ANNEX

Original publications (I-V)

I

Development of Spherical Crystals of Acetylsalicylic Acid for Direct Tablet-making

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The production of spherical crystals has recently gained great attention due to the fact that the crystal habit (form, surface, size, *etc.*) can be modified during the crystallization process. Spherical crystals of ASA were developed by non-typical and typical spherical crystallization techniques. The non-typical spherical crystallization process (conventional stirred tank method) resulted in few monocrystals and non-spherical crystal agglomerates. The typical spherical crystallization process was carried out by the three solvent-system (ethanol–water–carbon tetrachloride). The products were qualified by morphological study, NIR investigation, salicylic acid content, dissolution rate, studies on flowability, compactibility, cohesivity and tablettability. The results demonstrate that only typical spherical crystallization can be recommended for the production of spherical crystals of ASA. Only product made by this technique shows excellent flow properties and favourable compactibility, cohesiveness and tablettability values.

Key words   acetylsalicylic acid; spherical crystallization; flowability; roundness; diffuse reflectance

Direct compression is the most efficient process used in tablet manufacturing because it is the fastest, simplest and least expensive tablet-compression procedure.[1] However, although this technique seems quite simple, it requires that different properties be observed simultaneously:
— good flowability of the materials,
— a suitable bulk density of the powder, in order that the correct amount of drug may be fed into a die cavity,
— appropriate particle size distribution, and
— good compressibility of the powder.

Many drug crystals do not exhibit these properties: they have poor flowability and compressibility.[2] In tablet making from these materials, possible solutions may be as follows:
— the use of wet granulation (if this is possible with regard to the drug stability),
— the use of direct tablet making with a good excipient, or
— the use of direct pressing with spherical crystals or crystal agglomerates of drug material with good flowability and compactibility properties.

The production of spherical crystals has recently gained great attention and importance, due to the fact that the crystal habit (form, surface, size and particle size distribution) can be modified during the crystallization process. In consequence of such modifications in the crystal habit, certain parameters of materials can also be changed: bulk density, flow property, compactibility, dissolution rate, stability,[3] *etc.*

"Spherical crystallization" was defined by Kawashima as "an agglomeration technique that transforms crystals directly into a compacted spherical form during the crystallization process."[4] A few methods are to be found in the literature. The typical spherical crystallization process employs three solvents: one is the substance dissolution medium, another is a medium which partially dissolves the substance, and the third is the wetting solvent for the substance. Of course, the traditional crystallization processes (salting-out precipitation,

cooling crystallization, crystallization from the melting, *etc.*) can also be used to produce spherical crystal agglomerates.[5] The traditional crystallization process is carried out by controlling the physical and chemical properties and can be called the non-typical spherical crystallization process.

Many drugs which do not have suitable technological properties have been transformed successfully into spherical agglomerates with good flowability and compressibility during manufacturing (salicylic acid, tolbutamide, dibasic calcium phosphate anhydrous, norfloxacin, DL-methionine, phenytoin, ferrous sulfate, *etc.*).[6—13] Other materials are currently awaiting such transformation.

A few years ago Aoki *et al.* (Japan) and Deshpande *et al.* (India) were employed in making spherical ASA crystals from a mixture of heptane–pentane–methanol[14] and a mixture of methanol–chloroform–acid buffer.[15] The commercial ASA crystals are tetragonal and prism-shaped, with different sizes and particle size distribution. Their flow property is poor due to the crystal habit and the electrostatic charge. Since ASA crystals can be compressed to tablets (*e.g.*, effervescent or chewable) only *via* direct tablet-making methods (stability!), good flowability, cohesivity and tablettability of the crystals are very important.

Therefore in the work reported here, ASA crystals were developed by means of non-typical and typical spherical crystallization processes by different solvent mixtures.

Experimental

Development of Spherical ASA Crystals   Three different samples were produced by variation of the experimental conditions. The experiments were carried out in a mechanically stirred tank with a volume of 500 ml. A Julabo thermostat with computer control was used for the cooling process. A non-typical spherical crystallization process was used for the samples ASA 1 and ASA 2. ASA 3 was developed, however, by the typical spherical crystallization procedure.

ASA 1: 160 g of ASA was dissolved in 500 ml of ethanol (40% v/v) at 60 °C, followed by cooling at 1 °C/min to 20 °C with stirring (200 rpm).
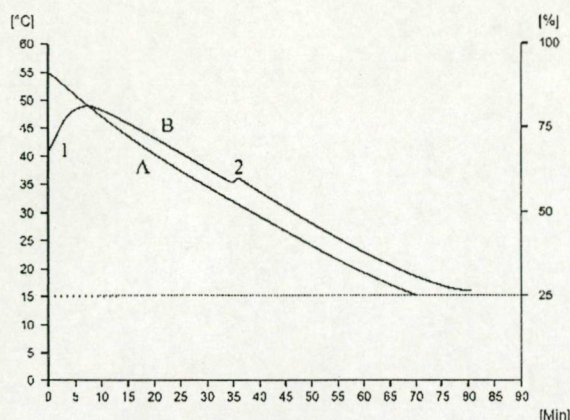

Fig. 1.　Cooling Curves of Crystallization Process of ASA3

A, cooling curve of equipment; B, cooling curve of solution; 1, dissolution of ASA crystals with addition of a carbon tetrachloride–water mixture (4% w/v) to the solution; 2, appearance of ASA crystals.

ASA 2: 160 g of ASA was dissolved in 500 ml of ethanol (40% v/v) at 60 °C, followed by cooling at 0.5 °C/min to 20 °C with stirring (200 rpm).

ASA 3: 121.6 g of ASA was dissolved in 225 ml of ethanol (40% v/v) at 50 °C, and a carbon tetrachloride–water mixture (4% w/v) was added to the solution, followed by cooling at 0.6 °C/min to 20 °C with stirring (200 rpm). The ASA 3 crystallization process can be followed in Fig. 1.

Particle Size Analysis Determination of the particle size (length, breadth and roundness) was carried out with a Laborlux S light microscope and a Quantimet 500MC (Q500MC) image processing and analysis system (LEICA Cambridge, Ltd., U.K.).

Roundness is a shape factor that provides information on the circularity of particles. It is calculated by software according to the following formula:

$$\text{roundness} = \text{perimeter}^2/4\pi \cdot \text{area} \cdot 1.064 \qquad (1)$$

The perimeter was calculated from the horizontal and vertical projections, with an allowance for the number of corners. An adjustment factor of 1.064 corrected the perimeter for the effect of the corners produced by digitization of the image. When roundness value is close to one, the particles are nearly spherical.

Morphological Study The ASA crystals were observed with a scanning electron microscope (Hitachi Scientific Instrument, Ltd., Tokyo, Japan). A Polaron sputter coating apparatus (Polaron Equipment, Ltd., Greenhill, U.K.) was applied to induce electric conductivity on the surface of the sample. The air pressure was 1.3—13 mPa.

Friability Test ASA3 sample was investigated by Heberlein apparatus (Flisa, Le Locle, Switzerland). Five grams of sieved sample (<0.32 mm) was put into the apparatus and 100 revolutions were performed. After this process the fine particles were removed by sieve (<0.32 mm) and the percentage of weight loss was calculated.

Determination of Salicylic Acid (SA) Contents of the ASA Samples The SA contents of the samples were controlled by a spectrophotometer (Spectromom, MOM, Budapest, Hungary); 0.250 g of sample was dissolved in 25 ml of ethanol (96%) and diluted with water up to 100 ml. After additional dilution (5 ml aliquot+95 ml water), the absorbance was read at 297 nm for SA. The testing was done with a near-infrared spectroscope.

Dissolution Test The investigations were performed with the USP dissolution method (paddle). The medium was artificial gastric juice (pH=1.2) at a temperature of 37±0.5 °C. The paddle speed was 50 rpm. The samples were analyzed spectrophotometrically (Spectromom) at 276 nm. The dissolution rate of ASA was determined from the capsules, and the hard gelatin capsules (No. 1) were filled with 100 mg of ASA crystals.

Study of Flow Properties The flow time was determined with a powder testing instrument (PTG-51, Pharma Test Apparatebau GmbH, Hamburg). Poured and tapped densities were measured with a Stampfvolumeter 2003 (J. Engelsmann AG Apparatebau, Ludwigshafen, Germany). The Carr index was calculated from the bulk densities[16]:

$$\text{Carr index (\%)} = \frac{\text{tapped density} - \text{poured density}}{\text{tapped density}} \cdot 100 \qquad (2)$$

The Carr index reflects the compactibility of a powder, and there is a correlation between this index and the flowability of the crystals.[17]

Compactibility and Cohesiveness The Stampfvolumeter measurements allow calculation of the compactibility and cohesiveness values via the modified Kawakita equation[18,19]:

$$\frac{N}{C} = \frac{1}{a} \cdot N + \frac{1}{ab} \qquad (3)$$

where N is the number of taps, C is the degree of volume reduction, and a and b are constants: a describes the degree of volume reduction at the limit of tapping and is called the compactibility; $1/b$ is considered to be a constant related to cohesion and is called the cohesiveness. C is calculated via the following equation, and graphs of N/C vs. N are plotted.

$$C = \frac{V_0 - V}{V_0} \qquad (4)$$

The compactibility a and cohesiveness $1/b$ are obtained from the slope ($1/a$) and the intercept ($1/ab$) of the plot of the modified Kawakita equation.

Recording Diffuse-Reflectance Spectra Near-infrared spectroscopy furnishes useful information for qualitative and quantitative analysis of materials without invasive sample preparation. It can be used for the control of differences among the particle forms of the samples.[20] Diffuse reflectance was measured by a Hitachi (Japan) U-3501 UV/VIS/NIR spectrophotometer equipped with integrating sphere (d=60 mm) and PbS detector. The reflectance (R%) of samples was determined in the wavelength range 200—2500 nm using a 5 mm layered cell

$$R\% = (I_R/I_0) \cdot 100 \qquad (5)$$

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.[21]

Production of ASA Tablets The materials without any excipients were pressed into tablets by a KORSCH EKO single punch tablet machine (Emil Korsch Maschinenfabrik, Berlin, Germany). The compression tools were single flat punches 10 mm in diameter. The rate of compression was 30 tablets/min with a pressure force of 18 kN, at an air temperature 24 °C and an air relative humidity of 30%.

Investigation of ASA Tablets Investigations were carried out 24 h after pressing. Tablet weight was measured to the order of 0.1 mg. The relative standard deviation (RSD) was calculated from 20 data points and breaking hardness was determined using a Heberlein apparatus (Flisa, Le Locle, Switzerland) (20 tablets).

Statistical Calculation The standard deviation and the regression analysis were carried out with the Statgraphics package (copyright STSC Inc. and Statistical Graphics Co. U.S.A.); the confidence limit was 95%.

Results and Discussion

The ASA1 crystals were tetragonal monocrystals with plane boundaries (Fig. 2). The cooling rate of 1 °C/min resulted in formation of a great number of seeds and did not act favourably either on crystal growth or on seed build-up.

Decreasing the cooling rate (0.5 °C/min) (ASA2) led to the appearance of a small number of crystal agglomerates beside the monocrystals (Fig. 3). Due to the slow cooling, the monocrystals were very large and well-developed. Agglomerates were formed by the accidental encounter of 4—5 crystal seeds. Crystals built up at one point have a habit characteristic of monocrystals.

Further reduction of the cooling rate and changes in the other parameters of crystallization did not cause many changes in the formation of agglomerates either. For example the use of higher stirring speed decreased the possibility of the agglomeration of ASA2 monocrystals but increased the danger of crystal breakage. Let us remark here that commercially available ASA products have a habit similar to that of ASA1 and ASA2 products.

During the formation of ASA3, the crystals were transformed into spherical agglomerates (Fig. 4). The process was
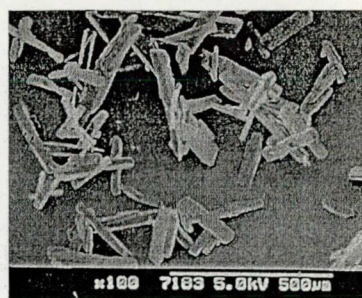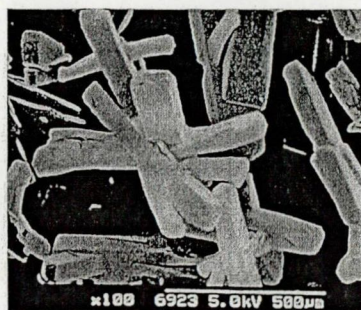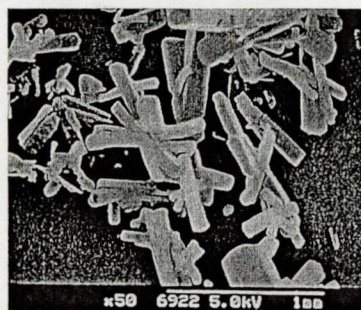
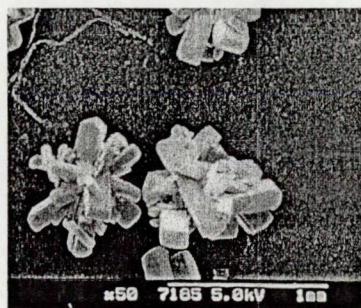Fig. 2. Crystals of ASA1

Fig. 3. Crystals of ASA2

Fig. 4. Crystals of ASA3

the typical spherical crystallization (agglomeration) with three solvents (ethanol–water–carbon tetrachloride). In the three-solvent system the dissolved ASA was carried in the emulsion drops. Due to the effect of diffusion, the ethanol molecules left the emulsion drop and entered the aqueous phase through the emulsion film. The drop became oversaturated with respect to the ASA, and the *in situ* seed-formation started at 37 °C (see Fig.1), followed by crystal formation, which was also influenced by the cooling and mixing rates. Thus, in this process it was not the accidental encounter of the crystals which resulted in the formation of crystal agglomerates. As a matter of fact, crystallization in emulsion drops was the case here, where the driving force was oversaturation caused by solvent diffusion. Although the built-up ASA crystals had a habit characteristic of monocrystals, the size of the agglomerates did not exceed the size of monocrystals and crystal agglomerates produced by non-typical spherical crystallization. ASA3 agglomerates were very hard, open structures. Their friability, which is very important during further processing, was very favorable. The fri-

Table 1. Particle Size Data of ASA Samples

Sample		Length (μm)	Breadth (μm)	Roundness
ASA1	Average	273.85	72.09	2.54
	S.D.	61.93	13.33	0.29
	Max.	367.91	95.73	3.28
	Min.	168.52	44.02	2.19
ASA2	Average	667.94	314.69	1.72
	S.D.	173.36	96.74	0.25
	Max.	1200.00	747.69	2.38
	Min.	391.54	179.23	1.26
ASA3	Average	521.72	332.01	1.40
	S.D.	143.16	98.65	0.13
	Max.	913.85	690.77	1.66
	Min.	300.31	136.61	1.15

ability of the ASA3 sample was found to be $6.24 \pm 0.45\%$, while the maximum friability of granules is usually limited to 20% in pharmacopoeias.

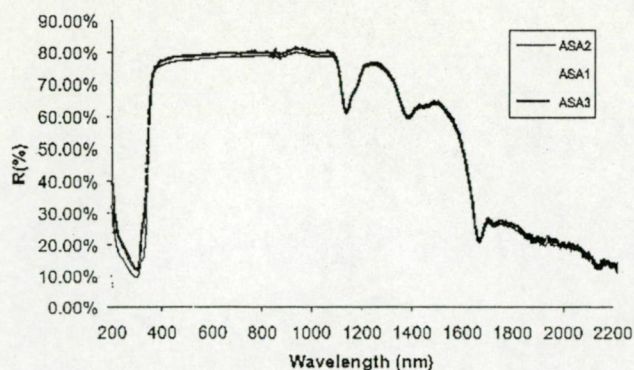The length, breadth and roundness of the samples are de-
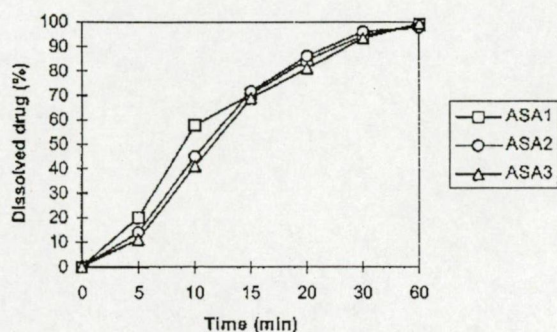
Fig. 5. Diffuse-Reflectance Spectra of ASA Samples

Fig. 6. Dissolution Rate of ASA Samples

Table 2. Parameters of Powder Rheological Investigation of ASA Samples

Sample	Flow time (s/100 ml)	Poured density (g/ml)	Tapped density (g/ml)	Carr index (%)
ASA1	no flow	0.3613	0.4517	19.99
ASA2	12.1	0.3730	0.4025	7.33
ASA3	8.4	0.4337	0.4613	5.99

Table 3. Compactibility (a) and Cohesiveness ($1/b$) Values of ASA Crystals by Kawakita Model

Sample	$1/ab$ intercept	$1/a$ slope	a	$1/b$	r^2
ASA1	91.75	3.97	0.2519	23.10	0.9872
ASA2	210.64	9.83	0.1017	21.42	0.9515
ASA3	131.34	9.55	0.1017	13.76	0.9764

Table 4. Physical Parameters of ASA Tablets

Material	Pressing force (kN)	Average height (mm)	Average weight (g)	Weight variation (R.S.D.) (%)	Breaking hardness (N)
ASA1	10—15	2.8923 (S.D.=0.0153)	0.2757	2.5025	75.4 (S.D.=3.5339)
ASA2	10±1.5	3.0394 (S.D.=0.060)	0.2948	2.3258	66.8 (S.D.=2.6998)
ASA3	10±0.5	3.1323 (S.D.=0.0427)	0.3054	1.4833	71.4 (S.D.=1.6576)

S.D.=Standard Deviation, R.S.D.=Relative Standard Deviation.

tailed in Table 1. The different crystallization processes strongly influenced the habit of the crystals or their agglomerates. A faster cooling process resulted in very small crystals (ASA1) with an unfavorable roundness value. Slower cooling helped the build-up of crystal agglomerates, but they were few in number and the structure was built up only partly (ASA2). Table 1 shows that ASA3 had the best roundness value.

The ASA and salicylic acid content of the samples were qualified by NIR method. The diffuse-reflectance spectra of the ASA1 and ASA3 samples in the wavelength range of 200—350 nm was the same, which can be attributed to the uniform ASA content of the samples (Fig. 5). In this range only the ASA2 sample showed a small peak for the salicylic acid as a decomposition product. The amount of the salicylic acid determined by spectrophotometer was 1.02%. In spite of the higher temperature, the decomposition of ASA2 was low because the crystallization time was only about 1 hour. The data for the slower cooling rate (0.1 °C/min) and the longer process time (about 5 h) showed higher salicylic acid content in the sample (about 10%). Between 350—2500 nm ASA2 and ASA3 samples with larger particle sizes and the best values of roundness showed smaller diffuse reflectances than that of ASA1 with a smaller particle size and a unfavourable roundness value.

As the dissolution rate of the samples was basically influenced by particle size, this was also checked. It is clearly shown in Fig. 6 that the dissolution rate of the samples was almost the same, and only the ASA1 crystals, which have a small particle size and consequently a great surface, showed more rapid dissolution at the beginning of the examination.

A very important fact to be pointed out is that the spherical crystal agglomerates of ASA3 did not exert unfavourable influence on the dissolution rate.

The change in the habit of the crystals was reflected in the flowability of the samples. The spherical ASA3 had 'excellent' flow properties, as shown by the flow time and the Carr index (5—15%) (Table 2). The flow time of the prism-shaped monocrystals of ASA1 could not be determined with the Pharmatest apparatus because the substance did not flow from the funnel of the apparatus. The Carr index of ASA1 was very high (19.99%). This means 'fair to passable' (18—21%) flow properties.

The data from the modified Kawakita equation can be seen in Table 3. The compactibilities (a) of ASA2 and ASA3 hardly differed; the compactibility of ASA1 was poorer. The cohesiveness ($1/b$) of ASA3 was outstanding, while those of the other two samples were higher and more disadvantageous. ASA3, which contained spherical crystals, had the best flowability, compactibility and cohesivity properties. ASA1, which did not form spherical agglomerates, gave the worst results. Hence, the transformation of commercial ASA crystals into spherical agglomerates led to improved flowability and compactibility. For ASA which did not undergo complete agglomeration, investigation revealed worse technological parameters.

As ASA samples were developed for direct tabletting, the preformulation results to date were completed with tablettability studies. The samples were compressed to tablets without excipient and the physical parameters of the tablets were determined (Table 4). During the pressing of the ASA1 crys-

tals great friction was indicated by a powerful machine sound. The die cavity was filled unevenly due to the unfavourable habit of the crystals and their electrostatic charge. In consequence of this a high degree of pressure force variation could be observed, which also influenced the other parameters, thus, *e.g.*, deviation from the theoretical mass was high and weight variation exceeded 2%. The ASA2 sample, which has a greater particle size and is only partially spherical, exhibited better properties of compressibility. The machine sound caused by friction became less intense but the weight variation value of the tablet was still over 2%, which is related to the great cohesivity value of the crystals. The latter can be attributed not only to the shape and size parameters of the crystals but also to their surface properties. The results obtained with tablets compressed from ASA3 were in harmony with the values of flow property, compactibility and cohesivity of the sample. At the same time the importance of spherical crystallization was stressed for the purpose of the direct pressing of ASA crystals. There was no sign whatsoever of electrostatic charging during the pressing of ASA3. The crystal agglomerates can be compressed to tablets almost in a frictionless manner. This was confirmed by the slight variation of the pressing force, average weight and weight variation value. The extreme hardness of the tablets as well as their small standard deviation also proved the important role of the ASA3 sample.

Conclusions

The typical spherical crystallization process can be used successfully to manufacture spherical crystals of ASA with good flowability, compactibility and cohesivity. The ASA3 crystallization process is optimized concerning the form of the crystal agglomerates and the reproducibility of the product. On the basis of the results this product can be recommended for direct tablet-making.

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II

Development of spherical crystal agglomerates of an aspartic acid salt for direct tablet making

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Abstract

Agglomerates of an aspartic acid salt were developed by means of a non-typical spherical crystallization technique. The aspartic acid salt was crystallized by a salting-out method combined with cooling. Traditional mechanical stirring crystallization (samples A and B) and the recirculation process (sample C) were used. The control material was commercial aspartic acid salt with very poor flowability and compressibility. The particle sizes of the samples were measured by sieve analysis. The morphology of the crystals and crystal agglomerates was controlled by SEM. The specific surfaces of the products were determined by the BET method and the micropore volumes were calculated via the BJH theory. The Carr index, rearrangement constant, plasticity and compressibility values were calculated. The samples were controlled by thermoanalytical investigations (TG, DTG and DSC). Both of the crystallization techniques used resulted in spherical agglomerates of the aspartic acid salt with very good flowability and compressibility parameters. Primarily sample B, with a closed "cauliflower-like" structure, can be suggested for tablet making involving a large mass (e.g., chewable tablets) by direct tablet pressing. Faster initial cooling rate and slower stirring rate were very favourable in the building-up of crystal agglomerates of sample B with a closed structure and a large particles. Sample B can be suggested further for capsule filling because of its high poured density, very good flowability and fast rearrangement. © 2001 Elsevier Science S.A. All rights reserved.

Keywords: Aspartic acid salt; Crystallization; Spherical agglomerates; Flowability; Compressibility

1. Introduction

Direct compression is a modern method in tablet manufacturing. Many processing steps (granulation, drying, etc.) are eliminated in direct compression, and additionally wet technology cannot be used with sensitive agents (e.g., in effervescent tablet making) [1]. However, the use of this technique, which seems quite simple, depends on

- the particle size and the particle size distribution of the materials, and in connection with this,
- the flowability of the crystals, consistent with the production rates of modern compression technologies,

- the bulk density of the powder, in order to feed the correct amount of drug into a die cavity, and
- the compressibility of the powder.

Some drug crystals exhibit appropriate such properties, but many materials have very poor flowability and compressibility [2]. For tablet making from the latter materials, possible solutions may be the following:

- the use of wet granulation, agglomeration [3] (if this is possible with regard to the drug stability;
- the use of direct tablet making with "good" excipients, which promote direct compression (though this might not be favourable in terms of powder flow);
- the use of direct pressing with spherical agglomerates of drug crystals with good flowability and compressibility properties.

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The third of these possibilities recently came into the forefront of interest because the habit of the particles (form, size, particle size distribution, surface, etc.) can be changed by the crystallization process. It is well known that the morphology of crystals depends strongly on the crystal growth conditions. The influence of the rates of the nucleation and crystal growth processes (temperature, stirring, method, additives, etc.) is very important, as has been shown by many examples in the literature [4–6].

One of the crystal growth processes is the development of crystal agglomerates by spherical crystallization. In the pharmaceutical field, Kawashima et al. [7–9] have given impulse to this research. Typical spherical crystallization employs three solvents: one is the substance dissolution medium; another is a medium which partially dissolves the substance; and the last one is immiscible with the substance. For certain materials, spherical crystal agglomerates can be developed by a traditional crystallization process (salting-out, cooling, precipitation, etc.). This process is carried out by controlling the physical and chemical factors. It may be called a spherical crystal agglomeration technique or a non-typical spherical crystallization process. Through the use of the spherical crystal agglomeration technique, the physicochemical properties of the pharmaceutical crystals are dramatically improved for the pharmaceutical processes, e.g., mixing, filling and tabletting, because of the resulting excellent flowabilities and compressibilities [10–14].

In this work, agglomerates of an aspartic acid salt were developed by salting-out combined with a cooling crystallization process for direct pressing. The control material was a commercial aspartic acid salt with very poor flowability and compressibility properties.

Aspartic acid salts (e.g., magnesium and potassium salts) are widely used in therapy, e.g., in cardiology. They improve the heart work and act as adjuvants in angina pectoris and arrhythmia.

2. Experimental

2.1. Materials

The investigated materials were as follows: as control material a commercial aspartic acid salt (Merck, Darmstadt, Germany) and samples A, B and C (aspartic acid salt crystal agglomerates), produced by crystallization.

The spherical crystal agglomeration of the aspartic acid salt was carried out by salting-out combined with cooling (Fig. 1). The formation of salt preceded the crystallization process. The samples were produced under different experimental conditions. The experiments were carried out in a mechanically stirred tank with a volume of 1000 ml. A Julabo thermostat with computer control (Julabo Labortechnik, Seelbach, Germany) was used for the cooling process. A total of 500 ml of 15–25 wt.% aspartic acid
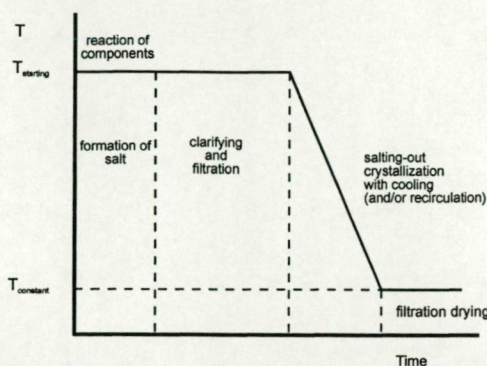

Fig. 1. Schematic representation of the spherical agglomeration of an aspartic acid salt.

salt solution was placed in the crystallizer tank. The solvent was water. The salting-out agent was methanol (25–100%, in relation to the measured solution). Traditional mechanical stirring crystallization was used for samples A and B. The stirring rate was higher (100 rpm) for sample A than for sample B (60 rpm). The feeding rate of salting-out agent (0.36 l/h) was constant in the experiments. The temperature interval was 90–10°C. The crystallization processes of sample A and sample B differed further in cooling rate. For sample A, slower initial cooling (0.3°C/min) was used than for sample B (0.7°C/min). The duration of the crystallization process was 140–260 min.

Sample C was prepared in a mechanically stirred tank (800 ml) with an external circulation loop (recirculation process). Methanol was added to the external loop [15]. The initial concentrations, the stirring rate and the temperature interval were the same as for sample A. The mother liquor recirculation rate (20 l/h), the methanol feeding rate (0.3 l/h) and the cooling rate (0.5°C/min) were different. The duration of the crystallization process was 190 min. After the precipitation of crystal agglomerates, the solvent mixture (water–methanol) was removed by filtration in vacuum (100 mbar). The concentration of aspartic acid salt in the filtrates was 2–2.5 wt.%. The agglomerates were washed with cold methanol (0°C), and subsequently dried at 50°C till mass constancy. The products were finally kept in a dark and dry place.

2.2. Methods

2.2.1. Particle size analysis

The particle sizes of the materials were measured by sieving (DIN sieve, German Standard). A total of 100 g of material was sieved with an Erweka vibration sieve (Erweka Apparatebau, Heusenstamm, Germany). The vibration rate was 200 strokes/min and the sieving time was 10 min. The powder fractions retained by the individual sieves were measured and expressed in mass percentages.

Table 1
Interpretation of Carr index for powder flow [19]

Carr index (%)	Flow
5–15	excellent
12–16	good
18–21*	fair to passable
23–35*	poor
33–38	very poor
> 40	very very poor

*Adding glidant, e.g., 0.2% Aerosil, should improve flow.

2.2.2. Morphological study

The morphology of the crystals was controlled by scanning electron microscopy (SEM) (JEOL JSM 50A, 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).

2.2.3. BET and BJH methods

The specific surfaces and micropore volumes of samples were determined with Micromeritics ASA 2000 equipment (Instrument Corp., Norcross, GA, USA)) from data (20 points each) of nitrogen adsorption and desorption isotherms at the boiling point of liquid nitrogen under atmospheric pressure (− 196°C). The specific surface was calculated, in the validity range of the BET-isotherm [16], from the slope and intercept of a line characterized by five measuring points. The samples (1.5–2.0 g) were degassed at 60°C by vacuum up to 1 Pa absolute pressure. After degassing, the samples were weighed again and the morphological parameters were calculated for the "surface-cleaned" mass of samples. The micropore volumes were calculated via the BJH method [17]. The investigations were repeated three times.

2.2.4. Thermoanalytical investigations

The products were checked through thermogravimetry (TG, DTG), using a MOM instrument (MOM, Budapest, Hungary). The sample mass was 6 mg, and the heating rate was 5°C/min in an air atmosphere. Differential scanning calorimetry (DSC) with Perkin-Elmer DSC-2C equipment (Perkin-Elmer, Norwalk, CT, USA) provided additional information. The sample mass was 3–4 mg, and the heating rate was 5°C/min in an air atmosphere. The results were caculated from three measurements.

2.2.5. Carr index and rearrangement constant

The Carr index was calculated from the poured and tapped densities [18]:

$$\text{Carr index (\%)} = \frac{\text{tapped density} - \text{poured density}}{\text{tapped density}} \times 100 \tag{1}$$

For the determination of poured and tapped densities, a Stampfvolumeter 2003 (J. Engelsmann Apparatebau, Ludwigshafen, Germany) was used. Initially, 250 ml of substance was poured by hand into a measuring cylinder and the mass was determined by weighing. The poured density (minimum density) was calculated from the powder mass and the volume (250 ml). The cylinder was then tapped until the volume did not change (0–100 taps with 10 tap intervals) and the volume was read again, giving the tapped density, and thus the maximum density possible. The mass of the measuring cylinder and clamp was 675 g, the speed of the camshaft was 250 min^{-1} and the dropping height of the guide punch was 3 mm. The Carr index reflects the compactability of the crystals, and there is a correlation between the Carr index and the flowability of the crystals (Table 1) [19].

Stampfvolumeter measurements allow calculation of the rearrangement constant (k) [20]:

$$\frac{V_n - V_\infty}{V_0 - V_\infty} = (1 + kn)^{-0.25} \tag{2}$$

where n is the number of taps, V_0 is the initial volume of powder, V_n is the volume after n taps, and V_∞ is the final volume.

After transformation of the equation, regression analysis was performed. The relationship between the variables can be described in terms of a linear model ($y = 1 + kn$) or an exponential model ($y = \exp(1 + kn)$), where the slope of the curve is the rearrangement constant. If the constant is too small, the compression during tablet pressing can give rise to brittle fracture and plastic flow in certain regions before a close arrangement has been achieved in other regions.

2.2.6. Study of plasticity and compressibility

A Korsch EKO eccentric tablet machine (Emil Korsch Maschinenfabrik, Berlin, Germany) was applied for tablet making. The compression tools were single, flat punches 10 mm in diameter, furnished with strain gauges and a

Table 2
Particle size distribution of aspartic acid salt samples (weight percentage)

	> 400 μm	400–315 μm	315–250 μm	250–200 μm	200–100 μm	100–71 μm	< 71 μm
Control	–	–	–	–	2.0	7.0	91.0
Sample A	–	2.4	3.3	5.1	39.5	17.8	31.9
Sample B	14.5	11.9	35.9	16.5	17.7	2.3	1.2
Sample C	3.6	5.6	13.0	15.9	41.1	10.0	10.8

displacement transducer. The strain gauges allow the pressure forces on the upper and lower punches to be followed with force-measuring equipment, which was 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 load (Mitutoyo, Tokyo, Japan). The rate of compression was 30 tablets/min with a pressure force of 17 kN, at an air temperature of 24°C and an air relative humidity of 45%. The tablets were pressed from the control and denoted samples A, B and C with 0.5% magnesium stearate as lubricant. The components were mixed for 5 min with a Turbula mixer (W.A. Bachofen Maschinenfabrik, Basel, Switzerland) at 50 rpm. A total of 1000 tablets were pressed electrically in continuous operation. During tablet pressing, the data were collected by computer. The energy parameters of 10 tablets were fixed for the calculation of plasticity and compressibility values. The measurements were repeated three times during the pressing.

Plasticity (Pl_{S-M}) was described by Stamm–Mathis [21]:

$$Pl_{S-M} = \frac{E_2}{E_2 + E_3} \times 100 \, (\%) \tag{3}$$

where E_2 is the effective work, which includes the useful work invested in deformation and the friction work. E_3 is the degree of elastic recovery during pressing. E_2 and E_3 could be calculated from the force–displacement curve. If the plasticity value is near 100, the material has a plastic property.

Compressibility $Pr_{(mass)}$ was calculated via the following equation [22]:

$$Pr_{(mass)} = \frac{\sigma_x}{W_{spec}} = \frac{\sigma_x}{E_2/m} \left(\frac{Pa}{J\,kg^{-1}} \right) \tag{4}$$

where σ_x is the tensile strength and W_{spec} is the specific work. W_{spec} expresses the effective work (E_2) invested into
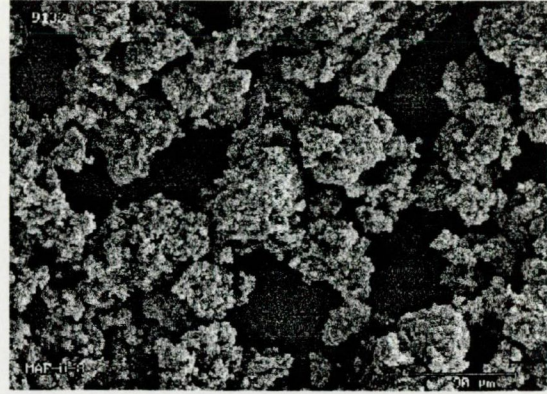

Fig. 3. Crystal agglomerates of sample A (see No. 9132).

the compression of the unit mass of substance (m) at a given compression force. σ_x includes the crushing strength (H), the diameter (d) and the height of the comprimate [23]:

$$\sigma_x = \frac{2H}{\Pi dh} \tag{5}$$

The crushing strength was investigated with a Heberlein apparatus (Flisa, Le Locle, Switzerland). The geometrical
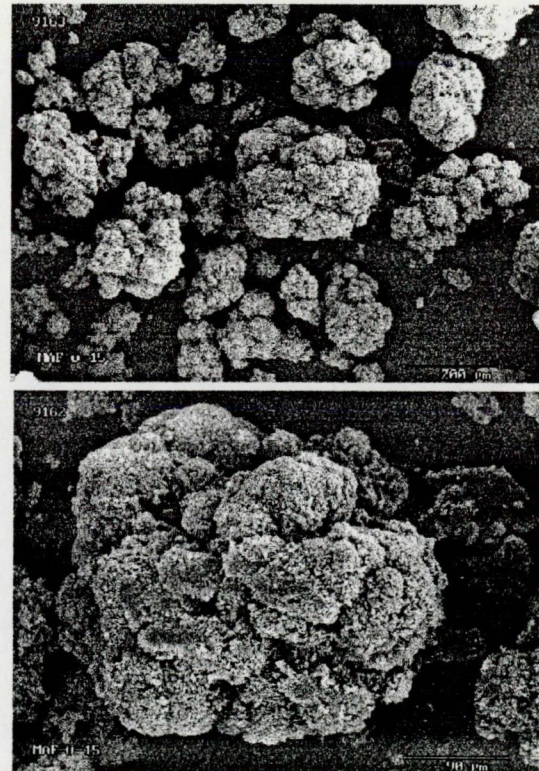

Fig. 4. (a) Crystal agglomerates of sample B (see No. 9163). (b) Sample B with "cauliflower-like" structure (see No. 9162).
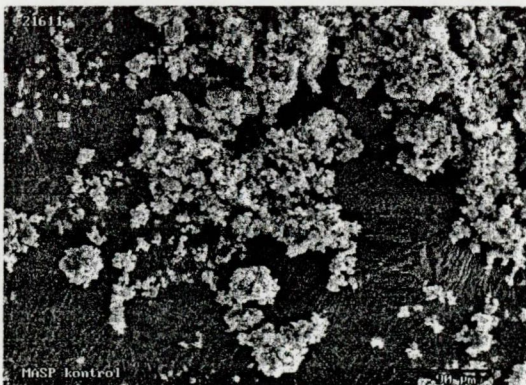

Fig. 2. Control (commercial) aspartic acid salt crystals (see No. 21611).

Table 3
Micromorphology properties of aspartic acid salt crystals

	Specific surface (m^2/g)	Micropore volume* (cm^3/g)	Average diameter of pores (nm)
Control	0.76	0.0028	13.5
Sample A	0.63	0.0025	10.4
Sample B	0.42	0.0028	27.3
Sample C	0.46	0.0014	12.8

*Desorption micropore volumes were measured in range of 1.7–300 nm in diameter.

parameters of the tablets were measured with a screw micrometer (Mitutoyo). The parameters of the tablets were determined after pressing (24 h) because of the texture change (elastic recovery).

In fact, the compressibility (Pr_{mass}) includes the useful and the friction work, and also the hardness and the bulk density of the comprimate. This value can therefore provide more information on the behaviour of the materials than the plasticity or the crushing and the tensile strengths.

The weights of the tablets were measured to the order of 1 mg. The relative standard deviation (RSD) was calculated from 30 data points.

The statistical analyses were carried out with the Statgraphics package (Copyright STSC and Statistical Graphics USA); the confidence limit was 95%.

3. Results and discussion

The investigated crystals and crystal agglomerates were found to have different particle sizes (Table 2). The spherical crystal agglomeration technique is very important in crystal growing (samples A, B and C). The control (commercial) aspartic acid salt consists of single, very small crystals and agglomerated crystals with an unfavourable
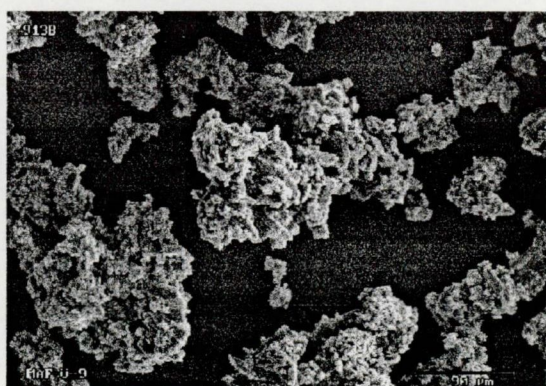

Fig. 5. Crystal agglomerates of sample C (see No. 9138).

Table 4
Thermogravimetric results of aspartic acid salt samples

	TG step (°C) Start	End	Weight decrease (%)
Control	132.4	190.4	−19.1
Sample A	131.9	189.0	−18.2
Sample B	133.0	188.8	−19.7
Sample C	133.5	189.7	−20.0

habit for direct pressing (Fig. 2). The size of 91% of the crystals is less than 71 μm. The structure, surface, size and particle size distribution of the crystal agglomerates are determined by the parameters of the crystallization process. In the same way, samples A and B were crystallized by salting-out combined with cooling, using the traditional mechanical stirring method. Sample A (Fig. 3) consists of smaller particles than those of sample B (Fig. 4a) because of the slower initial cooling and the larger stirring rate. The spherical crystal agglomerates of sample B have a closed "cauliflower-like" structure with a relatively large particle size (62% of the particles larger than 250 μm) (Fig. 4b). In fact, a faster initial cooling rate and slower stirring rate are very favourable in the building-up of crystal agglomerates with a closed structure.

The specific surfaces of the samples differ considerably; this is in keeping with their different particle sizes (Table 3). The micropore volumes of samples A and B are the same, but the average diameter of the pores of sample B is significantly higher. The micromorphology properties of sample A are nearest to the corresponding parameters of the control sample (Table 3). The particle size distribution of sample C (produced in a recirculation process) is placed between the particle size distribution of sample A and sample B. Agglomerates of sample C have a small specific surface, small micropore volume and small average pore diameter (Fig. 5; Table 3).

The different macro- and micromorphologies of samples A, B and C do not involve modification of the inner crystal structure of the agglomerates. This is documented by thermoanalytical investigations. The TG curve does not

Table 5
DSC parameters of aspartic acid salt samples

	Melting point (°C)	Transition (onset) temperature (°C)	ΔH_t (cal/g)
Control	169.5	152.9	170.8
Sample A	170.4	155.7	171.7
Sample B	171.8	163.2	161.4
Sample C	170.9	150.4	189.8

Table 6
Bulk densities, Carr index and the rearrangement constant of aspartic acid salt crystals

	ρ_{poured} (g/cm³)	ρ_{tapped} (g/cm³)	Carr index (%)	Rearrangement constant (k) $y = \exp(1 + kn)$
Control	0.51	0.82	37.61	0.038 ($r = 0.9975$)
Sample A	0.43	0.58	26.41	0.155 ($r = 0.9995$)
Sample B	0.61	0.64	5.32	0.389 ($r = 0.9865$)
Sample C	0.40	0.49	18.71	0.290 ($r = 0.9844$)

reveal any decrease in mass up to 132°C. The samples have no adsorbed water or residual solvent on the surfaces of the crystals and crystal agglomerates. All of the curves exhibit a step (132–189°C) with a mass decrease of about 20% (Table 4). The loss in mass relates to the elimination of four molecules of crystal water (20%). This and the melting of the crystals are accompanied by an endotherm in the DTA curve. The onset temperature of the transition, the melting point and the transition energy (ΔH_t) are given in Table 5. The differences in the results can be ascribed to the crystallization process, but do not relate to the change in structure.

The Carr index (17) revealed that the flowability of the control product was "very poor" (Table 1 and Table 6), and the rearrangement constant of Takieddin (19) indicated a slow-packing character (Table 6). The spherical crystal agglomerates of sample B, with a closed "cauliflower-like" structure, have "very good" flowability. The poured density is high, which is very important in the case of tablets with large mass. The favourable particle form, size and surface result in fast rearrangement, with a very high rearrangement constant. Samples A and C have "fair to passable" flow capacities with a slower rearrangement.

The compressibility parameters of the samples are collected in Table 7. The energy parameters (E_2 and E_3) determined on the basis of the force–displacement curves indicate approximately the same plasticity values for the samples. It is very important that the deformability of the aspartic acid salt (Pl_{S-M}) is not influenced by the crystallization parameters. Therefore, the internal crystal structure of the spherical agglomerates does not change; only the external morphology (size, form, surface, etc.) is affected.

The same result is documented by the thermoanalytical investigations. The tablets containing the spherical crystal agglomerates and the control sample differ considerably in mass of tablet, weight variation (RSD) and tensile strength. The tablet pressing was carried out by maximal space filling of the die cavity of tablet machine. The difference in the mass of tablet could be explained by the bulk density and the arrangement of the samples in the die cavity. This is reflected by the compressibility values (Pr_{mass}), too. The compressibilities of the spherical crystal agglomerates (samples A, B and C) are better than that of the control product (Table 7). The greater tensile strength and the compressibility value of the tablet containing sample A can be explained in terms of enhanced binding connected with the small particle size.

Both the traditional mechanical stirring crystallization and the recirculation process are suitable for the development of spherical crystal agglomerates of an aspartic acid salt. Samples A, B and C have very good flowability and compressibility, in contrast with the commercial (control) sample. Samples A, B and C can be used for direct tablet making according to the parameters of the tablets (mass, tensile strength, etc.). However, primarily sample B can be suggested for the production of tablets with a high active agent content.

The results support the importance of the spherical crystal agglomeration technique. There are many active agents in the pharmaceutical industry with unfavourable flowability and compressibility properties (theophylline, phenylbutazone, etc.). The close cooperation of chemists and pharmaceutical technologists can lead to progress in this field.

Table 7
Compressibility parameters of aspartic acid salt samples (pressure force: 17 kN) (space filling of the die cavity of tablet machine: 864 mm³) (SD = standard deviation)

	Mass of tablet (g)	Weight variation (RSD) (%)	Pl_{SM} (%)	Tensile strength (MPa)	Pr_{mass} (Pa/J kg⁻¹)
Control	0.394	5.2	92.3 (SD = 1.49)	0.13 (SD = 0.10)	13.5 (SD = 7.81)
Sample A	0.475	0.7	89.9 (SD = 0.85)	0.75 (SD = 0.03)	26.3 (SD = 0.86)
Sample B	0.639	0.8	93.3 (SD = 1.03)	0.58 (SD = 0.03)	20.5 (SD = 0.57)
Sample C	0.484	0.8	90.2 (SD = 0.81)	0.67 (SD = 0.02)	22.3 (SD = 0.46)

Acknowledgements

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III

TOVÁBBKÉPZŐ KÖZLEMÉNYEK

Poliolok jelentősége a rágótabletták formulálásában

Göcző Hajnalka, Szabóné dr. Révész Piroska

A szerzők rágótabletták tervezésével és előállításával foglalkoznak. A rágótabletta az utóbbi időben igen népszerű gyógyszerforma. Előállításának legelőnyösebb módja a direkt préselés. Erre a célra töltő- és kötőanyagként is egyaránt poliolokat (cukoralkoholokat) alkalmaznak. A cikk áttekintést ad a rágótabletták előállításának fontosabb alapelveiről, majd ismerteti a direkt préselésre alkalmas poliolok legfontosabb sajátságait.

Bevezetés

Napjainkban a gyógyszerformák sokszínűsége biztosítja a betegek számára a gyógyszerkészítmények jobb elfogadhatóságát. A gyógyszert rendelő orvos a betegségnek ill. a beteg ember állapotának, életkorának és személyiségének figyelembevételével többféle, ugyanolyan hatóanyagot tartalmazó gyógyszerforma közül (pl. tabletta, drazsé, pezsgőtabletta, oldat stb.) kiválaszthatja a beteg számára leginkább tolerálhatót. A készítmény elfogadása a beteg részéről a gyógyulás felé vezető út egyik fontos mérföldköve.

Az utóbbi időben az egyik legkedveltebb gyógyszerforma a rágótabletta, amely a perorális tabletták csoportjába tartozik [1]. A rágótabletták (Compressi manducabilis) kellemes ízű és aromájú, viszonylag nagy átmérőjű tabletták. Tekintve, hogy dezintegráló anyagot nem tartalmaznak, így csak lassan esnek szét ill. oldódnak fel. A beteg a tablettát szétrágja, majd lenyeli. A hatóanyag – a szopogató tablettával ellentétben – a gyomor-bél traktusból abszorbeálódik [2]. Amerikai kardiológusok legújabb kutatásai alapján az acetil-szalicilsav tartalmú rágótabletták alkalmazásával a hatóanyag felszívódási sebessége kb. a kétszeresére nő a perorális tablettával szemben, ami különösen előnyös az infarktusra hajlamos betegek gyógykezelésében.

A rágótabletta tehát gyakran előnyösebb, mint a hagyományos, perorális tabletta, a pezsgőtabletta vagy a kapszula. Előnyei a következők:

– a betegek szívesen elfogadják, különösen a gyermekek és az idősek, akiknek a tabletta lenyelése gondot okoz;

– az elfogadhatóságot javítja a kellemes íz is;

– gyorsabb a hatáskezdet, pl. antacid hatóanyagot tartalmazó rágótabletták esetében;

– lehetővé teszi nagy mennyiségű hatóanyag bevitelét, hiszen a tablettaméret nem akadály;

– víz nélkül is bevehető.

A továbbiakban a gyógyszerforma előállításának alapelveit, ill. az összetételekben leggyakrabban alkalmazott segédanyagok – különös tekintettel a poliolokra – tulajdonságait részletezzük.

A rágótabletták előállításának fontosabb alapelvei

A rágótabletták előállításánál nagyon fontos követelmény, hogy kellemes ízűek legyenek (figyelembe kell venni a készítmény ízét, aromáját, a szájban keltett érzetet és az utóérzetet) [3]. Emellett elengedhetetlen, hogy más szempontból is megfeleljenek. Ilyen követelmény pl. a stabilitás, a hatékonyság, a gyógyszerforma minősége stb. Rágótabletták hatóanyagaként napjainkban már számos anyagot feldolgoztak, így a vitaminokon, ásványi anyagokon és nyomelemeken túl egyéb anyagokat, pl. analgetikum, antiepileptikum stb. is. A teljesség igénye nélkül néhányat az *I. táblázatban* mutatunk be.

I. táblázat

Néhány törzskönyvezett rágótabletta adatai

Készítmények	Hatóanyagok	Javallat
Multi-Tabs	vitaminok, ásványi anyagok és nyomelemek	vitamin- és ásványianyag hiányállapotok
Unicap	vitaminok, ásványi anyagok és nyomelemek	vitamin- és ásványianyag hiányállapotok
Centrum jr. extra C Centrum jr. extra calcium	vitaminok, ásványi anyagok és nyomelemek	vitamin- és ásványianyag hiányállapotok
Active jr.	vitaminok, ásványi anyagok és nyomelemek	vitamin- és ásványianyag hiányállapotok
Aspirin	acidum acetylsalicylicum	fájdalom, rheumatikus panaszok, láz,
Digestif Rennie	papayotinum, pancreatinum, calcium carbonicum, magnesium carbonicum, oleosum menthae piperitae	emésztési zavarok
Maalox	magnesium hydroxydatum aluminium hydroxydatum	gyomorsósav túltermelés
Ceolat	dimeticonum	meteorismus, puffadás, teltségérzet Roemheld-szindr.
Lamictal	lamotriginum	epilepszia

Mivel a formulálandó összetétel sok esetben nedvességre érzékeny hatóanyagot (vitaminok, acetil-szalicilsav [4]) tartalmaz, így előállításuk legelőnyösebb módja a direkt préselés. A megfelelő mennyiségben alkalmazott segédanyagok (vivőanyag, kötőanyag, ízjavító, lubrikáns stb.) hozzáadásával megfelelő minőségű porkeverék (folyási sajátság, préselhetőség, kompatibilitás-stabilitás) és tabletta (hatóanyag-tartalom, adagolási pontosság, szilárdság) állítható elő [1].

A kellemes íz elérése érdekében vivőanyagként mono- és diszaccharidokat, valamint polihidroxi-vegyületeket alkalmaznak és szükség esetén ezeket egyéb ízjavítókkal egészítik ki. A mono- és diszaccharidok közül a szacharóz, a glükóz, a fruktóz és a laktóz, a cukoralkoholok közül a mannit, a szorbit, a xilit és a maltit használatosak a leggyakrabban. A hatóanyag kellemetlen íze esetenként megkívánja az édes íz erőteljes fokozását. Erre a célra szaccharimid-nátriumot és ciklamátokat használnak kis mennyiségben. (Megjegyzendő, hogy számos országban betiltották ill. jelentősen korlátozták a mesterséges édesítőszerek alkalmazását.) A hatóanyag kellemetlen íze esetén fontos, hogy melyik segédanyagnak milyen az ízfedő képessége. Ezt a szacharóz édes ízéhez viszonyítva adják meg.

Az ízérzés javítására a természetben is előforduló illat- és aromaanyagokat is lehet használni, aszerint, hogy milyen ízérzést akarunk kiváltani. Pl.:
– édes íz: vanília, méz, gyümölcsök keveréke,
– savanyú íz: citrom, málna, eper,
– kesernyés íz: ánizs, dió, fűszerek stb. [5].

A rágótabletták jobb elfogadhatóságát színezésük is javítja. Általában a színanyagok is természetes eredetűek. Néhányat felsorolunk közülük, aszerint, hogy milyen színű tablettát szeretnénk előállítani:
– sárgától narancssárgáig: citrom, narancs, banán,
– a rózsaszíntől pirosig: cseresznye, tutti-frutti, eper,
– kék: fekete áfonya, szilva,
– zöld: pisztácia, fodormenta, menta,
– barna: csokoládé, burgundi, karamell.

A legtöbb esetben a vivő- és ízjavító anyagok mellett lubrikáns alkalmazására is szükség van a rágótabletták préselésénél. A leggyakrabban alkalmazott lubrikánsok: a magnézium-sztearát, a sztearinsav, a kalcium-sztearát 0,5–1,5%-os mennyiségben. Kivételt képez a mannit, mint vivőanyag, ugyanis ez esetben közel 3% lubrikánsra van szükség.

A rágótabletta előiratok kidolgozása tehát többlépcsős folyamatként valósítható meg:
1. A hatóanyag sajátságainak meghatározása: alapíz, aroma, utóhatások, ezen sajátságok intenzitása, egyéb organoleptikus jellemzők alapján.
2. A hatóanyag kellemetlen ízének elfedésére irányuló kísérletek, ízanyag hozzáadása nélkül: pl. mikrokapszulázás, adszorpció, ioncsere, sóderivátumok létrehozása, granulátumképzés stb. (Ha a hatóanyag mennyisége kevés vagy nem kellemetlen az íze, ez a lépés mellőzhető.)
3. Kiválasztani a vivőanyagot és egyéb segédanyagokat (pl. kötőanyag, színanyag, glidáns stb.). Először ízesítetlen tablettákat állítanak elő. Ez lesz a kísérlet alapvonala, és ebből kiindulva legalább két ízesítési módszert kell kifejleszteni, majd kiválasztani a legjobbat.
4. Optimalizált kísérleti körülmények és berendezések biztosítása [5].

A gyártási technológia kifejlesztését és a velejáró vizsgálatokat ill. a gyártást a kész termék széleskörű vizsgálata követi. A rágótabletták minősítésével kapcsolatban a VII. Magyar Gyógyszerkönyv külön fejezetben nem rendelkezik ill. a gyógyszerforma nevét sem említi, ezért vizsgálatukra a Tabletták c. fejezetben ill. a gyártási előiratban rögzített szabályok vonatkoznak.
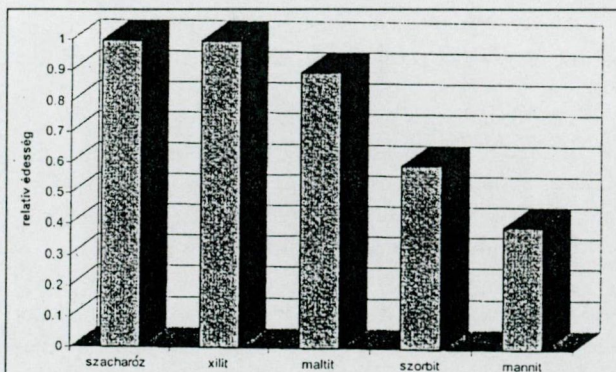
A hatályban lévő III. Európai és 23. Amerikai Gyógyszerkönyv a szájban alkalmazott gyógyszerkészítményeknél említi a rágótablettákat és vizsgálatukra előírja a tömegállandóság és az egységes hatóanyag-tartalom ellenőrzését.

A rágótabletta-összetétel kidolgozását, csakúgy, mint minden előirat tervezését jelentősen megkönnyíti, ha kisszámú segédanyag felhasználására van szükség. A gyógyszertechnológusok számára az ideális vivőanyag ennél a gyógyszerformánál kellemesen édes ízű, jó folyási sajátsággal és préselhetőséggel rendelkezik, tehát alkalmas direkt préselésre; önmagában egyesíti a megfelelő íz és a gyógyszerforma minőségének biztosítását. Ilyen anyagok a már korábban is említett poliolok.

Poliolok

A poliolok kémiailag polihidroxi-alkoholok. Mindegyik cukoralkoholból többféle védjegyzett nevű származék ismeretes a kereskedelemben, amelyek szemcseméretben, térfogattömegben és egyéb sajátságokban különböznek egymástól, és ezeknek a származékoknak a felhasználási területe is eltérő. Szoros kapcsolatban vannak a cukrokkal, de az aldehid- vagy ketoncsoport helyett hidroxil-csoportot tartalmaznak. Ez a hidroxil-csoport kevésbé reaktív, mint az aldehid- vagy ketoncsoport, pl. nem reagál az aminosavakkal [6].

A poliolok nagyon stabilak a hűtéssel és a melegítéssel szemben, vizes oldatukban a hidrolízis rendkívül lassan megy végbe. Kellemes, édes ízűek és nem keltenek a szájban kellemetlen utóérzetet. Relatív édességük a szaccharózhoz viszonyítva az *1. ábrán* látható. A xilit édes íze egyenértékű a szaccharózéval.

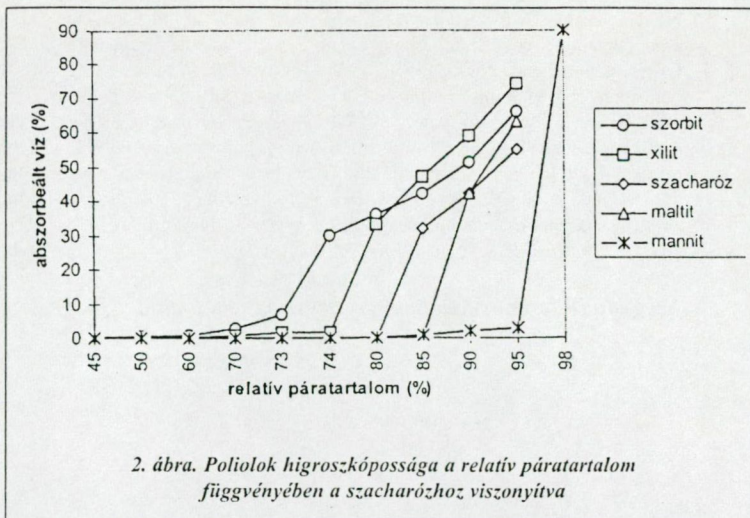*1. ábra. Néhány poliol relatív édessége a szaccharózhoz viszonyítva*

A poliolok a bélrendszerben a vékonybél szakaszon, a szőlőcukor aktív transzportjától lassúbb folyamat segítségével, ozmotikus passzív transzporttal szívódnak fel. A monoszaccharid poliolok esetében (mannit, xilit, szorbit) ez egy egyszerű folyamat, viszont a diszaccharid maltitnak először hidrolizálódnia kell szőlőcukorrá és szorbittá, ezután következik a felszívódás. A bélrendszer további szakaszára is eljutó molekulák a kolonban illékony zsírsavakká fermentálódnak. A poliolok energiaértéke 2,4 kcal/g (összehasonlításként: az egyéb szénhidrátoké 4,0 kcal/g). A metabolizmusukban résztvevő enzimek működése független az inzulintól, így csak kisfokú glikémiát és inzulinválaszt okoznak a szervezetben, ezért a cukorbetegek számára szőlőcukor helyett alkalmazhatók.

2. ábra. Poliolok higroszkópossága a relatív páratartalom függvényében a szacharózhoz viszonyítva

A poliolok nem metabolizálódnak a száj baktériumflórája által, nem acidogének és nem kariogének, ezért a cukrok helyett való alkalmazásuk különösen javasolható kozmetikai termékekben: pl. fogkrémekben, szájöblítő folyadékokban, ill. rágógumikban, édességekben, folyékony gyógyszerformákban.

Az amerikai JECFA (Joint FAO/WHO Expert Committee on Food Additives) szerint teljes biztonsággal alkalmazhatók élelmiszerekben is, és az elfogyasztható napi mennyiséget sem korlátozzák [6].

Amint a felsorolt tulajdonságaik is bizonyítják, a poliolok felhasználhatósága a gyógyszergyártás területén és azon kívül is rendkívül sokszínű [7–9].

Ami a tablettagyártást illeti, néhány cukoralkoholt közvetlen, előzetes granulálás nélküli préselésre fejlesztettek ki (II. táblázat). Ezek a termékek egyaránt alkalmazhatók töltő- és kötőanyagként a tabletták gyártása során. A felhasználónak tehát lehetősége van – a hatóanyag sajátságainak figyelembevételével – a leginkább alkalmas cukoralkohol kiválasztására.

II. táblázat
Néhány direkt préselésre alkalmazott poliol adatai

Védjegyzett név	Anyag	Szemcseméret (a szemcsék több, mint 90%-a) (mm)	Térfogattömeg (g/100ml)
Karion Instant Pharma® (MERCK, Darmstadt)	szorbit	0,30-1,0	37.25
Neosorb P 20/60® (Roquette, Lestrem)	szorbit	0,30-1,0	59.37
Pearlitol 400 DC® (Roquette, Lestrem)	mannit	0,20-0,63	64,67
Pearlitol SD 200® (Roquette, Lestrem)	mannit	0,01-0,40	44,93
Xylisorb 700® (Roquette, Lestrem)	xilit	0,20-0,80	73,36

A II. táblázat adatai, valamint saját kutatási eredményeink alapján [10] tulajdonképpen minden poliol javasolható direkt préselésre. Számított Carr index [11] értékük 4,27 és 13,60 között volt, ami kiváló folyási sajátság-

ra és tömöríthetőségre utal. A préselhetőségi vizsgálatok során a poliolok jó plasztikus sajátságot mutattak, ami a préstestek nagy szilárdságában (150-200 N) is megnyilvánult. A gyógyszerforma tervezőjének azonban figyelembe kell venni a hatóanyag sajátságait (folyás, tömöríthetőség, préselhetőség) is. Így pl. javasolható, hogy viszonylag nagy szemcseméretű hatóanyag esetében segédanyagként a Karion-t vagy a Neosorb-ot alkalmazza, s ezzel préselés során elkerülhető a porkeverék frakcionálódása, vagyis az apróbb szemcsék áthullása a nagyobbak között. Ebben az esetben viszont nagy térfogattal ill. töltési mélységgel kell számolni, ami súrlódási problémát vethet fel. Nagytömegű tabletták préselésénél viszont ajánlatos a nagy térfogattömeggel rendelkező Xilisorb 700-at választani. Megjegyezzük, hogy igen jó paraméterekkel rendelkező rágótabletták állíthatók elő mindkét Pearlitol (400 DC, SD 200) felhasználásával, amennyiben a hatóanyag szemcsemérete 0,01 és 0,6 mm között van. Célszerű azonban itt is figyelembe venni a két termék eltérő térfogattömegét.

Természetesen a tabletták tervezésénél a környezeti paramétereket is figyelembe kell venni, pl. azt, hogy az anyagok adott klimatikus viszonyok között hogyan viselkednek. A polioloknak ugyanis különböző a vízmegkötő képessége. A 2. ábra alapján látható, hogy nagyon magas relatív páratartalom ill. nedvességre érzékeny hatóanyag esetén a mannitol és a maltitol alkalmazása előnyösebb.

A bemutatott eredmények alapján tehát megállapítható, hogy a poliolok sokféle típusa biztosítja a gyógyszertechnológus számára a választás szabadságát, valamint kiváló minőségű gyógyszerforma megtervezését és kivitelezését.

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H . G ö c z ö , P . R é v é s z - S z a b ó : *Importance of the poliols in the formulation of tablets.*

The authors are employed in planning and making of chewable tablets. The chewable tablet is recently very popular form. Direct pressing is the most advantageous method to product these tablets. The polyols are used as filler and binder materials for making chewable tablets by direct pressing.
This article gives summary about basic principles of preparing of chewable tablets and properties of polyols.

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IV

Polyols in the Development of Chewable Tablets Containing Magnesium Aspartate

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Summary

Polyols are materials that are successfully used in many fields of the pharmaceutical industry in consequence of their favourable properties. This work reports on preformulation studies (particle size distribution, mass by volume and flowability) of different polyols (sorbitol, xylitol and mannitol) used as vehicles to produce chewable tablets containing magnesium aspartate by direct tabletting. The physical parameters (uniformity of mass, friability and crushing strength) and the magnesium content of tablets were determined. The magnesium content was measured by atomic absorption spectrometry. The results allow Pearlitol SD 200® and Neosorb P 20/60® to be suggested as filler and binder materials for the manufacture of chewable tablets.

Zusammenfassung

Polyalkohole in der Entwicklung der Magnesiumaspartat-Kautabletten

Polyalkohole (Sorbitol, Xylitol und Mannitol) sind Materialien, die wegen ihrer günstigen Eigenschaften mit Erfolg in der pharmazeutischen Industrie eingesetzt werden. Vorformulierungsuntersuchungen mit verschiedenen Polyalkoholen wurden durchgeführt und ihr Einfluß auf den Herstellungsprozeß von Magnesiumaspartat-Kautabletten bei der Direkttablettierung untersucht (Korngrößenverteilung, Schüttdichte, Fließeigenschaften). Die physikalischen Parameter (Dosierungsgenauigkeit, Abrieb- und Bruchfestigkeit) und der Magnesium-Gehalt der Tabletten wurden bestimmt. Der Magnesium-Gehalt wurde mit dem Atomabsorptionsspektrometer geprüft. Die Ergebnisse erlauben es, Pearlitol SD 200® und Neosorb P 20/60® für die Herstellung von Magnesiumaspartat-Kautabletten vorzuschlagen.

1. Introduction

Polyols (sorbitol, mannitol and xylitol) are widely used materials with a pleasant sweet taste, and no aftertaste. They have many applications in the pharmaceutical, food and cosmetic industries [1–6]. They are used as sweetening agents in the confectionery industry and for dental protection, because polyols are not metabolized by oral bacteria and are therefore not acidogenic or cariogenic.

Polyols are polyhydric alcohols and closely related to sugars, but with the sugar aldehyde or ketone group replaced by a hydroxy group. The hydroxy group is less reactive than the sugar aldehyde or ketone group, and does not react, for example, with amino acids. The polyols have low hygroscopicity (especially mannitol), stabilize moisture content and improve storage. They are very stable to heat and melt without decomposition. The polyols induce very low glycaemia, and are suitable for diabetics. These materials are completely safe for use in food. The acceptable daily intake for all polyols is given as "not specified" by the JECFA (Joint FAO/WHO Expert Committee on Food Additives). The relative sweetness of these materials is compared with that of sucrose: sucrose: 1; sorbitol: 0.7; mannitol: 0.4. The sweetness of xylitol is equivalent to that of sucrose [7].

They can be used as filler and binder excipients in chewable tablets. These tablets usually contain refreshment materials (e.g. mint), vitamins and minerals.

Chewable tablets are produced by direct tabletting, which is the most efficient process, because it is a faster, simpler and less expensive method [8] than wet granulation and tabletting, but only if powders with good flowability and compressibility are used. Accordingly, these and other preformulation investigations [9] (e.g. determination of particle size distribution and mass by volume) precede tablet formulation.

Chewable tablets are becoming increasingly popular in the pharmaceutical and food industries. The special advantages of this class of tablets [8] include their convenience and popular acceptance (e.g. for young children and some geriatric persons), and in certain cases chewable tablets are more advantageous than effervescent tablets for supplying vitamins and minerals (e.g. there is no dissolving). The pleasant taste is a very important attribute, but chewable tablets have to meet other requirements (e.g. stability, efficiency and quality of tablet form).

The aim of this work is the study of some registered brands of polyols developed for direct tabletting as filler and binder materials. They are compared by producing chewable tablets containing magnesium. In this respect, magnesium aspartate is an up-to-date form for magnesium supplementation. It is well known that magnesium is an important mineral for the human body [10]. Various quantities of magnesium enter the organism with the food, but in many cases care should be taken to guarantee supply (e.g. in children, pregnants and elderly people). The recommended daily intake of magnesium as a food complement is from 50 to 450 mg per day, depending on the age and the geographical location. The level was maximized by the WHO as 200 to 300 mg per day.

After the preformulating investigations and compression of the materials, the investigation of chewable tablets followed: measurement of the physical parameters and the active agent consistency of the tablets by means of atomic absorption spectrometry. These investigations allow an assessment of the different excipients and suggest compositions for chewable tablets.

2. Materials and methods

2.1. Materials

Magnesium aspartate (magnesium aminosuccinate tetrahydrate) was used as active agent (Chemical Works of Gedeon Richter Ltd., Budapest, Hungary). It is a white, odourless and tasteless crystalline powder.

The polyols were as follows: Neosorb P 20/60® (Roquette, Lestrem, France) containing D-sorbitol, Karion® (Merck, Darmstadt, Germany) containing D-sorbitol, Pearlitol SD 200® (Roquette) containing D-mannitol, Pearlitol 400 DC® (Roquette) containing D-mannitol, and Xylisorb 700® (Roquette) containing xylisorb. Magnesium stearate was applied in the tablet technology as an antiadhesive substance.

2.2. Preformulation studies

The particle sizes of the materials were controlled by sieving (DIN sieve, German standard). The powder fractions retained by the individual sieves were measured and expressed in mass percentages.

ASTM D 392-38 equipment was used for the determination of mass by volume (according to U.S. Pharmacopoeia XXIII and National Formulary XVIII).

Carr index was calculated from the poured and tapped densities [11]:

$$\text{Carr index (\%)} = \frac{\text{tapped density} - \text{poured density}}{\text{tapped density}} \cdot 100$$

The poured and tapped densities were determined with a Stampfvolumeter 2003 (J. Engelsmann AG Apparatebau, Ludwigshafen, Germany).

The relationship between Carr index and the flowability of materials is well known, and the Carr index reflects the compressibility of the crystals [9].

2.3. Formulation of chewable tablets

Five compositions were elaborated, in which magnesium aspartate was the active agent. 20 mg of magnesium was planned for each tablet because of the daily repeated applicability and the needs of children. The polyols have a pleasant sweet taste, so the application of other corrigents was not necessary. 1 % of magnesium stearate was used to promote lubrication. The composition of one tablet was as follows (mg per tablet):

Magnesium aspartate	250.0
Excipient (filler and binder material)	245.0
Magnesium stearate	5.0
Total mass:	500.0

Numbering according to excipients is a follows:
Composition 1: Karion
Composition 2: Neosorb P 20/60
Composition 3: Xylisorb 700
Composition 4: Pearlitol SD 200
Composition 5: Pearlitol 400 DC

The components were mixed for 5 min with a Turbula mixer (W. A. Bachofen Maschinenfabrik, Basel, Switzerland) at 50 rpm. The powder mixture was pressed to tablets by a Korsch EKO eccentric tablet maschine (Emil Korsch Maschinenfabrik, Berlin, Germany). The compression tools were single flat punches 12 mm in diameter. The rate of compression was 30 tablets/min with a pressure force of 18 kN at an air temperature of 24 °C and an air relative humidity of 45 %.

2.4. Investigation of chewable tablets

Investigations were carried out 24 h after pressing. The masses of the tablets were measured to the order of 0.1 mg. The relative standard deviation (RSD) was calculated from 20 data points. The crushing strength was determined using Heberlein apparatus (Locle, Zürich, Switzerland) (20 tablets). The friability was determined with an Erweka friabilator (Erweka Apparatebau GmbH, Heusenstamm, Germany).

The magnesium content of chewable tablets was determined by atomic absorption spectrometry. The Pharmacopoeias (e.g. US and Euroepan) usually prescribe the determination of magnesium by a tritrimetric method. Atomic absorption spectrometry is more sensitive and more exact than titrimetry. The measurement of the solutions of excipients preceded the measurement of the chewable tablets. A small absorption in the case of magnesium stearate was measured at the applied wavelength, and this was subtracted from the results. The measurements were carried out with a Perkin-Elmer 4100 (Bodenseewerk Perkin Elmer GmbH, Überlingen, Germany) atomic absorption spectrometer under the following conditions: flame-atomizing, wavelength 285.2 nm, slit width 0.7 nm, air-acetylene gas mixture (air: 8.0 l/min, acetylene: 3.5 l/min), read time 5 s.

Table 1: Mass by volume and Carr index of the applied materials.

Materials	Mass by volume (g/100 ml)	Carr index (%)
Magnesium aspartate	78.97	9.07
Karion	37.25	13.60
Neosorb P 20/60	59.37	4.27
Xylisorb 700	73.36	13.10
Pearlitol SD 200	44.93	8.53
Pearlitol 400 DC	64.67	5.60

2.5. Statistical calculation

The standard deviation (SD), relative standard deviation (RSD) and the two-sample analysis were carried out with the Statgraphics package (STSC, Inc. and Statistical Graphics Co., USA); the confidence limit was 95 %.

3. Results and discussion

The raw materials applied for direct pressing must have good flowability and compressibility. Therefore, in the first step preformulation studies were performed in order to control these properties of the applied powders.

The particle size distribution was the subject of the first preformulating investigation. The investigated materials were found to have different particle sizes (Fig. 1). The particles were more or less spherical in shaper. 90 % of the magnesium aspartate crystals were smaller than 400 µm. Pearlitol SD 200 had a similar particle size. 90 % of the crystals of Pearlitol 400 DC ranged between 200 and 630 µm, but Xylisorb, Neosorb and Karion consisted of much larger crystals (particularly Neosorb and Karion). Thus, the particle size of Pearlitol SD 200 was the most similar to that of magnesium aspartate, and those of Neosorb and Karion were the most different.

The results of the determination of mass by volume are presented in Table 1. It can be seen that the mass by volume of Xylisorb (73.36 g/100 ml) corresponded most closely to that of magnesium aspartate (78.97 g/100 ml), and that of Karion was the most different, with approximately half the mass by volume of the active agent.

The similar particle size distribution and mass by volume ensure the homogeneous distribution of the active agent in the powder mixture and help prevent the separation of particles with different sizes in the tablet manufacture. Therefore, these properties influence the constantness of active agent content (uniformity of content) in the chewable tablets.

The results of the determination of Carr index are given in Table 1. The connection between Carr index and flowability reveals that the applied materials had excellent flow properties (Carr index = 5–15 %); this was particularly true for Neosorb, Pearlitol 400 DC and Pearlitol SD 200 due to their crystal habit (form and surface). The preformulation results allow Neosorb P 20/60 and two sorts of Pearlitol to be suggested as filler and binder materials for direct tablet manufacture.
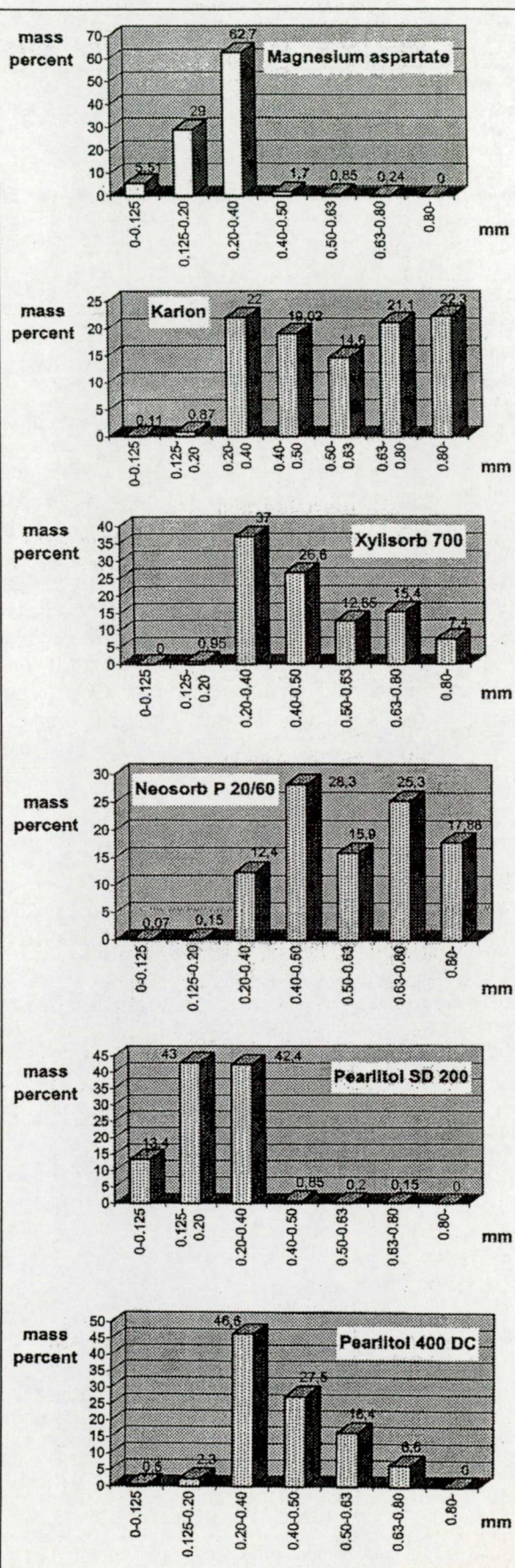

Fig. 1: Particle size distributions of the applied polyols.

Table 2: Physical parameters of chewable tablets.

Composition of chewable tablets	Filling depth (mm)	Average mass (g)	Mass variation (RSD)	Friability (%)[a]	Crushing strength (N)[a]
Composition 1 (Karion)	6	0.5275	0.65	0.92 (0.03)	105.8 (13.14)
Composition 2 (Neosorb)	5	0.5117	0.33	1.16 (0.07)	66.0 (7.11)
Composition 3 (Xylisorb)	4	0.4561	6.65	tablets broken	not measurable
Composition 4 (Pearlitol SD 200)	6	0.5035	0.18	1.20 (0.06)	77.9 (4.18)
Composition 5 (Pearlitol 400 DC)	5	0.5031	0.24	1.62 (0.09)	46.9 (2.79)

[a] Values in parentheses: standard deviation.

During the compression process, there were no problems except in the case of the mixture containing Xylisorb, because the filling depth was very low (4 mm) due to the big mass by volume, and this caused problems in filling and pressing. These problems are reflected in the physical properties of Xylisorb tablets. The physical parameters of the chewable tablets are listed in Table 2. In respect of mass, mass variation, friability and crushing strength, the tablets proved of good quality, except for the tablets of Xylisorb. Tablets containing Karion exhibited the best hardness, whereas those of Pearlitol 400 DC displayed a very low hardness.

Table 3: Results of analytical investigation of chewable tablets.

Composition of chewable tablets	Tablet mass (g)	Magnesium content (mg)	Deviation of magnesium content (mg)
Composition 1 (Karion)	0.5113	20.17	0.45
	0.4838	17.70*	−2.02*
	0.5399	24.33*	4.61*
	0.5300	21.80*	2.81*
	0.5074	19.72	0.00
Composition 2 (Neosorb)	0.4937	20.17	0.45
	0.5037	19.72	0.00
	0.4975	20.79	1.07
	0.4996	20.56	0.84
	0.5146	19.72	0.00
Composition 3 (Xylisorb)	0.4822	19.10	−0.62
	0.4603	18.43	−1.29
	0.4512	17.93	−1.79
	0.4840	19.16	−0.56
	0.4805	19.21	−0.51
Composition 4 (Pearlitol SD 200)	0.4908	20.28	0.56
	0.4785	19.72	0.00
	0.5078	20.96	1.24
	0.4937	20.00	0.28
	0.5085	20.34	0.62
Composition 5 (Pearlitol 400 DC)	0.4010	20.17	0.45
	0.4905	20.84	1.12
	0.4916	21.18	1.46
	0.4941	20.73	1.01
	0.5030	21.35	1.63

* Values are out of the range of the magnesium content: 17.75–21.69 mg (theoretical value: 19.72 mg).

The results of analytical investigations can be seen in Table 3. For a tablet of 0.50 g, the theoretically measurable magnesium content is 19.72 mg, and Table 3 shows the deviations from this theoretical value. The results in the case of tablets containing Karion indicate deviations in excess of the value set by US Pharmacopeia (± 10 %). In this case, the tablet mass, mass variation and hardness were suitable, and the uniformity of mass (presuming homogeneity of the powder mixture) suggests the uniformity of the active agent content. However, there was a great difference between the particle size and the mass by volume of Karion and those of magnesium aspartate, so that these differences gave rise to separation of the particles of the powder mixture during the tabletting process. In consequence of this, the active agent content of Karion tablets was not suitable.

The magnesium content in Xylisorb tablets was good, because of the similar mass by volume to that of magnesium aspartate, but the physical parameters of these tablets were not suitable (filling depth). Other compositions did not exhibit large differences from the theoretical value.

These investigations established that two of the applied vehicles (Pearlitol SD 200 and Neosorb) are suitable in all respects (physical parameters and analytical investigation) for direct tabletting and the formulation of chewable tablets with these compositions. These polyols display a better flow property, a similar particle size distribution (Pearlitol SD 200) and mass by volume (Neosorb) to those of magnesium aspartate. Pearlitol 400 DC, Xylisorb and Karion have different particle size distributions and masses by volume from those of the active agent, and in these cases the physical parameters or the magnesium content were not suitable. These problems can probably be eliminated by modification of the composition.

The differences in particle size, mass by volume and flowability (Carr index) of the applied materials appeared in the preformulation studies. These differences caused problems in the tabletting process and with the magnesium content of the chewable tablets. These in-

vestigations are therefore suitable for prediction of the results of investigation of the final product and help in the planning of appropriate good compositions of the tablets.

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V

Crystal growth of drug materials by spherical crystallization

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Abstract

One of the crystal growth processes is the production of crystal agglomerates by spherical crystallization. Agglomerates of drug materials were developed by means of non-typical (magnesium aspartate) and typical (acetylsalicylic acid) spherical crystallization techniques. The growth of particle size and the spherical form of the agglomerates resulted in formation of products with good bulk density, flow, compactibility and cohesivity properties. The crystal agglomerates were developed for direct capsule-filling and tablet-making. © 2002 Elsevier Science B.V. All rights reserved.

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1. Introduction

The production of spherical crystal agglomerates which is one possibility of the crystal size growth has recently gained great attention and importance, due to the fact that the crystal habit (form, surface, size and particle size distribution) can be modified during the crystallization process. In consequence of such modifications in the crystal habit, certain parameters can also be changed: bulk density, flow property, compactibility, cohesivity, dissolution rate, stability, etc. [1–3].

In the pharmaceutical industry, the crystal size growth and the formation of the spherical crystal agglomerates are very important for preparing the solid dosage forms (e.g. capsules, tablets, etc.). The particle size of the agglomerates produced by the spherical crystallization techniques is ≈300–500 μm in diameter and their form is more or less spherical. The agglomerates have very good flow property, high bulk density and compressibility values. They can be used directly for capsule-filling (without excipients) and direct tablet-making (without granulation, drying, etc.). The drug materials produced by the spherical crystallization technique result in the economical process in the development of the solid dosage forms.

In the pharmaceutical field, Kawashima et al. [4] have given impulse to the research of the spherical crystallization process. The *typical spherical crystallization technique* employs three solvents: one is

the substance dissolution medium, another is a medium, which partially dissolves the substance, and the third is the wetting solvent for the substance. Of course, the traditional crystallization processes (salting-out precipitation, cooling crystallization, crystallization from the melting, etc.) can also be used to produce spherical crystal agglomerates [5]. It may be called a *non-typical spherical crystallization process*. The commercial magnesium aspartate and acetylsalicylic acid crystals are tetragonal and prism-shaped, with different sizes and particle size distributions on the market. Their flow property and compactibility are poor due to the crystal habit and the electrostatic charge. Since these drug materials are used to direct tablet-making (e.g., effervescent or chewable tablets) and capsule-filling, the particle size ($\approx 500\,\mu$m) and the spherical form are very important because of their processibility.

In this work, agglomerates of magnesium aspartate and acetylsalicylic acid were developed by non-typical and typical spherical crystallization techniques. This process and the solvent mixtures were used first in making spherical magnesium aspartate and acetylsalicylic acid. The control materials were commercial samples.

2. Experimental procedures

2.1. Development of spherical magnesium aspartate (MASP) crystals by the non-typical spherical crystallization process (MASP developed)

The agglomeration of magnesium aspartate was carried out by salting-out combined with cooling. The formation of salt preceeded the crystallization process. The experiments were carried out in a mechanically stirred tank with a volume of 1000 ml. A Julabo thermostat with computer control (Julabo Labortechnik, Seelbach, Germany) was used for the cooling process. A total of 500 ml of 20 wt% magnesium aspartate was placed in the crystallizer tank. The good solvent for MASP was water and the poor solvent was methanol (10–50%, in relation to the measured solution). The other parameters of the crystallization were as follows: stirring rate: 50–100 rpm,

feeding rate of methanol: 0.36 l/h, temperature interval: 90–10°C and cooling rate: 0.7°C/min.

2.2. Development of spherical acetylsalicylic acid (ASA) crystals by the typical spherical crystallization process (ASA developed)

The experiments were carried out in a mechanically stirred tank with a volume of 500 ml. A Julabo thermostat with computer control was used for the cooling process. 121.6 g of ASA was dissolved in 225 ml of ethanol (20–40% v/v) at 40–70°C, and a carbon tetrachloride–water mixture (1–5% w/v) was added to the solution, followed by cooling at 0.6°C/min to 20°C with stirring (200 rpm).

Control materials were the commercial magnesium aspartate (*MASP control*) and acetylsalicylic acid (*ASA control*) products.

2.3. Particle size analysis

Determination of the particle size (length, breadth and roundness) was carried out with a Laborlux S light microscope and a Quantimet 500MC (Q500MC) image processing and analysis system (LEICA Cambridge Ltd., UK). Roundness is a shape factor that provides information about the circularity of particles. It is calculated by software according to the following formula:

$$\text{roundness} = \text{perimeter}^2/4\pi \times \text{area} \times 1.064. \qquad (1)$$

The perimeter was calculated from the horizontal and vertical projections, with an allowance for the number of corners. An adjustment factor of 1.064 corrected the perimeter for the effect of the corners produced by digitization of the image. When roundness value is close to one, the particles are close to spherical.

2.4. Morphological study

The morphology of the crystals was controlled by scanning electron microscopy (SEM) (JEOL JSM 50A, 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.

2.5. BET and BJH methods

The specific surfaces and micropore volumes of samples were determined with a Micromeritics ASA 2000 equipment (Instrument Corp., Norcross, GA, USA)) from data (20 points each) of nitrogen adsorption and desorption isotherms at the boiling point of liquid nitrogen under atmospheric pressure (−196°C). The specific surface was calculated, in the validity range of the BET-isotherm [6], from the slope and intercept of a line characterized by 5 measuring points. The micropore volumes were calculated via the BJH method [7].

2.6. Study of flow time, bulk density and Carr index

The flow time (s/100 ml) was measured with an ASTMD 329–38 equipment (according to Ph. Eur 3rd).

The bulk densities (poured and tapped densities) were determined with a Stampfvolumeter 2003 (J. Engelsmann AG Apparatebau, Ludwigshafen, Germany). The Carr index [8] was calculated from the densities:

$$\text{Carr index } (\%) = \frac{\text{tapped density-poured density}}{\text{tapped density}} \times 100. \tag{2}$$

The Carr index reflects the compactibility of the powders, and there is a correlation between the Carr index and the flowability of the crystals [9].

2.7. Compactibility and cohesivity

The Stampfvolumeter measurements allow calculation of the compactibility and cohesivity values via the modified Kawakita equation [10,11]

$$\frac{N}{C} = \frac{1}{a}N + \frac{1}{ab}, \tag{3}$$

where N is the number of taps, C is the degree of volume reduction, and a and b are constants: $1/a$ describes the degree of volume reduction at the limit of tapping and is called the compactibility;

$1/b$ is considered to be a constant related to cohesion and is called the cohesiveness. C is calculated via the following equation, and graphs of N/C vs. N are plotted:

$$C = \frac{V_0 - V}{V_0}. \tag{4}$$

The compactibility $1/a$ and cohesivity $1/b$ are obtained from the slope $(1/a)$ and the intercept $(1/ab)$ of the plot of the modified Kawakita equation.

3. Experimental results and discussion

The control (commercial) MASP sample consists of single, very small and agglomerated crystals (Fig. 1; Table 1). The agglomeration of these materials on salting out with cooling resulted in the formation of spherical agglomerates (Fig. 2). The developed MASP sample has a closed structure with a relatively large particle size (4 times bigger particles) (Table 1). In fact, a higher initial cooling rate and a lower stirring rate are favourable in the building-up of crystal agglomerates with a closed structure. The particles are nearly spherical, with a roundness value close to one (Table 1). The favourable macromorphological properties of the developed MASP agglomerates result in a sorter flow time, a higher bulk density and a smaller Carr index than those of the control sample (Table 2).
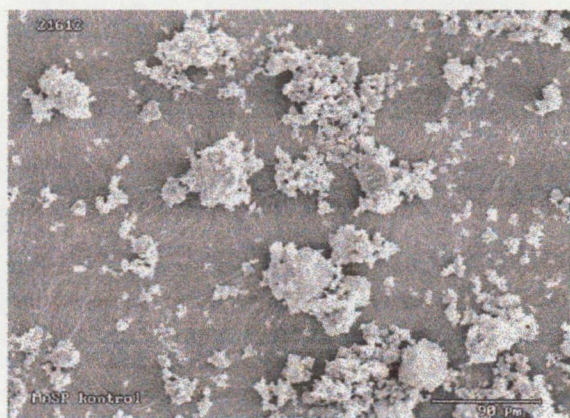

Fig. 1. Crystals of control MASP.

The micromorphological properties of the control and developed MASP samples are in keeping with their crystal structure and habit (Table 3). The bigger particle size and the associated decreased specific surface of the agglomerates resulted in better compactibility and cohesivity

Table 1
Particle size data of the samples

	Length (µm)	Breadth (µm)	Roundness
MASP control	75	52	1.37
SD	22	12	0.12
MASP developed	310	270	1.12
SD	35	32	0.10
ASA control	274	72	2.54
SD	62	13	0.29
ASA developed	522	332	1.40
SD	143	99	0.13

Fig. 2. Crystal agglomerates of developed MASP.

properties for the developed MASP sample than for the control sample (Table 4).

The control ASA crystals are tetragonal and prism-shaped monocrystals, with a very high roundness value (Fig. 3; Table 1). Their flow properties are poor due to the crystal habit and the electrostatic charge (Table 2). The non-typical spherical crystallization process (conventional stirred tank method) resulted in a few monocrystals and non-spherical crystal agglomerates. For the ASA sample, only typical spherical crystallization (agglomeration) can be used for the development of spherical particles with three solvents (ethanol–water–carbon tetrachloride). In the three-solvent system, the dissolved ASA was carried in the emulsion drops. In consequence of diffusion, the ethanol molecules left the emulsion drop and entered the aqueous phase through the emulsion film. The drop became oversaturated with respect to ASA, and in situ seed formation started at 37°C, followed by crystal formation. The built-up spherical ASA crystal agglomerates have a very hard, open structure. The small crystals in the agglomerates have the characteristic habit of the ASA monocrystals (Fig. 4; Table 1). The open structure of the particles did not influence the flow properties of the developed sample disadvantageously (Table 2). The Carr index indicates that the flowability of the developed ASA is about 4 times better than that of the control ASA sample.

The micromorphology parameters reveal that the developed ASA sample has a very low specific surface and micropore volume, and also an unusually large average pore diameter, which is connected with the typical building of the spherical crystal particles (Table 3). The reduced specific surface involves a decrease in the electrostatic charge, which appears in the better compactibility

Table 2
Parameters of powder rheological investigation of the samples

	Flow time (s/100 ml)	Poured density (g/ml)	Tapped density (g/ml)	Carr index (%)
MASP control	No flow	0.51	0.82	37.61
MASP developed	9.0	0.81	0.88	8.27
ASA control	No flow	0.36	0.45	19.99
ASA developed	8.4	0.43	0.46	5.99

Table 3
Micromorphological properties of the samples

	Specific surface (m^2/g)	Micropore volume[a] ($10^{-3} cm^3/g$)	Average diameter of pores (nm)
MASP control	0.76	2.80	13.5
MASP developed	0.58	3.01	28.6
ASA control	0.11	0.14	7.31
ASA developed	0.04	0.04	32.26

[a] Desorption micropore volumes were measured in the range of 1.7–300 nm in diameter.

Table 4
Compactibility $(1/a)$ and cohesiveness $(1/b)$ values of the samples by Kawakita model

	$1/ab$ intercept	$1/a$ slope	$1/b$	r^2
MASP control	122.18	4.23	28.88	0.9772
MASP developed	184.66	24.43	7.62	0.9272
ASA control	91.75	3.97	23.10	0.9872
ASA developed	131.34	9.55	13.76	0.9764

Fig. 4. Crystals of developed ASA.

Fig. 3. Crystals of control ASA.

and cohesivity of the developed ASA sample (Table 4).

4. Conclusion

The results allow a comparison of the parameters of MASP and ASA samples grown by different crystallization techniques. Overall, it can be stated that the two types of spherical crystallization (non-typical and typical) can be used very well not only for spherical particle forming, but also for size growing. This method can be suggested for the crystallization of drug materials if the material is pressed directly into tablets or made into filled capsules without excipients.

Acknowledgements

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