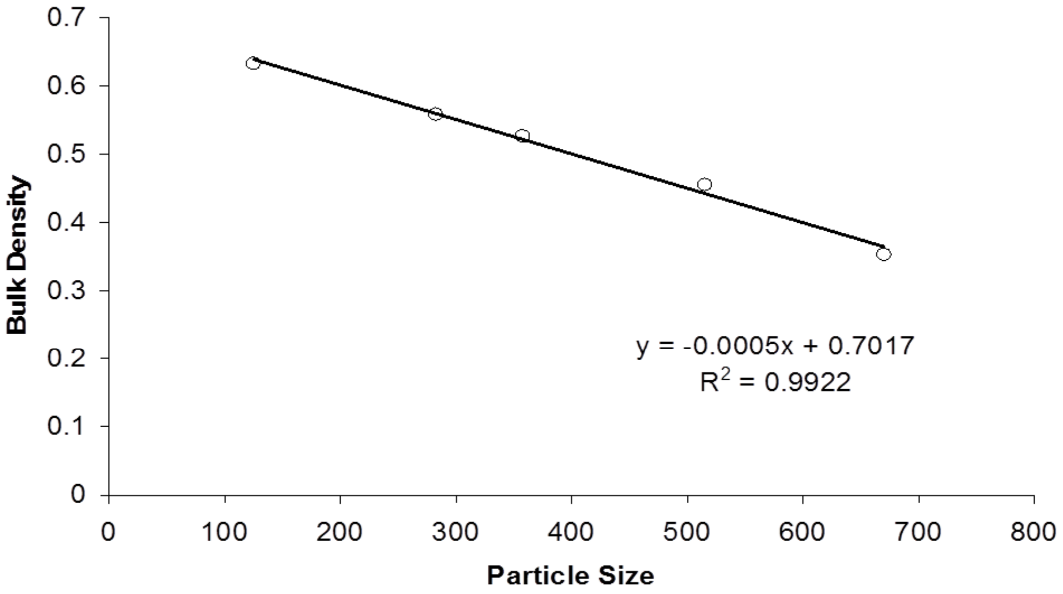


Fig. 13 Relationship between mean particle size and bulk density of sieved sorbitol fractions

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. Besides the exact size determination of the particles, the exact knowledge of their shape and surface was also in focus, as they have a strong effect on tabletting parameters.
The application of the method of scanning electron microscopy (SEM) was a suitable tool for the detection of the shape and the surface of the individual particles.

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 [4, 10, 11, 20-32, 62-64] 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.

5.4 The influence of the cohesion on the flowability characteristic [65]

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 [66]. No simple definition of good flowability is to be found in the literature, but it is known that flowability is influenced by the particle size and shape, the particle size distribution and the bulk density [18, 67, 68].

On the basis of these new possibilties, the relationship between the particle parameters and the flowability well deserves consideration.

5.4.1 Calculation of cohesional coefficient (C)

It is 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 **[**69, 70**]**. 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:

The mass of powder *(m)* which flows from the funnel is measured by a balance. It is determined by various parameters, as follows:

$$m = \rho \frac{\pi D^2}{4} h \qquad \textit{Eq. (8)}$$

where h is the height of the wall of orifice*,* D is the diameter of the orifice and ρ is the density of the powder (bulk).

The outflow of unit mass from the funnel can be described by the Second Law of Newton:

$$m\vec{a} = \sum_i \vec{F}_i \qquad \textit{Eq. (9)}$$

where m is unit mass of the powder, $\vec{a}$ is an acceleration vector, and $\vec{F}_i$ describes the forces. The forces involve gravitational force and frictional forces. The gravitational force acts in a downward direction:

$$F_{gravitational} = \rho \frac{\pi D^2}{4} hg \qquad \textit{Eq. (10)}$$

The forces of friction are caused by the interactions of the moving particles with the walls of the orifice and act in an upward direction:

$$F_{frictional} = C(\pi D)h \qquad \textit{Eq. (11)}$$

where C is the cohesional coefficient (including the friction coefficient between the particles and the wall of the orifice). The critical diameter D at which there is no flow can be calculated via the Newton equation of motion:

$$\rho \frac{\pi D^2}{4} ha = \rho \frac{\pi D^2}{4} hg - C\pi Dh \qquad \textit{Eq. (12)}$$

In the event of no flow, the acceleration of unit mass is zero.

This gives

$$D = \frac{4C}{\rho g h} \qquad \textit{Eq. (13)}$$

The cohesion force between the powder particles can be determined from the angle of repose *(α) (Fig. 14.)* [71]

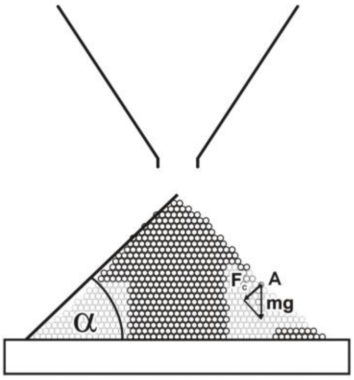


Fig. 14 Schematic presentation of parameters influencingcohesion force.

An individual particle at *A* on the surface of the cone is subjected to gravitational force *(mg)* in the downward direction and a cohesion force *(F_c)* in a direction perpendicular to the cone. When the particle is just about to move, the equation of motion can be expressed as follows:

$$mg \sin \alpha = C(F_c + mg \cos \alpha) \qquad \textit{Eq. (14)}$$

where *C* is the cohesional coefficient between the particles, α is the angle of repose and *m* is the mass of the particle. *Equation 14* shows that the more cohesive the powder, the larger the angle of repose. However, the cohesive stress, i.e. the cohesive force per surface area, is inversely proportional to *d,* the diameter of the particles. For the surface unit:

$$F_c = \frac{C}{d} mg \qquad \textit{Eq. (15)}$$

The solution of *equation 14* for *C* gives:

$$C = \frac{1}{2} d \left(\sqrt{\cos^2 \alpha + \frac{4 \sin \alpha}{d}} - \cos \alpha \right) \qquad \text{Eq. (16)}$$

The main characteristics of particles are presented in *Table 1* and the shape of the samples can be seen in *Figs 8, 9 and 10*. 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 3*).

The orifice of the equipment was 10 mm in all cases. The flow properties were tested without stirring.

Table 3. 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. A high deviation in particle size is unfavourable because it affects the flowability and the good filling in the die. If the deviation of the tablet mass is too high, there will be a high deviation in the active agent content in the tablets. 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 4.*

Table 4 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 4. 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 5*. 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 5 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

In order to characterize the most important particle parameters and flow properties, three commercial sorbitol samples were tested. 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.

As it was mentioned in the Introduction, 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.

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 [72] or in pediatrics [36, 37, 73]. They can be filled into capsules or further compressed into larger tablets; and the latest developments are the multiparticulate modified release dosage forms [74,75].

Section III.

5.5. Compactibility/compressibility study

5.5.1. *Study of the distribution of magnesium stearate* [76]

According to the practice of tabletting and the relevant literature [77-81], 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. They 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. Lubrication itself, in pharmacy, consists in adding a small amount of a lubricant to a powder or granule, this lubricant being a substance capable of eliminating the projections and thereby reducing friction when inserted between two rough surfaces [80-82].

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. Many researches, especially Rubinstein, have already dealt with the migration of magnesium stearate during tablet production [77-79; 83-86].

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. As mentioned above, the purpose of lubricants is to prevent two solids from making contact wich each other, or at least to limit such contact. Lubrication is also a surface phenomenon [83,84]. For this reason, the upper and lower surfaces of the tablets were analysed by energy dispersive X-ray fluorimeter.

The spectrum can be seen in *Figure 15*, and the relevant data are displayed in *Table 6.*

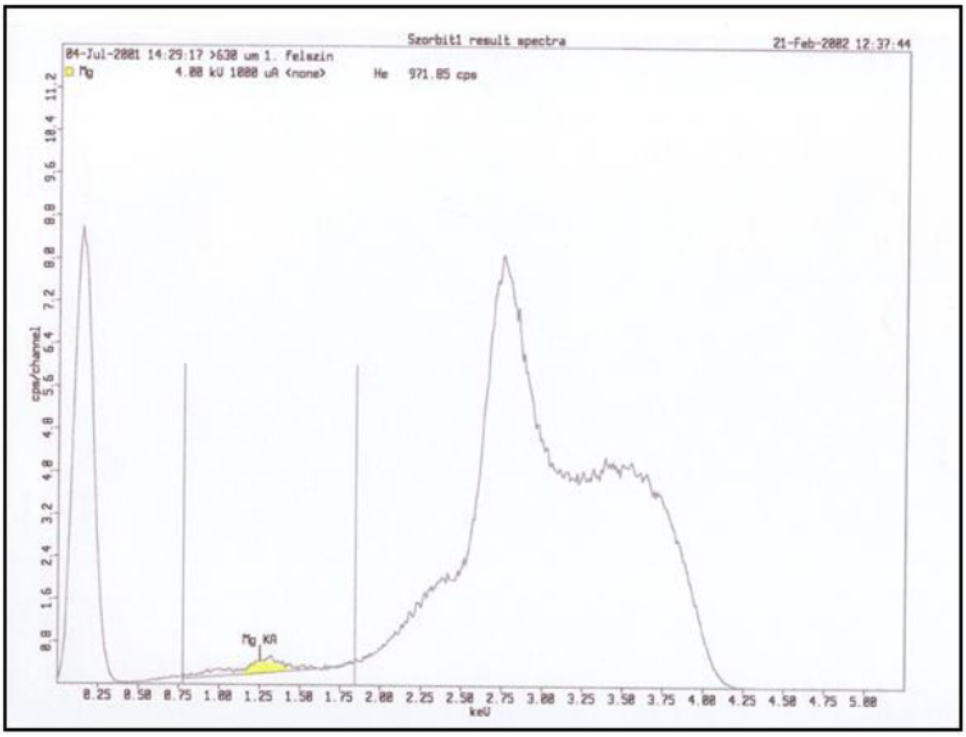


Fig. 15 X-ray energy dispersive spectrum of magnesium stearate

Table 6 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. It can be steated that 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 7.*

Table 7: 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. Measurement with the energy dispersive X-ray spectrometer is very simple and the evalution of the results is very easy, other equipment (e.g. TEM, SEM) is not necessary for the determination of the elements. The preparation is very simple and the measurement is very rapid.

5.5.2. 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 of my Ph.D. Thesis, 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.

Previously, the influence of the cohesion coefficient on the flowability of particles of sorbitol different sizes was presented *(see in Chapter 5.4)*. This coefficient can be applied very well in the development of solid dosage forms, and especially in the case of mini-tablets **[**35-49, 87**]**.

Later, the effects of particle size on the compactibility of normal sorbitol samples were investigated, and a mathematical model for mini-tablets through the extrapolation of the compression data was developed.

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 8.*

Table 8. 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

The principles and details of the method of compression were presented in *Chapter 4.2.7.*

The rate of compression was 35 tablets/min at 15 kN, an air temperature of 26 °C and a relative humidity of 48%. The tablet mass was about 400 mg, and the diameter of punches was 10 mm.

The masses of the tablets were measured with an analytical balance with an accurancy of 1 mg. 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 [88].

Table 9 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 10 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 9 and 10)* 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 10)* were higher than those of the mixture containing 50% sorbitol (*Table 9)* 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 10*), 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 11.*

Table 11 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 [89] 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,* magnesium stearate being well known to be more extensively distributed on the surface of the tablet. According to our findings, in the interior of the tablet, the degree of distribution of magnesium stearate depends on the particle size *(see in Chapter 5.5.1)*.

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 9, 10, and 11* 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.

5.5.3. 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 [90], but this is not valid in the case of mini-tablets [87]. 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:

$$\frac{2 \cdot F}{\pi \cdot D \cdot h} = \frac{2F^m}{\pi \cdot D^m \cdot h^m} \qquad \textit{Eq.(17)}$$

$$\frac{\sigma_x}{E_2 / m} = \frac{\sigma_x^m}{E_2^m / m^m} \qquad \textit{Eq. (18)}$$

$$\frac{E_2}{E_2 + E_3} = \frac{E_2^m}{E_2^m + E_3^m} \qquad \textit{Eq. (19)}$$

where ^{m} denotes the corresponding values for the mini-tablets. From *equation 17*, the size of the breaking force of the mini-tablet can be calculated as

$$F^m = \frac{D^m \cdot h^m}{D \cdot h} \cdot F \qquad \textit{Eq. (20)}$$

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:

$$F^m_{pressure} = \frac{F^m}{F} \cdot F_{pressure} \qquad \textit{Eq. (21)}$$

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 (18) and (19),* respectively, via the forms

$$E_2^m = \frac{m^m}{m} \cdot E_2 \qquad \textit{Eq. (22)}$$

$$E_3^m = \left(\frac{E_2 + E_3}{E_2} - 1 \right) \cdot E_2^m \qquad \textit{Eq. (23)}$$

The extrapolated values are listed in *Tables 12, 13 and 14* 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 12 Important compression parameters extrapolated to mini-tablets 3 mm in diameter (Samples 1-4)

Sample	**Fraction** (μm)	***E₂*** (Nm)	***E₃*** (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 13 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 14 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.

6. 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.
- ➢ 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.

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ACKNOWLEDGEMENTS

First of all, let me express my warmest gratitude and honour to my supervisor **Prof. Dr. Klára Pintye-Hódi** for her support during my Ph. D. work.
I am grateful for her wisdom, help, patience and ideas during the experimental work, the publications and the preparation of my Thesis.

I would like to say thanks to
Prof. Dr. Piroska Szabó-Révész and **Prof. Dr. István Erős; -** present and former Heads of the Ph.D. Programme in the Institute of Pharmaceutical Technology, Faculty of Pharmacy, University of Szeged - for providing me with the possibility to start and to complete my Thesis under their guidance, as well as for their encouragement, kindness, help and good pieces of advice.

I would like to express my kindest thanks to my co-authors, especially to
Dr. István Antal Ph.D. and Dr. András Kelemen Ph.D. for their collaboration and help in this work.

I have to say thanks to all the members of the Staff in the Department of Pharmaceutical Technology with whom I worked together for their help and kindness.

I owe my thanks to **my Family** – especially to **my Mother, Dr. Anna Szalay-Szabó** – for their love, support, encouragement and understanding attitude during these years; and to my Husband, András Czeglédi for encouraging me to finish the Thesis.

I dedicate this work to my little Daughter, Annamária Czeglédi-Szalay, hoping that it will inspire Her during her forthcoming schools, education and studies…

ANNEX

Related articles

I

Study of the Distribution of Magnesium Stearate with an Energy Dispersive X-ray Fluorescence Analyser

Annamária Szalay[a], Klára Pintye-Hódi[a], Katalin Joó[b], and István Erős[a]

Department of Pharmaceutical Technology, University of Szeged[a], Szeged (Hungary),
and Testor GmbH[b], Budapest (Hungary)

Summary

The formulation of tablets requires various auxiliaries. One group of these ingredients is the lubricants, which prevent tablets from sticking to the die and punches and minimize their wear. In the pharmaceutical industry, one of the well-known and probably the most widely used lubricants is magnesium stearate. Its use is considered essential, as magnesium stearate forms a film of low shear strength between the die wall and the compact and reduces friction; it has few properties which negatively influence the overall.

The aim of this work was to study whether particle size of sorbitol has any effect on the distribution of magnesium stearate in a tablet during compression. The distribution of magnesium stearate on the surface of the particles was measured with an energy dispersive X-ray fluorescence analyser.

Zusammenfassung

Untersuchung der Verteilung von Magnesiumstearat mit einem Röntgen-Fluoreszenz-Analysator

Bei der Tablettierung ist es notwendig, ein Schmiermittel zu verwenden, das die Tabletten vor dem Festkleben an der Matrize und den Stempeln schützt und den Abrieb vermindert. In der pharmazeutischen Industrie ist Magnesiumstearat eines der am weitesten verbreiteten und am häufigsten verwendeten Schmiermittel. Es wird als unverzichtbar angesehen, weil es zwischen Maschinenteilen und dem zu verpressenden Material einen Film mit niedrigen Scherkräften bildet und die Reibung vermindert; dabei hat es nur wenige Eigenschaften, die sich nachteilig auswirken.

Ziel dieser Arbeit war es, zu untersuchen, ob die Korngrößen von Sorbitol bei der Tablettierung einen Einfluß auf die Verteilung von Magnesiumstearat haben. Die Verteilung von Magnesiumstearat auf den Partikeln wurde mit einem Energiedispersions-Röntgen-Fluoreszenz-Analysator bestimmt.

Key words

- **Magnesium stearate**
- **Sorbitol, particle fractions, tabletting**
- **Tabletting lubricants, magnesium distribution**
- **X-ray fluorescence analysis**

Pharm. Ind. 66, No. 2, 221–223 (2004)

1. Introduction

Lubricants 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. Lubrication itself, in pharmacy, consists in adding a small amount of a lubricant to a powder or granule, this lubricant being a substance capable of eliminating the projections and thereby reducing friction when inserted between two rough surfaces [1–3].

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. Many researchers, especially Rubinstein, have already dealt with the migration of magnesium stearate during tablet production [4–10].

Pharm. Ind. 66, Nr. 2, 221–223 (2004)

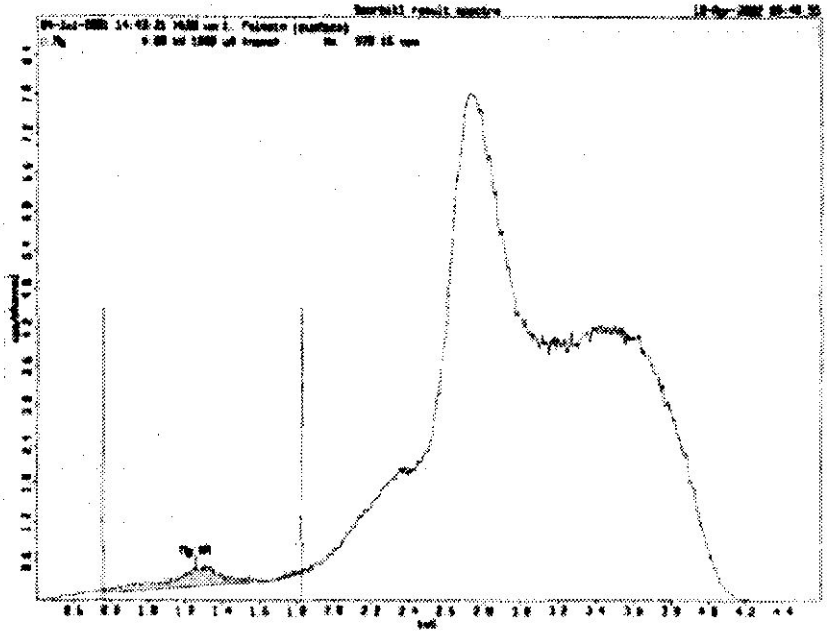

Fig. 1: X-ray energy dispersive spectrum.

The aim of this work 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.

The advantage of this new apparatus is that other equipment (e.g. TEM, SEM) is not necessary for determination of the elements. The preparation is very simple and the measurement is very rapid.

2. Material and methods

2. 1. Materials

Various fractions of sorbitol (Ph.Eur.), sorted according to size with a vibration sieve, comparised the basic substance: 250–315, 316–400, 401–630, and 601–1000 µm. Magnesium stearate (Ph.Eur) was used as lubricant in a quantity of 1 %. The specific surface area of the magnesium stearate was 0.69 m^2/g (BET, Brunauer-Emmett-Teller method).

2.2. Sieving

Analytical sieve (Retsch, Haan, Germany) with variable sieve apertures of 250, 315, 400, 630 and 1000 µm was used to obtain various fractions of the sorbitol sample. The individual sieving time was 5 min.

2. 3. Mixing

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

2.4. Compression

Compression was carried out with a Korsch EK0 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.

Parameters:
Pressure force (upper punch): 15 ± 1 kN
Relative air humidity: 48–50 %
Air temperature: 26 °C
Rate of pressing: 35 tabl./min
Extent of compression: 3 × 10 tablets

2.5. X-ray analysis

X-ray analysis was carried out with an energy dispersive X-ray fluorescence analyser (MiniPal, Philips Analytical, Almelo, The Netherlands). The spectrum was evaluated by non-linear least squares fitting, based on the AXIL algorithm developed at the University of Antwerp.

- Sample handling: Types of samples: powder, pressed; sample size: solids, 12 mm in diameter and < 40 mm in height; sample changer: 12 positions with removable tray.
- X-ray tube: Type: low-powered with side window; anode material: Rh; software controlled tube setting; voltage: 4–30 kV; current: 1–1000 µA, max. tube power: 9 W; tube filters: 5 filters selected by software.
- Detector: High-resolution Si-PIN diode (< 250 eV at 5.9 keV).
- He purge: to improve identification of low atomic number elements such as Na, Mg and Al.
- Inlet pressure: 1 bar

Table 1: 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)

Table 2: 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)

- Gas purity: 99.996 %
- Operating ambient temperature: 5–35 °C.
- Measurement:
  Channel code: Mg; compound name: Mg
  Unit: ppm
  Line name: KA
  Measuring time: 600 s
  Condition set: 4 kV, 1000 µA, He purge, without filter
  Induced deep of Mg K_α: 20 µm
  The measurements were repeated 5–10 times.

Some powder mixtures with different magnesium stearate contents were prepared for the calibration. The magnesium stearate contents were 2.1, 4.3, 8.5, 12.8, and 17.0 ppm.

The calibration demonstrated a linear model ($k = 0.000667$; $r = 0.9533$).

3. Results

As mentioned above, the purpose of lubricants is to prevent two solids from making contact with each other, or at least to limit such contact. Lubrication is also a surface phenomenon. For this reason, the upper and lower surfaces of the tablets were analysed.

The spectrum can be seen in Fig. 1 and the data are displayed in Table 1. 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. It can be stated that 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 2.

It can be seen from 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).

4. Discussion

Finally, 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. Measurement with the energy dispersive X-ray spectrometer is very simple and the evaluation of the results is very easy.

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Acknowledgements

This work was supported by Testor and by Philips Analytical.

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Editor-in-chief: Viktor Schramm, Claudius Arndt. Publisher: ECV · Editio Cantor Verlag für Medizin und Naturwissenschaften GmbH, P.O.B. 12 55, 88322 Aulendorf (Germany), Phone +49 (0) 7525-9400, Fax +49 (0) 7525-940 180; e-mail: redaktion@ecv.de; http://www.ecv.de. Printed by VeBu Druck + Medien GmbH, Am Reutele 18, 88427 Bad Schussenried (Germany).

Terms of supply: The journal is published monthly and can be obtained from the publisher or via bookstores. Rates per annum for the print + online subscription (VAT included, minimum 12 issues): *Germany:* 193.– € plus 25.– € postage. *Abroad (Europe* with *VAT ID number)*: 199.07 € plus 30.17 € postage (air mail: 94.82 €). *Abroad (Europe* without *VAT ID number and other countries)*: 213.– € plus 35.– € postage (air mail: 110.– €). Price for a single copy: 35.– € plus postage. Please ask for extended network licences. A subscription remains legally valid unless it is cancelled at 3 months notice for the end of the period of computation. Free specimen copies are supplied by the publisher upon request.

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II

Technical Note:
Study on the Relationship between Particle Size and Near Infrared Diffuse Reflectance Spectroscopic Data

Annamária Szalay*, István Antal, Zsolt Zsigmond***, Sylvia Marton**, István Erős*, Géza Regdon jr.*, Klára Pintye-Hódi***

(Received: 22 July 2003; in revised form: 8 December 2004; accepted: 8 July 2005)

Abstract

Since the particle size distribution is a critical parameter of pharmaceutical excipients used for tablet manufacturing by direct compression, the mean particle size of sieved sorbitol powder was studied by near-infrared diffuse reflectance spectroscopy (NIRDRS).

The aim of this study was to investigate the effect of the particle size (reciprocally proportional to the bulk density) on the reflectance spectrum. The effects of the particle characteristics on the spectral changes were described on the basis of the Kubelka-Munk theory taking the scattering into consideration. A smaller particle size fraction was associated with a lower spectral value, and at the characteristic wavelength of 1584 nm a linear relationship was established for the particle size range from 125 to 670 μm. The diffuse reflectance measurement was sensitive to the particle characteristics, which offers a fast, non-destructive alternative test method that can be applied after detailed calibration.

Keywords: diffuse reflectance, linear relationship, near-infrared spectroscopy, particle size of sorbitol

1 Introduction

The physical properties of pharmaceutical excipients used for direct tablet compression, such as the average particle size, the flowability, and the sphericity, are usually tested during the in-process control of the manufacturing [1]. Control of the particle characteristics is therefore important in ensuring the processability. With the steadily increasing importance of direct compression during the past few years, many new excipients with interesting tableting properties have become commercially available.

Direct compression is the most economic, energy efficient, and expeditious tableting method because it involves the least handling of the materials. No drying steps are involved (as in wet granulation), the effects of heat and moisture on the drugs are eliminated, and the optimization of tablet disintegration is straightforward. However, in many cases the flexibility in the formulation of high-dose drugs has to be compromised. When low-dose drugs are processed by direct compression, problems of segregation and of content uniformity are also common. In order to be suitable for direct compression, an excipient must possess good flowability, favourable mixing properties, and high cohesion after compression. The particle size and particle size distribution influence these properties.

The particle size of a drug has fundamental effects on two important features in solid dosage formulation: the dose uniformity and the dissolution rate.

Small particles are particularly important in low-dose, high-potency tablets, since large particle populations are necessary to ensure adequate blend homogeneity, and for any drug whose aqueous solubility is poor, since the dissolution rate is directly proportional to the surface area. The cohesion, adhesion, and powder flow are also dependent on the particle size.

The particle characteristics of pharmaceutical excipients have therefore been the focus of interest during recent

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DOI: 10.1002/ppsc.200500870

decades. The literature contains numerous methods for measurement of the size and shape of powder particles. Accurate measurements or estimates of particle size are important because the quality and performance of most powder-based dosage forms are closely related to the size distribution of the fine particles. It should be borne in mind that the measurement of particle size and particle size distribution is difficult and complex [2].

2 Near Infrared Spectroscopy

Among the numerous techniques for the measurement of particle features (e.g., sieving, optical and electron microscopy, powder flowability analysis, laser diffraction spectroscopy, etc. [3–5]), near-infrared (NIR) spectroscopy is a relatively new alternative method which is playing an increasing role in manufacturing as industry strives to improve quality and process efficiency while reducing costs. The wavelength range that constitutes the NIR region of the electromagnetic spectrum and the demarcation of that range from other spectral regions are somewhat indistinct. NIR is interpreted by BL-Analytics as the area between the visible and the infrared regions, thus covering the range from around 800 nm to 2500 nm.

The absorption bands observed in NIR spectra originate from overtones of hydrogen-stretching vibrations or from combinations of stretching and bending modes of vibration [6]. Since the absorption in the NIR region is much weaker than in the middle-IR region, NIR spectra can be obtained by direct measurement on samples without dilution, an integrating sphere being used to measure the diffuse reflection [7].

As the reflectance of solid samples varies with the concentration, absorptivity, and scattering coefficient according to the Kubelka–Munk theory [8], the NIR spectrum of a solid material depends both on its chemical composition and on its physical properties, such as the particle size and surface characteristics [9,12].

Reflection spectroscopy is the study of light reflected from the surface of a sample rather than the light transmitted through the sample. Light reflection can be either specular or diffuse. Diffuse reflection is reflection that occurs in all directions from the surface as a result of absorption and scattering processes.

The reflectance *($R\%$)* can be introduced by analogy to transmittance:

$$R\% = \left(\frac{I_R}{I_O}\right) * 100 \tag{1}$$

where I_R is the intensity of the diffusely reflected light collected by the integrating sphere, and I_0 is the intensity of the incident light.

The absorbance can be interpreted as the logarithm of the reciprocal reflectance: $A = log(1/R)$.

The relationship between diffusively reflected spectral values involving the scattering of solid particles can be evaluated by means of the Kubelka-Munk mathematical transformation [13, 14]:

$$F(R) = \frac{(1-R)^2}{2R} = \frac{K}{S} \tag{2}$$

where K is the absorption coefficient and S is the scattering coefficient. S depends on the number, size, shape, and refractivity of particles, while K depends on the absorbing species and the wavelength. It may be stated that R, the diffuse reflectance, is a function of the ratio K/S [15].

The relationship is a limiting equation like Beer's Law, and can be applied with the following most important assumptions [16]:

- the distribution of the scattered light is uniform and specular reflection is ignored
- the randomly distributed particles are smaller than the sample layer
- the particles are much larger than the wavelength of the illuminating light (to ensure the independence of S from wavelength).

Thus, the diffuse reflectance of solid samples can be measured at several wavelengths to obtain spectra, and both chemical and physical information can be gathered on various properties, including material identity, concentrations of chemical constituents, physical characteristics, and complex evaluation criteria. The universal capabilities of this method are based on statistical algorithms, through which it is possible to establish a correlation between spectral information and the above parameters [17, 18].

The aim of this study was to find a relationship between the particle size and NIR spectroscopic data by studying the diffuse reflectance of sorbitol.

3 Experimental

Sorbitol was used as a model material for study of particle size by NIR spectroscopy.

Sorbitol is commercially available in the form D-sorbitol, obtained by the catalytic hydrogenation of D-glucose. Sorbitol has very attractive characteristics for pharmaceutical technology, such as its cooling effect, compressibility, rapid dissolution, and pyrogen-free grade.

It can be directly compressed and it is used as a filler and binder in chewable tablets. It forms a relatively hard compact; it has a cool taste and a good mouth-feel. Its major disadvantage is its hygroscopic nature. If used in an area of high relative humidity, crystalline sorbitol loses its free-flowing character, clumps in the feed frame, and causes sticking on the surface of the die table. Moisture-resistant packaging is essential for sorbitol-containing tablets.

Five size fractions, obtained from a sample (Sorbitol Ph.Eur.) by using an analytical sieving machine (Retsch GmbH & Co., Haan, Germany), were tested: 0–250 μm, 251–315 μm, 316–400 μm, 401–630 μm, and 631–710 μm. The individual sieving time was 5 min.

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.

4 Discussion

Figure 1 reveals that all the spectra 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, and are due to the different extents of light reflectance. Smaller particles have a smaller *K/S* ratio, a lower absorbance, and hence a higher *R*. Figure 2 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.

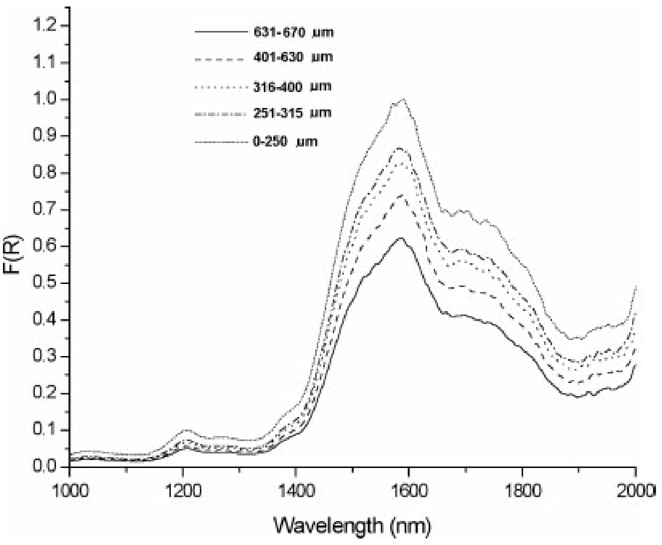

Fig. 1: Near-infrared spectrum of sieved fractions of sorbitol.

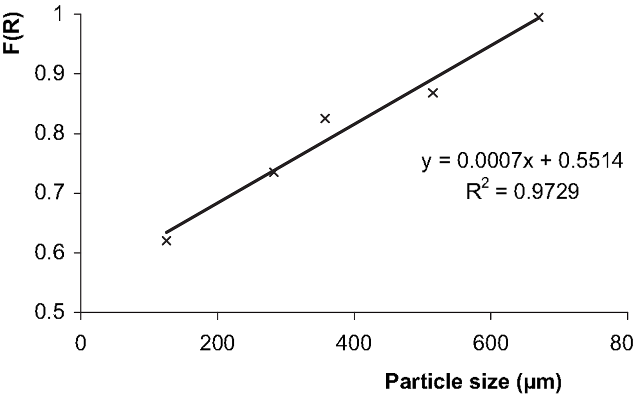

Fig. 2: Relationship between particle size and NIR spectral data.

In the early days of NIR spectrophotometric analysis, the results were usually interpreted as a function of log *1/R* rather than via the Kubelka-Munk relationship [16]; quantitative spectrometric analysis relies upon a linear relationship between the absorption or reflectance intensity and concentration [19].

However, our results indicate that in the evaluation of the physical characteristics of solid sorbitol samples the transformation of the spectral data in accordance with the Kubelka-Munk relationship can be appropriately used to find a good correlation between the particle characteristics and the diffuse reflectance data, even at the single wavelength for the sorbitol samples tested. A linear relationship was also found between the mean particle size and the bulk density of the sieved fractions (Figure 3).

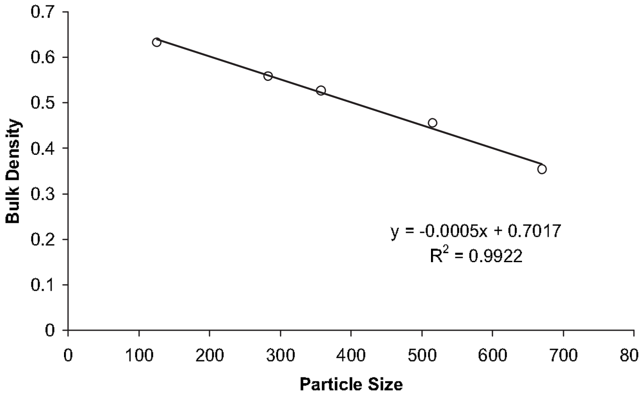

Fig. 3: Relationship between mean particle size and bulk density of sieved sorbitol fractions.

5 Conclusions

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.

6 Acknowledgement

This work was supported by Hungarian Scientific Research Fund (OTKA) grant T-043025.

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III

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Contents lists available at ScienceDirect

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The influence of the cohesion coefficient (C) on the flowability of different sorbitol types

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ABSTRACT

Particle size and shape play important roles in the powder industries, including the pharmaceutical industry. It is widely accepted that the flow properties of most powder-based products are closely related to the size distribution of the fine particles. Cohesion forces act between the particles, and friction forces between the particles and the walls of a funnel, which influence the flow properties. The higher the friction/cohesion force, the poorer the flowability, but free flow is essential during capsule filling or tableting processes. Good flowability is especially important during the manufacturing of minitablets where the diameter of dies is very small and the filling time is also very short. The development of a dosage form is based on a factorial design, but the flow properties are influenced by a number of parameters, including particle size, roundness, roughness, flow time and angle of repose. Accordingly, we looked for a cohesion coefficient which takes these parameters into account and can easily be used in the design process, and set out to determine the relationship between the small diameter of the die, which is a critical parameter in the compression of minitablets, and the cohesion coefficient.

In this work, different forms of commercial sorbitol were chosen as model material: sorbitol is frequently used as a filler in the preparation of capsules and tablets. The morphological parameters and particle size distributions were tested. Different size fractions were separated by sieving, their powder rheological parameters were determined and the cohesion coefficients were calculated.

Keywords: Sorbitol; Shape factor; Flowability; Mass flow; Funnel flow; Cohesion coefficient

1. Introduction

A 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 (Leuenberger and Lanz, 2005). No simple definition of good flowability is to be found in the literature, but it is known that flowability is influenced by the particle size and shape, the particle size distribution and the bulk density (Prescott and Barnum, 2000; Liu et al., 2012; Saw et al., 2013). It is especially important in the case of the 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 (Abd El-Gawad et al., 2012) or in paediatrics (Breitkreutz, 2008; Bain, 2009). They can be filled into capsules or further compressed into larger tablets. The latest developments are the multiparticulate modified release dosage forms (Vuong et al., 2008; Dey et al., 2008).

On the other hand, 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. The prediction of the smallest diameter of die has been suggested.

Accurate measurements or good estimations of particle size are important. Moreover, it should be borne in mind that the measurement of particle size and particle size distribution is difficult and complex, andthe use of different particle

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http://dx.doi.org/10.1016/j.cherd.2014.05.008
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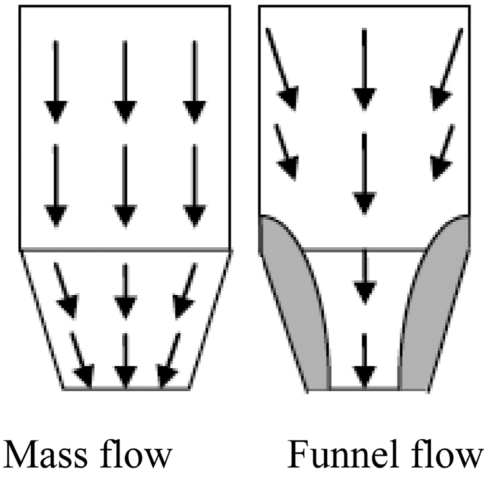

Fig. 1 – Types of flow through a funnel (Faqih et al., 2007)

size principles can lead to different results (Kaye and Trottier, 1995; Podczeck and Révész, 1993; Podczeck and Miah, 1996). Many authors have studied the advantages and disadvantages of various methods for particle size analysis (Podczeck, 1997; Fu et al., 2012; Povey, 2013). Laser diffraction is a method that is very frequently used to measure particle size and particle size distribution. Visual observation (a light microscope or a scanning electron microscope (SEM)) is also very important. A microscope equipped with an image analysis system is suitable to test the shape parameters and dimensions of particles, and it is possible to determine the roundness and roughness of the particles, these parameters influencing the flow properties.

In flowability studies, the angle of repose is considered to be a parameter that can be measured well. An inverse relationship has been reported between the particle size and the angle of repose (Hedge et al., 1985). Besides the angle of repose, powder flow can be described by the flow time, the Carr index and the Hausner ratio.

Powder flow can be characterized in two ways: as *mass flow*, when the particles can flow comparatively easily, as the cohesion between the particles is very low; and as *funnel flow*, when the particles flow much more poorly as the frictional forces acting at the funnel wall and the cohesion between the particles are much higher (Faqih et al., 2007) (Fig. 1).

In the case of mass flow, all of the powder particles in the funnel are in motion (Prescott and Barnum, 2000; Fitzpatrick et al., 2004). In the case of funnel flow, the central core of powder flows from the funnel first, followed by the remaining powder from closer to the walls of the funnel. Good flowability requires mass flow for in funnel flow the powder particles are held together more strongly by cohesion forces. Funnel flow leads to unevenness in filling during capsulation or compression, and high deviations can occur in the average mass of capsules of tablets. Accordingly, flowability testing is official in the Pharmacopoeias, and it is necessary to investigate flowability in the preformulation tests in the process of development of a solid dosage form.

The multiparticulate dosage forms that are currently at the focus of therapy include hard capsules filled with minitablets, which are very small tablets (2–3 mm in diameter). This means that good flowability is especially important during the manufacturing of these tablets, where the diameter of the dies is very small and the filling time is also very short.

The main aim of the present paper is to study the relationships between particle size shape and the angle of repose as a parameter of the flowability of pharmaceutical powders. We also set out to determine the particle size interval in which the powder flow exhibits the features of mass flow. We additionally hoped to use the resulting data to determine a "cohesion coefficient" (C) characteristic of the flow properties, shape and size of the powder particles.

2. Materials and methods

2.1. *Materials*

A sugar derivative (sorbitol) was chosen as model material, which is used worldwide as a filling agent for direct compression in the pharmaceutical and food industries.

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

3. Methods

3.1. *Particle size analysis*

A light microscope combined with an image analysis system (Quantimet 500 MC (Q500 MC), Leica Cambridge Ltd., UK) was used, which furnishes a general picture of the statistical dimension. The shape parameters of the particles (area, perimeter, length and width) were determined directly. The software of this system calculates roundness from the measured data. The data on 500 particles (average) were measured.

3.2. *Morphology of particles*

The morphology of the particles was observed with a scanning electron microscope (Hitachi 2400 S, Hitachi Scientific Instruments Ltd., Tokyo, Japan). A Polaron sputter coating apparatus (Polaron Equipment Ltd., Greenhill, U.K.) was applied to induce electric conductivity on the surface of samples.

3.3. *Sieving of size fraction*

After the examinations of the particle size distribution, the various size fractions were classified through the use of an analytical sieving machine (Retsch GmbH & Co., Haan, Germany), with vibration sieve apertures of 315, 400, 630 and 1000 μm. The duration of sieving was 5 min.

3.4. *Flowability test*

The parameters of flowability were determined with software-controlled PharmaTest PTG-1 powder testing equipment (PharmaTest, Hainburg, Germany) (Fig. 2). This equipment was developed in accordance with the recommendations of the Ph. Eur. and satisfied the Ph. Eur. Specifications. The powder was placed in a funnel with a capacity of 100 ml, and allowed to flow through an orifice with variable diameter onto a plate connected to a balance (Sartorius BP 310 S, Sartorius A.G., Göttingen, Germany). The powder flow was controlled by sensors. This apparatus measures the time for 100 ml of material to flow, and the mass and height of the powder heap formed, and calculates the angle of repose (α), the volume of the heap and the bulk density of the sample.

Fig. 2 – **Pharma Test PTG-1 powder testing equipment.**

3.5. *Calculation of cohesion coefficient (C)*

It is 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 *cohesion 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 (Serno et al., 2007; Kojima and Elliott, 2012). 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 cohesion coefficient, which can be calculated from the powder rheological parameters:

The mass of powder (m) which flows from the funnel is measured by a balance. The mass of a spherical particle (mass = density × volume of particle) is determined by various parameters, as follows:

$$m = \rho \frac{\pi D^2}{4} h \tag{1}$$

where h is the height of the wall of the orifice, D is the diameter of the orifice and ρ is the density of the powder (bulk).

The outflow of unit mass from the funnel can be described by the Second Law of Newton:

$$m\vec{a} = \sum_i \vec{F}_i \tag{2}$$

where m is unit mass of the powder, $\vec{a}$ is an acceleration vector, and $\vec{F}_i$ describes the forces. The forces involve gravitational force and frictional forces. The gravitational force acts in a downward direction:

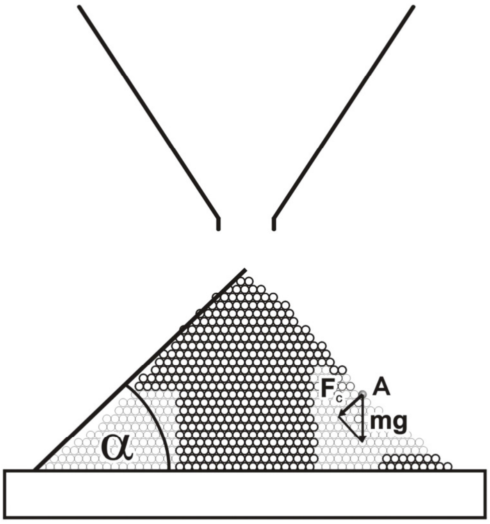

Fig. 3 – **Schematic presentation of parameters influencing cohesion force.**

$$F_{gravitational} = \rho \frac{\pi D^2}{4} hg \tag{3}$$

The forces of friction are caused by the interactions of the moving particles with the walls of the orifice and act in an upward direction:

$$F_{frictional} = C(\pi D)h \tag{4}$$

where C is the cohesion coefficient (including the friction coefficient between the particles and the wall of the orifice). The critical diameter D at which there is no flow can be calculated via the Newton equation of motion:

$$\rho \frac{\pi D^2}{4} ha = \rho \frac{\pi D^2}{4} hg - C\pi Dh \tag{5}$$

In the event of no flow, the acceleration of unit mass is zero. This gives

$$D = \frac{4C}{\rho gh} \tag{6}$$

The cohesional force between the powder particles can be determined from the angle of repose (α) (Fig. 3) (Carstensen, 1993).

An individual particle at A on the surface of the cone is subjected to gravitational force (mg) in the downward direction and a cohesional force (F_c) in a direction perpendicular to the cone. When the particle is just about to move, the equation of motion can be expressed as follows:

$$mg \sin\alpha = C(F_c + mg\cos\alpha) \tag{7}$$

where C is the cohesion coefficient between the particles, α is the angle of repose and m is the mass of the particle. This is the equation of motion of individual particle on the surface of the cone. Eq. (7) shows that the more cohesive the powder, the larger the angle of repose. However, the cohesive stress, i.e. the

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	

cohesive force per surface area, is inversely proportional to d, the diameter of the particles. For the surface unit:

$$F_c = \frac{C}{d} mg \tag{8}$$

The solution of Eq. (7) for C gives (If Eq. (8) is substituted into Eq. (7) and C is then expressed):

$$C = \frac{1}{2} d \left(\sqrt{\cos^2 \alpha + \frac{4 \sin \alpha}{d}} - \cos \alpha \right) \tag{9}$$

4. Results and discussion

4.1. *Measurement of particle size*

The most important particle size and morphology parameters of the model materials were determined (Table 1).

The software of the image analysis system calculates the roughness and roundness of the particles, which are also presented in Table 1.

- roundness = (perimeter)^2/(4π area 1.064)
- roughness = perimeter/convex perimeter

The differences in particle size can be seen from the data. Sample 1 consists of the smallest crystal agglomerates, 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 morphology 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.

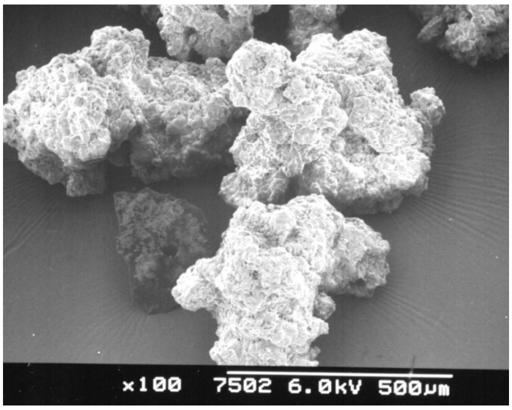

Fig. 4 – Sample 1.

4.2. *Particle morphology*

The morphology of the particles is illustrated in Figs. 4–6 (300 particles were analyzed in every case.) It is clear that the shapes of the particles of all the samples are irregular and the surface is very uneven. These particles are agglomerates of smaller crystals.

4.3. *Flowability tests*

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. 10 parallel measurements were made.

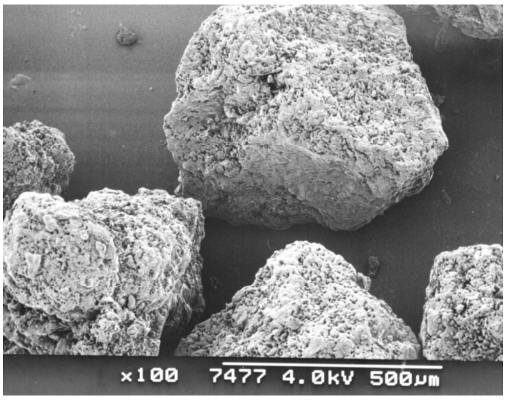

Fig. 5 – Sample 2.

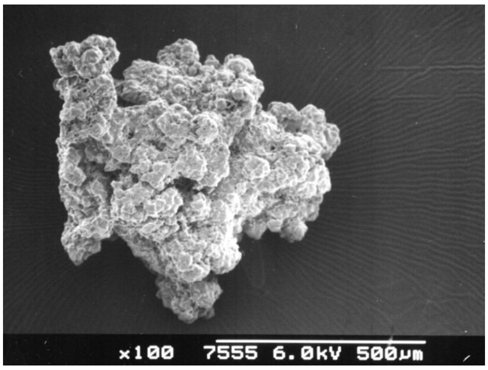

Fig. 6 – Sample 3.

Table 2 – Flowability parameters.

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

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

* Stirring rate: 10 rpm.
** Without stirring.

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. A high deviation in particle size is unfavourable because it affects the flowability and the good filling in the die. If the deviation of the tablet mass is too high, there will be a high deviation in the active agent content in the tablets. 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 accordingly we chose a smaller orifice (diameter 8 mm) in the flowability test 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.

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 large particles (over a certain size) hinder each other in free flow and close the orifice. 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 cohesion coefficient and the critical diameter were calculated from the data (Table 4). It is clear that the value of

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

C increased with increasing angle of repose. Accordingly, we considered the possibility of a relationship between the cohesion coefficient and the angle of repose in this range of particle size. The angle of repose was found to vary linearly with the cohesion coefficient ($y = ax + b$, where x = cohesion coefficient, a = slope, y = angle of repose and b = intercept) with a 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 cohesion coefficient therefore characterizes the flow properties of a powder.

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.

5. Conclusions

In order to characterize the most important particle parameters and flow properties, three commercial sorbitol samples were tested. A new coefficient (C = cohesion coefficient) was calculated, 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 can be calculated.

As mentioned in the Introduction, 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.

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