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Spherical crystallization of drug materials for direct tablet-making

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LIST OF ORIGINAL PUBLICATIONS AND PRESENTATIONS

This thesis is based on following publications and presentations. The original publications can be found in the Annex.

LIST OF PUBLICATIONS

I. **Göczö, H.**, P. Szabó-Révész, B. Farkas, M. Hasznos-Nezdei, S. F. Serwanis, K. Pintye-Hódi, P. Kása jr., I. Erös, I. Antal, S. Marton: Development of spherical crystals of acetylsalicylic acid for direct tablet-making
Chem. Pharm. Bull. (Japan) 48, 1877-1881 (2000) **IF: 1.113**

II. Szabó-Révész, P., **H. Göczö**, K. Pintye-Hódi, P. Kása jr., I. Erös, M. Hasznos-Nezdei, B. Farkas: Development of spherical crystal agglomerates of an aspartic acid salt for direct tablet-making
Powder Technol. 114, 118-124 (2001) **IF: 0.713**

III. **Göczö H.**, Szabóné Révész P.. Poliolok jelentösége a rágótabletták formulálásában
Gyógyszerészet 45, 123-126 (2001) **IF: -**

IV. **Göczö, H.**, P. Szabó-Révész, M. Pásztor-Turák, K. Pintye-Hódi, I. Erös, Gy. Dombi: Polyols in the development of chewable tablets containing magnesium aspartate
Pharm. Ind. 63, 639-643 (2001) **IF: 0.369**

V. Szabó-Révész P., M. Hasznos-Nezdei, B. Farkas, **H. Göczö**, K. Pintye-Hódi, I. Erös: Crystal growth of drug materials by spherical crystallization
J. Cryst. Growth 237-239, 2240-2245 (2002) **IF: 1.283**

LIST OF PRESENTATIONS

1. Szabó-Révész, P., B. Farkas, M. Hasznos-Nezdei, **H. Göczö**, K. Pintye-Hódi, P. Kása jr., I. Erös: Development of crystal agglomerates of an aspartic acid salt for direct tablet-making
4th International Workshop on Crystal Growth of Organic Materials, Bremen, 1997.

2. **Göczö H.**: Magnézium-aszparaginát rágótabletták formulálása és vizsgálata
SZOTE V. PhD elöadói napok, Szeged, 1999.

3. **Göczö, H.**, P. Szabó-Révész, B. Farkas, M. Hasznos-Nezdei, S. F. Serwanis, K. Pintye-Hódi, P. Kása jr., I. Erös: Development of spherical crystals of acetylsalicylic acid
7th International Workshop on Industrial Crystallization, Halle-Wittenberg, 1999.

4. Szabó-Révész, P., **H. Göczö**, K. Pintye-Hódi, P. Kása jr., I. Erös, B. Farkas, M. Hasznos-Nezdei: Qualification of crystal agglomerates of an aspartic acid salt for direct tablet-making
14th International Symposium on Industrial Crystallization, Cambridge, 1999.

5. **Göczö, H.**, P. Szabó-Révész, B. Farkas, M. Hasznos-Nezdei, S. F. Serwanis, K. Pintye-Hódi, I. Erös, I. Antal, S. Marton: Development of spherical crystals of acetylsalicylic acid
EUFEPS, Budapest, 2000.
Abstract: Eur. J. Pharm. Sci. 11, Suppl. 1 (2000) **IF: 1.842**

6. **Göczö H.**: A szférikus kristályosítás jelentösége a közvetlen préselés vonatkozásában: acetil-szalicilsav kristályosítása, Clauder Ottó Emlékverseny, Budapest, 2000.

7. Szabóné Révész P., Farkas B., Hasznosné Nezdei M., Pintyéné Hódi K., **Göczö H.**, Erös I.: Gyógyszeralapanyagok minöségjavítása tablettázási céllal: acetil-szalicilsav szférikus kristályosítása Mûszaki Kémiai Napok, Veszprém, 2000.

8. Pásztor-Turák, M., **H. Göczö**, P. Szabó-Révész, I. Erös, Gy. Dombi: Determination of the magnesium content of chewable tablets, 7th Hungarian Magnesium Symposium, Siófok, 2001.
Abstract: Magnesium Research 14, 318 (2001) **IF: 0.689**

1. INTRODUCTION

Direct compression is the most efficient process used in tablet manufacturing because it is the fastest, simplest, and least expensive tablet-compression procedure. However, although this technique seems quite simple, it requires that different properties of drug materials (free flow and plastic behaviour) should be manifested simultaneously. Many drugs do not exhibit these properties: they have poor flowability and compressibility. For tablet making from the latter materials, possible solutions may be as follows:

- the use of wet granulation and agglomeration [1] (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.

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. The spherical crystallization (agglomeration) technique has recently received great attention and gained considerable importance in the pharmaceutical field.

The particle diameter of drug materials produced by spherical crystallization is about 300-500 μm and their form is more or less spherical. The agglomerates exhibit very good flow, high bulk density and high compressibility.

Consequently, the spherical crystallization process allows raw materials with unfavourable technological properties to be utilized for direct tablet making.

2. LITERATURE

2.1. Crystallization (in general)

Crystallization is one of the oldest and most important operations. It is widely used in the chemical and pharmaceutical industries for purification, separation and/or production, yielding good-quality crystals. The number of phases in a crystallization process may be two, three or more than three. Crystallization can be carried out from a solution, vapour or melt [2-5]. 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 is demonstrated by many examples in the literature [6-9].

The simple solubility diagram provides a limited amount of information. The phase diagram graphically presents, in two or three dimensions, a more complete picture of the equilibria between various phases of the system over wide ranges of temperature, pressure and concentration. The Gibbs phase rule relates the numbers of components, *C*, phases, *P*, and degrees of freedom, *F*, of a system at equilibrium by means of the simple relation

$$P+F=C+2$$

The process of nucleation involves the formation of new crystals in a crystallizing environment. The supersaturated state of a solution is a prerequisite, but not a sufficient cause for a system to begin to crystallize, since a large number of minute entities known as centres of crystallization, embryos, or seeds first exist in the solution. The generation of a new crystalline phase from solution under conditions where a free energy barrier exists is a process of nucleation from solution.

The nucleation rate by a primary homogeneous nucleation mechanism may be expressed by

$$J=\exp(-\Delta G/kT)$$

where

J= nucleation rate,

ΔG= free energy between a small particle of solid solute and the solute in solution,

k= rate constant, and

T= temperature.

Various theories have been evolved to describe the crystal growth processes taking place at different magnification levels, spanning from the atomic to the macroscopic scale, and to develop growth rate expressions theoretically. For engineering purposes in crystallizer design and assessment, the simple empirical powder-law relationship expressing the specific rate of mass deposition is given by

$$\mathbf{R=(1/\ A_T)\cdot(dW/dt)=k_G\Delta c^g}$$

where

R= overall growth rate based on mass deposition,

A_T= total crystal surface area,

W= mass of crystals,

t= time,

k_G = growth rate constant,

Δc^g= concentration of crystal.

In general, the overall growth rate constant (k_G) depends on the temperature, the crystal size, the hydrodynamic situation and the presence of impurities [10-13].

Types of crystallization equipment

cooling crystallizer,

vacuum crystallizer,

crystallizing boiler,

reactor crystallizer, and

fluid bed crystallizer.

Methods of crystallization

salting-out precipitation,

cooling crystallization,

crystallization from the melt, etc. [14-17].

2.2. Spherical crystallization

One crystal growth process is the development of crystal agglomerates by spherical crystallization. In the pharmaceutical field, Kawashima et al. [18] gave an impulse to this research in the early 1980s. Spherical crystallization was defined by Kawashima as "an agglomeration technique that transforms crystals directly into a compacted spherical form during the crystallization process".

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 the medium which partially dissolves the substance; and the third is the wetting solvent for the substance. In the three-solvent system, the dissolved drug material is carried in emulsion drops (Fig. 1). Due to the effect of diffusion, the molecules of a good solvent (e.g. ethanol) leave the emulsion drops and enter the poor-solvent phase (e.g. water) through the emulsion film. The drops become oversaturated with respect to the drug material, and in situ seed formation starts at a given temperature, followed by crystal formation. The emulsion drops determine the size of crystal agglomerates. Therefore, the nature and the ratio of the solvents, the temperature, and the rates of cooling and stirring in the same way determine the quality of the product.

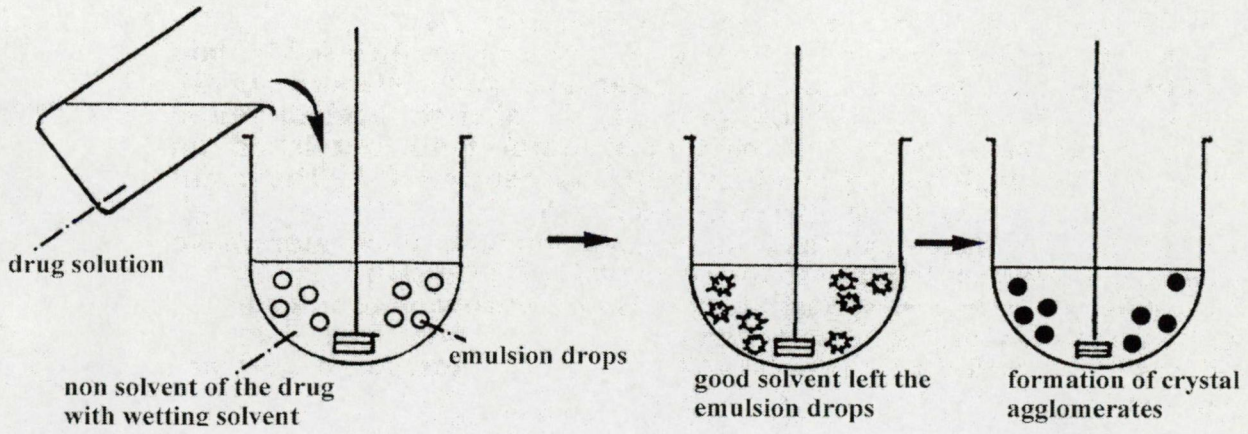
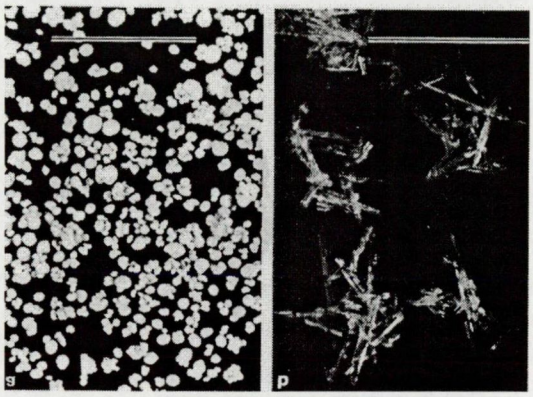


Fig. 1: Typical spherical crystallization process

Traditional crystallization processes (salting-out precipitation, cooling crystallization, crystallization from the melt, etc.) can also be used to produce spherical crystal agglomerates. The traditional crystallization process is carried out by controlling the physical and chemical properties. It may be called *a non-typical spherical crystallization process.*

The residual solvent content in crystal agglomerates is a very important question [19].

Many drugs which do not have suitable technological properties have been successfully transformed into spherical agglomerates with good flowability and compressibility during manufacturing, because the physicochemical properties of the pharmaceutical crystals are dramatically improved for the pharmaceutical processes, e.g. mixing, filling and direct tabletting (e.g. salicylic acid [20,21], enoxacin [22], DL-methionine [23], phenytoin [24], ferrous sulfate [25], propyphenazone [26], ketoprofen [27], meprobamate [28], acetylsalicylic acid [29], ibuprofen [30-33], 3-nitro-1,2,4,-triazol-5-one [34], acebutolol hydrochloride [35], paracetamol [36-38] and theophyllin [39,40] (Figs 2 and 3).



a b

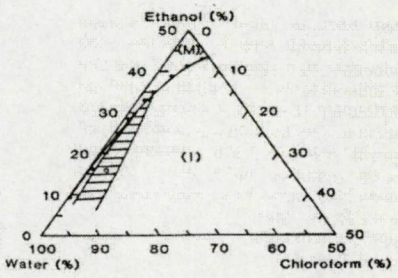


Diagram showing the solubility of chloroform in the ethanol-water mixture. Chloroform was miscible (*M*) in the region above the solid line and immiscible (*I*) in the region below the solid line. Acceptable spherical crystallization occurred in the shaded region.

Fig. 2: Spherical agglomerates (a) and the commercial product (b) of the salicylic acid [18]

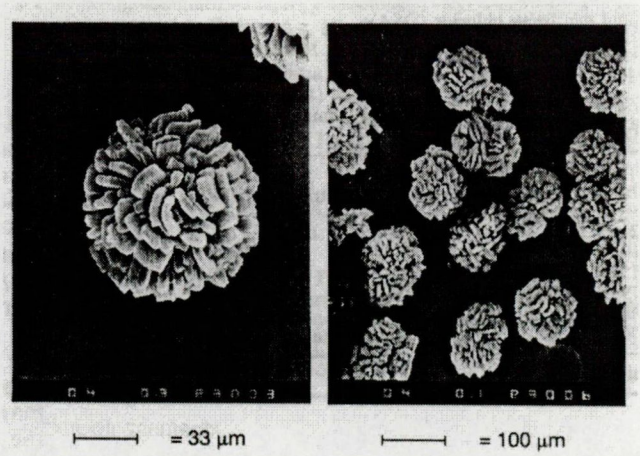


Fig. 3: Spherical agglomerates of the paracetamol [36]

Other materials are currently awaiting such transformation, to make them suitable for direct compression.

2.3. Direct tabletting

Direct compression is a modern method in tablet manufacturing. Many processing steps (granulation, drying, etc.) are eliminated in direct compression; additionally, wet technology can not be used with sensitive agents (e.g. in effervescent or chewable tablet-making) [41]. However, the use of this technique, which seems quite simple, depends on

⇒ the crystal form and surface,
⇒ 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 material.

Some drug crystals exhibit appropriate such properties, but many materials have very poor flowability and compressibility [42]. Previously, only the use of excipients with good technological properties made it possible to tablet such drugs, so these vehicles were developed [43-53].

The most advantageous crystals for direct tabletting are compacted, nearly spherical and shapeless and their particle size distribution is monodisperse. These good macromorphological attributes ensure suitable flowability and compressibility [54-65].

The flowability of materials (according to the Carr index) may be classified as excellent, good, fair to passable, poor, very poor, or very very poor [66].

It may be necessary to perform compressibility studies, and to calculate the Stamm-Mathis [67] or Emschermann plasticity [68] in order to determine tablettability [69]. The results allow the classification of materials from the aspect of direct tablet making.

2.4. Chewable tablets

Chewable tablets are becoming increasingly popular in the pharmaceutical and food industries. The special advantages of this class of tablets 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 the supply of vitamins and minerals (e.g. there is no dissolving).

These tablets exhibit good bioavailability and rapid absorption [70]. The pleasant sweet taste and mouth-feel are very important attributes, but chewable tablets have to meet other requirements too (e.g. stability, efficiency and quality of tablet form). In general, gritty or gummy textures are undesirable, whereas a soothing and cooling sensation with a smooth texture is preferred.

Chewable tablets are produced by direct tablet pressing because they usually contain vitamins, minerals, antacids and rarely other drugs (anodynes, antifebriles or antiepileptica) which are sensitive to moisture [71-78]. A good direct compression vehicle for chewable tablets must also possess a pleasant sweet taste and a good mouth-feel. To achieve this desired taste with good direct compression qualities, the monosaccharide and disaccharide classes of sugars or polyols are used. The monosaccharides and disaccharides include sucrose, dextrose, fructose and lactose, while mannitol, sorbitol, xylitol and maltitol are of the polyol type.

Establishment of chewable tablets

1. First, the formulator should determine the attributes of the pure drug: the basic taste, inherent flavour and aroma, mouth-feel and after-effects.

2. The second step is an attempt to mask the taste (without flavouring) by various physicochemical techniques such as microencapsulation, adsorption, ion-exchange, spray congealing, or the formation of different salts or derivatives. If the dose is low or the taste of the drug is not too unpleasant, this step may be unnecessary.

3. Third, it is necessary to choose a chewable vehicle and other adjuvants (e.g. binders, lubricants and colours) and their quantities in order to achieve optimum flow and compressibility.

4. The final step is to flavour the chewable tablets. It is necessary to consider two or three alternative flavours or masking methods and to choose the best among them.

3. AIMS

The topicality of the topic is given by the changed qualitative requirements in respect of the drug materials. The technological parameters come into prominence, which can result in a more economical process for the development of the solid dosage forms. The present research work relates to the improvement of the technological parameters of drug materials via the crystallization process, the quality of the products and the formulation of chewable tablets with control and developed active agents.

This work had three aims, as follows:

➪ *Improvement* of the technological properties (particle size and form, flowability, compressibility, etc.) of active drugs *(acetylsalicylic acid (ASA), magnesium aspartate(Mgasp))* by typical and non-typical *spherical crystallization* in order to make them suitable for *direct tablet making.*

➪ *Quality control* of the products:

-determination of macro- and micromorphological parameters (particle form, size, particle size distribution, specific surface and micropore volume);

-thermoanalytical investigations (TGA, DTA and DSC);

-atomicabsorption analysis (determination of magnesium content);

-recording of diffuse reflectance spectra (NIR);

-investigation of technological properties (flowability, rearrangement, cohesivity and compressibility).

➪ *Development* and investigation of *chewable tablets* containing Mgasp and different *polyols.*

4. MATERIALS AND METHODS

4.1. Materials

4.1.1. Commercial acetylsalicylic acid (ASA)

($C_9H_8O_4$=180.2) (Ph. Eur. 4)

Commercial ASA crystals are colourless or white, odourless or almost odourless tetragonal and prism-shaped, with different sizes and particle size distributions. ASA is stable in dry air, but gradually hydrolyses in contact with moisture to give acetic acid and salicylic acid (SA). The BP solubilities: slightly soluble in water, freely soluble in alcohol, soluble in chloroform and in ether.

ASA crystals exhibit poor flow 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!), the good flowability, cohesivity and tablettability of the crystals are very important.

ASA is used to treat pain, fever, inflammation and the prevention of myocardial infarction and stroke. The main adverse effects associated with the use of ASA are gastro-intestinal.

4.1.2. ASA developed by spherical crystallization (ASA1, ASA2 and ASA3)

ASA crystals were developed by means of non-typical and typical spherical crystallization processes with different solvent mixtures. 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 ASA1 and ASA2, whereas ASA3 was developed by a typical spherical crystallization procedure.

ASA1: 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 r.p.m.).

ASA2: 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 r.p.m.).

ASA3: 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, followed by cooling at 0.6 °C/min to 20 °C with stirring (200 r.p.m.) The ASA3 crystallization process can be followed in Fig. 4.

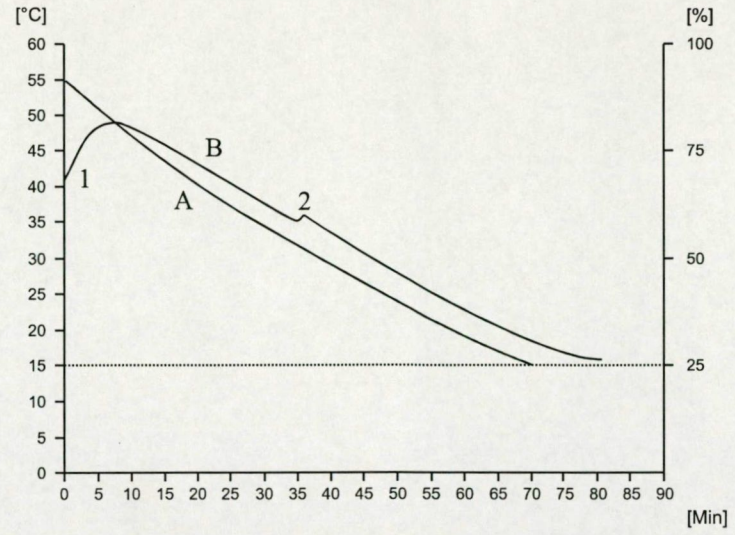


Figure 4: Cooling curves of crystallization process of ASA3

A/ cooling curve of equipment;

B/ cooling curve of solution

1/ dissolution of ASA crystals adding of carbon tetrachloride-water mixture (4%w/v) to the solution;

2/ appearance of ASA crystals

4.1.3. Commercial magnesium aspartate (Mgasp)

(magnesium aminosuccinate tetrahydrate, $C_8H_{12}MgN_2O_8 \cdot 4H_2O$=360.6)

Mgasp is a white, odourless and tasteless powder. The edges of the crystals are round; the surface is smooth. The particle size of the crystals is very small, so this material is unsuitable for direct pressing.

It is well known that magnesium is an important element for the human organism [79-85]. A mixture of equal parts of potassium aspartate and Mgasp has been claimed to be of value in the management of fatigue, heart conditions and liver disorders, but the claims are not supported by adequate evidence. Various quantities of magnesium enter the organism with the food, but in many cases care should be taken to guarantee the supply (e.g. in children, pregnant women and elderly people). The recommended daily intake of magnesium as a food supplement is from 50 to 450 mg, depending on the age and the geographical location. The level was maximized by the WHO as up 200 to 300 mg per day.

4.1.4. Mgasp developed by spherical crystallization (Mgasp1, Mgasp2 and Mgasp3)

The spherical crystal agglomeration of Mgasp was carried out by salting-out combined with cooling (Fig. 5). 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 GmbH, Seelbach, Germany) was used for the cooling process. 500 ml of 15-25 wt% Mgasp 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 Mgasp1 and Mgasp2 (Fig. 5). The stirring rate was higher for Mgasp1 (100 rpm) than for Mgasp2 (60 rpm). The methanol feeding rate was constant (0.36 l/h). The temperature interval was 90-10 °C. The crystallization processes of Mgasp1 and Mgasp2 differed further in cooling rate. For Mgasp1, slower initial cooling (0.3 °C/min) was used than for Mgasp2 (0.7 °C/min). The duration of the crystallization process was 140-260 min.

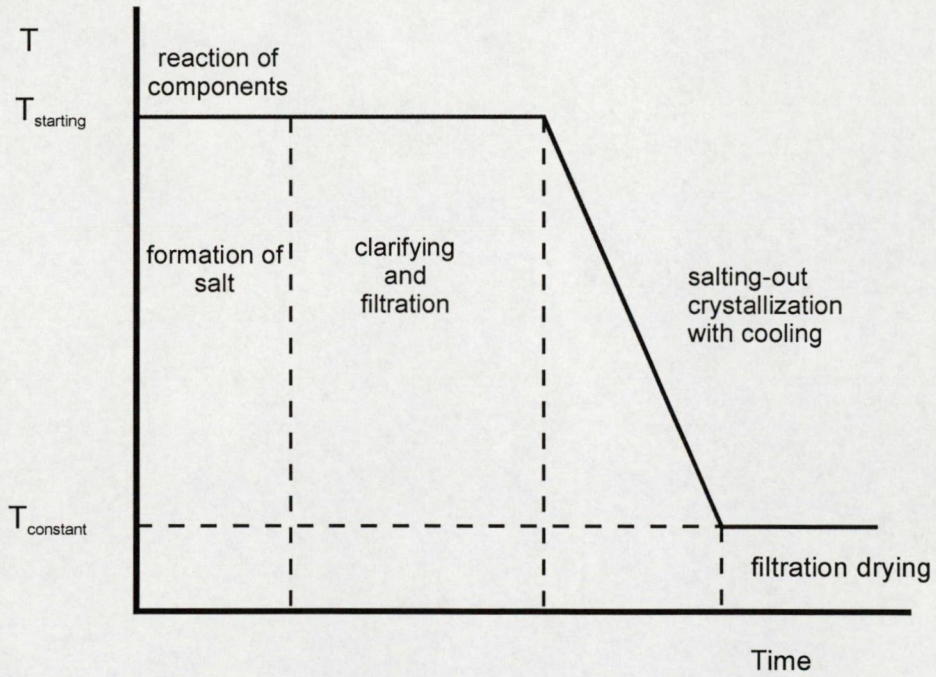


Fig. 5: Schematic representation of the spherical agglomeration of Mgasp

Mgasp3 was prepared in a mechanically stirred tank (800 ml) with an external circulation loop (recirculation process). Methanol was added to the external loop. The initial concentrations, the stirring rate and the temperature interval were the same as for Mgasp1. 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 Mgasp in the filtrates was 2-2.5 wt%. The agglomerates were washed with cold methanol (0 °C), and subsequently dried at 50 °C to mass constancy. The products were finally kept in a dark and dry place. The parameters of the crystallization processes are summarized in Table 1.

Table 1: Conditions of crystallization of Mgasp

	Mgasp1	**Mgasp2**	**Mgasp3**
	traditional mechanical stirring		traditional mechanical stirring with recirculation of mother liquor
Stirring rate (r.p.m.)	100	60	100
Feeding rate of salting-out agent (methanol) (l/h)	0.36	0.36	0.30
Temperature interval (°C)	90-10		90-10
Cooling rate (°C/min)	0.3	0.7	0.5
Process time (min)	140-260		190
Mother liquor recirc. rate (l/h)	-		20
Filtration in vacuum (mbar)	100	100	100
Washing (cold methanol) (°C)	0	0	0
Drying (°C)	50	50	50

4.1.5. Excipients

Polyols

Polyols (e.g. 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 [86-93]. 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. The polyols have low hygroscopicity (especially mannitol), stabilize the 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 foods. 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 [94]. They can usually be used as filler and binder excipients in chewable tablets.

During the formulation of chewable tablets with Mgasp, the following polyols were used:
Neosorb P 20/60 (D-sorbitol, Roquette, Lestrem, France)

A white, crystalline powder with a sweet taste. D-Sorbitol is produced by the catalytic hydrogenation of D-glucose. D-Sorbitol contains six alcohol groups, i.e.it is a hexitol.

Karion Instant Pharma (D-sorbitol, Merck, Darmstadt, Germany)

A white, granulated powder with a sweet taste and a low mass by volume.

Xylisorb 700 (xylitol, Roquette, Lestrem, France)

A white, crystalline powder with a sweet taste. Xylisorb is produced by the catalytic hydrogenation of xylose. Xylitol, containing five alcohol groups, is a pentitol.

Pearlitol SD 200 (D-mannitol, Roquette, Lestrem, France)

A white, crystalline powder with a sweet taste, produced by the catalytic hydrogenation of D-fructose. Mannitol is a hexitol, having six alcohol groups.

Pearlitol 400 DC (D-mannitol, Roquette, Lestrem, France)

A white, crystalline powder with a sweet taste.

Magnesium stearate (Ph. Eur. 4)

This is a white, sticky, fine and light powder. It is tasteless and odourless. It is insoluble in water, alcohol and diethyl ether. It is used in tablet manufacturing as an antiadhesive substance, in 0.1-1%.

4.2. Methods

Particle size analysis and roundness

The particle sizes of the materials were measured by sieving (DIN sieve, German Standard). (100 g of material was sieved with an Erweka vibration sieve (Erweka Apparatebau GmbH, 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.)

Determinations of particle size (length, breadth and roundness) were carried out with a Laborlux S light microscope and a Quantimet 500 MC (Q 500 MC) image processing and analysis system (LEICA Cambridge, Ltd., UK).

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

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

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 the roundness value is close to one, the particles are nearly spherical.

Scanning electronmicroscopic investigations

The crystals were observed with a scanning electron microscope (Hitachi Scientific Instrument, Ltd., Tokyo, Japan). A Polaron sputter coating apparatus (Polaron Equipment, Ltd., Greenhill, UK) was applied to induce electric conductivity on the surface of the sample. The surfaces of the Mgasp crystals were treated with gold for 60 s (coating thickness: 18 nm).

Micromorphological investigations: 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 the data (20 points each) of nitrogen adsorption and desorption isotherms at the boiling point of liquid nitrogen at atmospheric pressure (-196 °C). The specific surface was calculated, in the range of validity of the BET -isotherm [95], from the slope and intercept of a line characterized by 5 measuring points. The samples (1.5-2.0 g) were degassed at 60 °C by vacuum up to an absolute pressure of 1 Pa. 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 [96]. The investigations were repeated 3 times.

Thermoanalytical investigations

The products were checked through thermogravimetry (TG and DTG), using a MOM instrument (MOM Ltd., Budapest, Hungary). The sample mass was 6 mg, and the heating rate was 5 °C/min in air atmosphere. Differential scanning calorimetry (DSC) with Perkin-Elmer DSC-2C (Perkin-Elmer Co., Norwalk, Connecticut, USA) and Mettler DSC 821^e (Mettler-Toledo GmbH, Switzerland) equipment provided additional information. The sample mass was 3 to 4 mg, and the heating rate was 5 °C/min in an air atmosphere. The results were calculated from 3 measurements.

Friability testing of the crystal agglomerates

The samples were investigated with a Heberlein apparatus (Flisa, Le Locle, Switzerland). Five g 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 sieving (>0.32 mm) and the percentage loss in mass was calculated.

Study of flow properties: flow time, mass by volume, Carr index and rearrangement constant

The flow time and the mass by volume were determined by the ASTM method (Ph. Eur. 3).

The Carr index was calculated from the poured and tapped densities [97]:

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

For the determination of poured and tapped densities, a Stampfvolumeter 2003 (J. Engelsmann A. G. 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 Carr index reflects the compactibility of the crystals, and there is a correlation between the Carr index and the flowability of the crystals [66].

Stampfvolumeter measurements allow calculation of the rearrangement constant (k) [98]:

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

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_8 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.

Compactibility and cohesiveness

The Stampfvolumeter measurements allow calculation of the compactibility and cohesiveness via the modified Kawakita equation [99-100]:

$$\frac{N}{C} = \frac{1}{a} \cdot N + \frac{1}{ab}$$

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:

$$C = \frac{V_0 - V}{V_0}$$

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.

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 displacement transducer. The rate of compression

was 30 tablets/min with a pressure force of 17 kN, at an air temperature of 24 °C and a relative humidity of 45%. The tablets were pressed from the control and developed samples 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. 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 3 times during the pressing.

Plasticity ($Pl_{S\text{-}M}$) was described by Stamm-Mathis:

$$Pl_{S\text{-}M} = \frac{E_2}{E_2 + E_3} \cdot 100 \quad (\%)$$

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 compression. E_2 and E_3 can be calculated from the force - displacement curve. If the plasticity value is near 100, the material has a plastic character.

Compressibility $Pr_{(mass)}$ was calculated via the following equation [58]:

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

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 of substance (m) at a given compression force. σ_x includes the crushing strength (H), the diameter (d) and the height (h)of the comprimate [101]:

$$\sigma_x = \frac{2H}{\Pi \cdot d \cdot h}$$

The crushing strength was investigated with a Heberlein apparatus (Flisa, Le Locle, Switzerland). The geometrical parameters of the tablets were measured with a screw micrometer

(Mitutoyo, Tokyo, Japan). The parameters of the tablets were determined after compression (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.

Recording of diffuse -reflectance spectra

Near-infrared spectroscopy furnishes useful information for the qualitative and quantitative analysis of materials without invasive sample preparation. It can be used to control the differences between the particle forms of the samples [102].

Diffuse reflectance was measured with a Hitachi (Japan) U-2501 UV/VIS/NIR spectrophotometer equipped with an integrating sphere (d=60 mm) and a PbS detector. The reflectance (*R%*) of samples was determined in the wavelength range 200-2500 nm, using a 5 mm layered cell:

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

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 [103].

Determination of ASA and SA contents of the ASA samples

The SA contents of the samples were controlled with 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 and at 276 nm for ASA. The testing was performed with a near-infrared spectroscope.

Rate of dissolution of ASA samples

The investigations were performed with the USP method (paddle). The medium was artifical gastric juice (pH=1.2) at 37±0.5 °C. The paddle speed was 50 rpm. The rate of dissolution of ASA from capsules was determined. The hard gelatine capsules (No. 0) were filled

with 100 mg of ASA crystals. The samples were analysed spectrophotometrically (Spectromom, MOM, Budapest, Hungary) at 276 nm.

4.3. Tablet making and tablet investigations

Production of ASA tablets

The materials without any excipients were compressed 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 of 24 °C and a relative humidity of 30%.

Formulation of chewable tablets containing Mgasp

Five compositions were elaborated, in which Mgasp 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:

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

Numbering according to excipients was as follows:

Composition 1: Karion,
Composition 2: Neosorb P 20/60,
Composition 3: Xylisorb 700,
Composition 4: Pearlitol SD 200, and
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 compressed into

tablets with a Korsch EKO eccentric tablet machine (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 a relative humidity of 45%.

Investigation of tablets

Investigations were carried out 24 h after pressing. Tablet mass was measured to an accuracy of 0.1 mg. The relative standard deviation (RSD) as mass variation was calculated from 20 data points. The breaking hardness was determined through use of a 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 Mgasp tablets was determined by atomic absorption spectrometry. The Pharmacopoeias (e.g. U.S. and European) usually prescribe the determination of magnesium by a titrimetric 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, Ueberlingen, 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.

4.4. Statistical calculation

The standard deviation (SD), relative standard deviation (RSD), the two-sample analysis 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%.

5. RESULTS AND DISCUSSION

5.1. Results on crystallization of ASA

The ASA samples were developed by non-typical and typical spherical crystallization processes. The non-typical spherical crystallization technique (conventional stirred tank method) resulted in either monocrystals (ASA1) or non-spherical crystal agglomerates (ASA2).

The developed ASA1 crystals were tetragonal monocrystals with plane boundaries (Fig. 6). A cooling rate of 1°C/min resulted in the formation of a great number of seeds and did not act favourably either on the growth or the build-up of crystals.

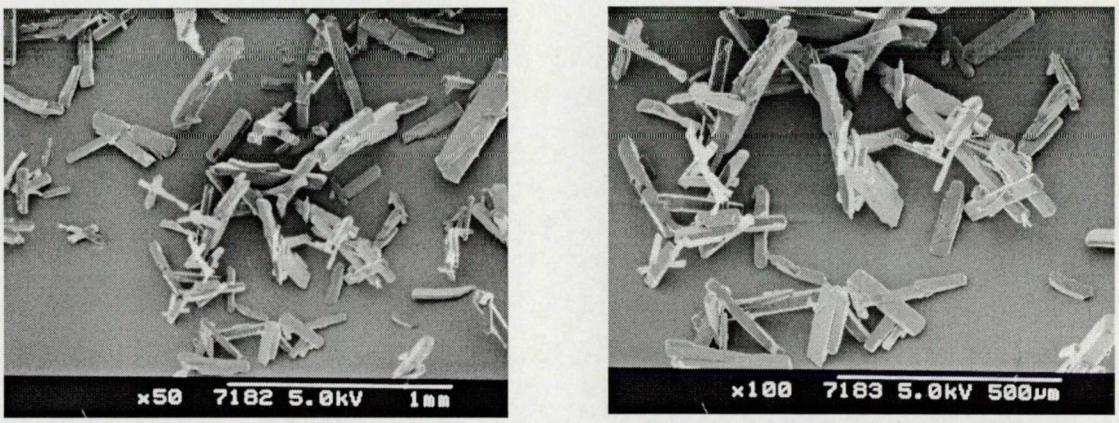


Fig. 6: Crystals of ASA1 developed by non-typical spherical crystallization

Decrease of the cooling rate (0.5 °C/min) (ASA2) led to the appearance of a small number of crystal agglomerates besides the monocrystals (Fig. 7). Due to the slow cooling, the monocrystals were large and well-developed. The agglomerates were formed by the accidental encounter of 4-5 crystal seeds. Crystals built up at one point have a habit characteristic of monocrystals.

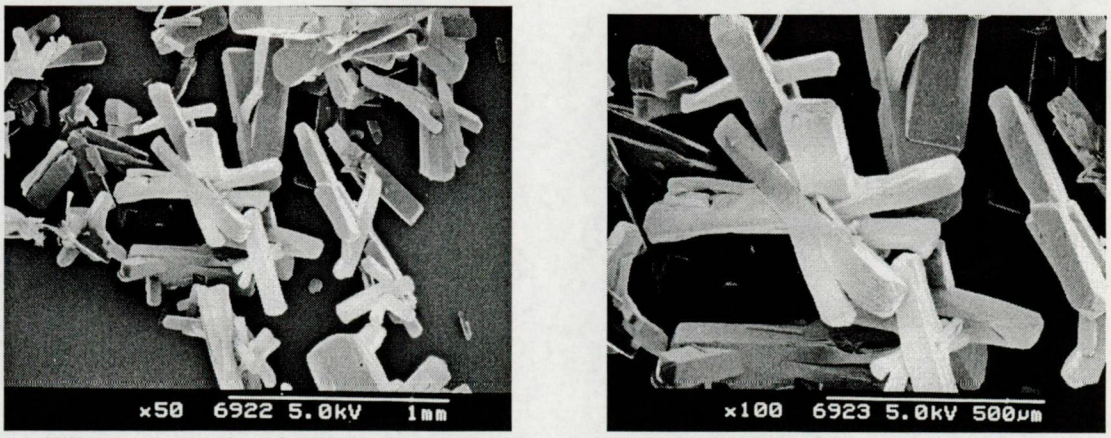


Fig. 7: Crystals of ASA2 developed by non-typical spherical crystallization

Further decrease of the cooling rate and changes of the other parameters of crystallization did not bring about considerable changes in the formation of agglomerates. It may be noted that commercially available ASA products have a habit similar to that of the ASA1 and ASA2 products.

During the formation of ASA3, the crystals were transformed into spherical agglomerates (Fig.8). The process was 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 ASA, and in situ seed formation started at 37 °C (see Fig. 4), followed by crystal formation, which was also influenced by the cooling and mixing rates. In this process, therefore, it was not the accidental encounter of the crystals which resulted in the formation of crystal agglomerates.

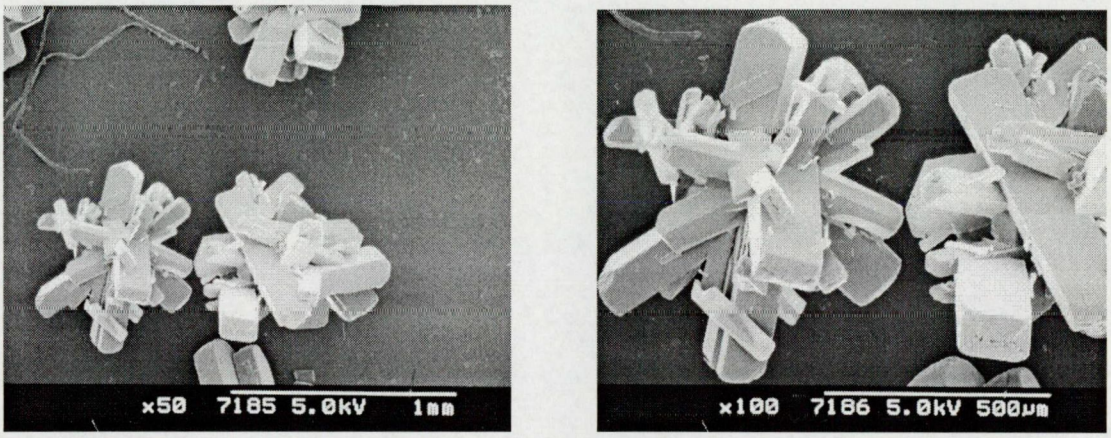


Fig. 8: Crystal agglomerates of ASA3 developed by typical spherical crystallization

In 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 the habit characteristic of monocrystals, the size of the agglomerate did not exceed the size of monocrystals and crystal agglomerates produced by non-typical spherical crystallization. ASA3 agglomerates were open structures with very great hardness. Their friability, which is very important during further processing, was very favourable. The friability of the ASA3 sample was found to be 6.24±0.45%. For comparison, the maximum friability of granules is usually limited to 20% in pharmacopoeias.

The length, breadth and roundness of the samples are detailed in Table 2. The different crystallization processes strongly influenced the habit of the crystals or crystal 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 their number was low and the structure was only partly built-up (ASA2). Table 2 shows that ASA3 has the best roundness.

Table 2: Particle size data on ASA samples

Samples	Length (μm)	Breadth (μm)	Roundness
ASA1 Average	**273.85**	**72.09**	**2.54**
SD	*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**
SD	*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**
SD	*143.16*	*98.65*	*0.13*
Max.	*913.85*	*690.77*	*1.66*
Min.	*300.31*	*136.61*	*1.15*

The micromorphology parameters reveal that the ASA2 and ASA3 samples have very low specific surfaces and micropore volumes. The larger average pore diameter of ASA3 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 and cohesivity properties of the samples.

Table 3: Micromorphology properties of ASA crystals

	Specific surface (m^2/g)	Micropore volume* (10^{-3} cm^3/g)	Average diameter of pores (nm)
ASA1	0.11	0.14	7.31
ASA2	0.06	0.08	8.32
ASA3	0.04	0.04	32.26

*Desorption micropore volumes were measured in the diameter range 1.7-300 nm

The thermoanalytical investigations of the samples furnished the following results. The TG curves do not reveal any decrease in mass up to 133 °C. The samples have no adsorbed water or residual solvent on the surfaces of the crystals and crystal agglomerates. After the melting point (133-138 °C), the samples undergo decomposition with significant mass loss. The onset

temperature of the transition and the transition energy (ΔH_t) of the samples show differences which can be ascribed to the crystallization process, but do not relate to the change in structure (Table 4).

Table 4: DSC parameters of ASA samples

	Melting point (°C)	**Transition (onset) temp. (°C)**	**ΔH_t (J/g)**
ASA1	136.0	132.8	192.6
ASA2	138.5	135.3	210.1
ASA3	133.0	129.9	180.8

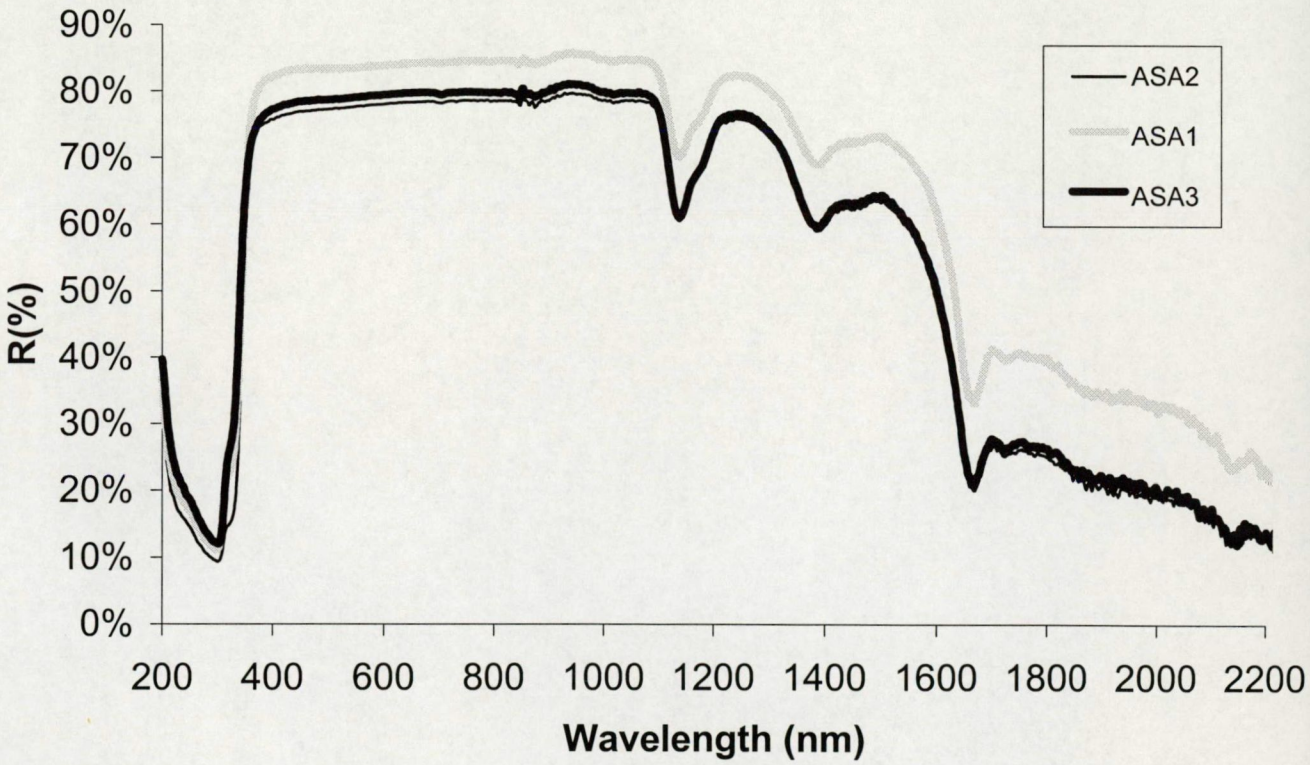


Fig. 9: Diffuse reflectance spectra of ASA samples

During the crystallization of ASA, the SA content of the samples can increase. This was checked by a near infrared method. The diffuse reflectance spectra of the ASA1 and ASA3 samples in the wavelength range 200-350 nm were the same, which can be attributed to the uniform ASA content of the samples (Fig.9).

In this range, only ASA2 exhibited a small peak for the SA as decomposition product. The amount of the SA determined spectrophotometrically was 1.02%. In the interval 350-2500 nm, the ASA2 and ASA3 samples (with larger particle sizes and the best values of roundness) displayed smaller diffuse reflectances than that of ASA1 (with a smaller particle size and an unfavourable roundness value).

As the rate of dissolution of the samples is basically influenced by the particle size, this was also checked. It is clearly shown in Fig. 10 that the rates of dissolution of the samples were almost the same, and only the ASA1 crystals, which have a small particle size and consequently a large surface, underwent 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 an unfavourable influence on the dissolution rate.

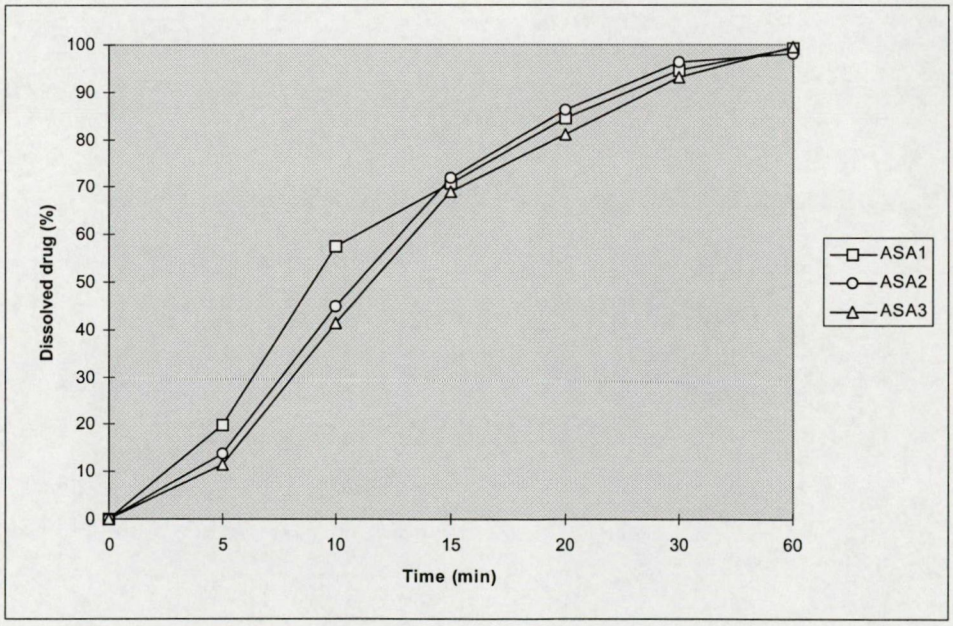


Fig. 10: Rates of dissolution of ASA samples

The check on the technological parameters of the samples with respect to direct tablet making yielded the following results. 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 5). 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.

Table 5: Powder rheological parameters of ASA samples

Samples	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

The data from the modified Kawakita equation can be seen in Table 6. 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, the investigation revealed worse technological parameters.

Table 6: Compactibility *(a)* and cohesiveness *(1/b)* of ASA crystals by the Kawakita model

Samples	1/ab intercept	a	1/b	r^2
ASA1	91.75	0.2519	23.10	0.9872
ASA2	210.64	0.1017	21.42	0.9515
ASA3	131.34	0.1047	13.76	0.9764

As the development of the ASA samples was carried out for the purpose of direct tabletting, the preformulation results to date were supplemented with tablettability studies. The samples were compressed to tablets without excipient and the physical parameters of the tablets were determined (Table 7).

During the compression of the ASA1 crystals, the 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, e.g. the deviation from the theoretical mass was high and the variation in mass exceeded 2%.

The ASA2 sample, which has a greater particle size and is only partially spherical, exhibited better compressibility properties. The machine sound caused by friction became less intense, but the variation in mass of the tablet was still over 2%, which is related to the great cohesivity 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 flow properties, 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 in an almost frictionless manner. This is confirmed by the slight variations in compression force, average mass and mass variation. The great hardness of the tablets and their small standard deviation also proved the important role of the ASA3 sample.

Table 7: Physical parameters of ASA tablets

Materials	**Compression force (kN)**	**Average height (mm)**	**Average mass (g)**	**Mass variation (RSD) (%)**	**Breaking hardness (N)**
ASA1	10-15	2.8923 (SD=0.0153)	0.2757	2.5025	75.4 (SD=3.5339)
ASA2	10±1.5	3.0394 (SD=0.060)	0.2948	2.3258	66.8 (SD=2.6998)
ASA3	10±0.5	3.1323 (SD=0.0427)	0.3054	1.4833	71.4 (SD=1.6576)

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 as concerns 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.

5.2. Results of crystallization of Mgasp

For the Mgasp samples, the non-typical spherical crystallization resulted in crystal agglomerates with suitable technological parameters.

The investigated Mgasp crystals and crystal agglomerates were found to have different particle sizes (Table 8).

Table 8: Particle size distribution of Mgasp samples

	>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
Mgasp1	-	2.4	3.3	5.1	39.5	17.8	31.9
Mgasp2	14.5	11.9	35.9	16.5	17.7	2.3	1.2
Mgasp3	3.6	5.6	13.0	15.9	41.1	10.0	10.8

The control (commercial) Mgasp consists of single, very small crystals and agglomerated crystals with an unfavourable habit for direct compression (Fig. 11). 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, Mgasp1 and 2 were crystallized by salting-out combined with cooling, using the traditional mechanical stirring method. Mgasp1 (Fig. 12) consists of smaller particles than those of Mgasp2 (Fig. 13a) because of the slower initial cooling and the higher stirring rate.

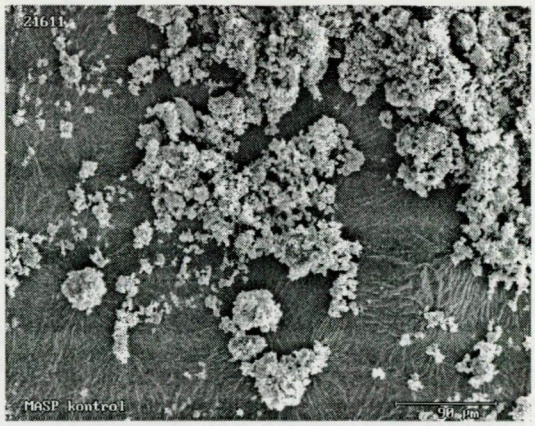


Fig. 11: Control (commercial) Mgasp

The spherical crystal agglomerates of Mgasp2 have a closed "cauliflower-like" structure with a relatively large particle size (62% of the particles larger than 250 µm) (Fig. 13b). In fact, a higher initial cooling rate and a lower stirring rate are very favourable in the building-up of crystal agglomerates with a closed structure.

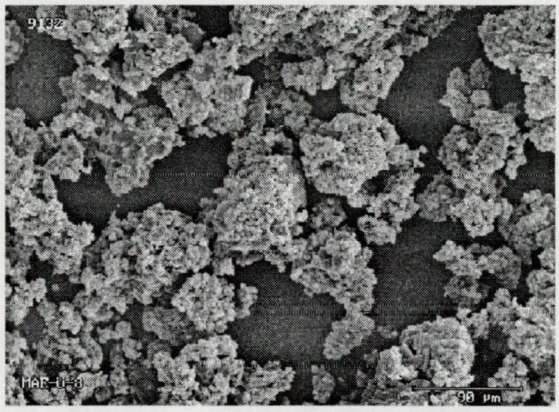


Fig. 12: Crystal agglomerates of Mgasp1

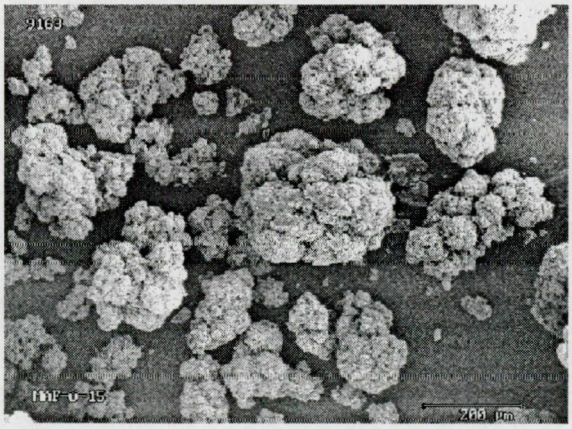


Fig. 13a: Crystal agglomerates of Mgasp2

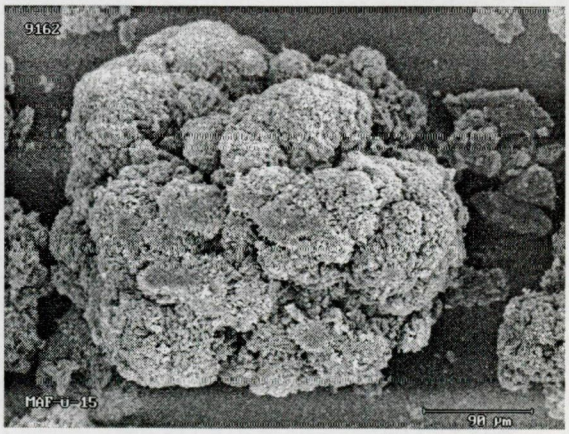


Fig. 13b: Crystal agglomerates of Mgasp2

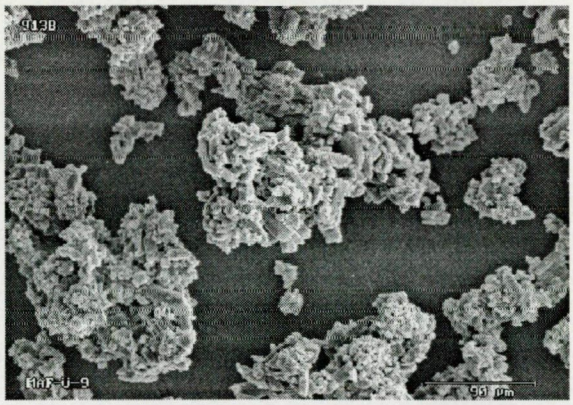


Fig. 14: Crystal agglomerates of Mgasp3

The specific surfaces of the samples differ considerably; this is in keeping with their different particle sizes (Table 9). The micropore volumes of Mgasp1 and Mgasp2 are the same, but the average diameter of the pores of Mgasp2 is significantly higher.

Table 9: Micromorphology properties of Mgasp samples

	Specific surface (m^2/g)	**Micropore volume* ($10^{-3}cm^3/g$)**	**Average diameter of pores (nm)**
Control	0.76	2.80	13.5
Mgasp1	0.63	2.51	10.4
Mgasp2	0.42	2.83	27.3
Mgasp3	0.46	1.41	12.8

* Desorption micropore volumes were measured in the diameter range 1.7-300 nm in.

The micromorphology properties of Mgasp1 are nearest to the corresponding parameters of the control sample (Table 9). The particle size distribution of Mgasp3 (produced in a recirculation process) is between those of Mgasp1 and Mgasp2. Agglomerates of Mgasp3 have a small specific surface, a small micropore volume and a small average pore diameter. (Figure 14, Table 9).

The different macro- and micromorphologies of Mgasp1, 2 and 3 do not involve modification of the inner crystal structures of the agglomerates. This is documented by the results of thermoanalytical investigations. The TG curve does not reveal any decrease in mass up to 132 °C. The samples have no adsorbed water or residual solvent on the surfaces of the crystals or crystal agglomerates. All of the curves exhibit a step (132-189 °C) with a mass decrease of

about 20% (Table 10). The loss in mass relates to the elimination of 4 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 11. The differences in the results can be ascribed to the crystallization process, but do not relate to the change in structure.

Table 10: Thermogravimetric results on Mgasp samples

	TG step (°C)		**Mass decrease (%)**
	start	**end**	
Control	132.4	190.4	-19.1
Mgasp1	131.9	189.0	-18.2
Mgasp2	133.0	188.8	-19.7
Mgasp3	133.5	189.7	-20.0

Table 11: DSC parameters of Mgasp samples

	Melting point (°C)	**Transition (onset) temp. (°C)**	**ΔH_t (cal/g)**
Control	169.5	152.9	170.8
Mgasp1	170.4	155.7	171.7
Mgasp2	171.8	163.2	161.4
Mgasp3	170.9	150.4	189.8

The technological parameters such as the Carr index revealed that the flowability of the control product was "very poor" (Table 12), and the Takieddin rearrangement constant indicated a slow-packing character (Table 12). The spherical crystal agglomerates of Mgasp2, 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 a large mass. The favourable particle form, size and surface result in fast rearrangement, with a very high rearrangement constant. Mgasp1 and 3 have “fair to passable” flow capacities with a slower rearrangement.

Table 12: Bulk densities, Carr indices and rearrangement constants of Mgasp samples

	Poured density (g/cm^3)	**Tapped density (g/cm^3)**	**Carr index (%)**	**Rearrangement constant (k) $y=\exp(1+kn)$**
Control	0.51	0.82	37.61	0.038 (r=0.9975)
Mgasp1	0.43	0.58	26.41	0.155 (r=0.9995)
Mgasp2	0.61	0.64	5.32	0.389 (r=0.9865)
Mgasp3	0.40	0.49	18.71	0.290 (r=0.9844)

The compressibility parameters of the samples are collected in Table 13. 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 samples ($Pl_{S\text{-}M}$) 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 was documented by the thermoanalytical investigations.

Table 13: Compressibility parameters of Mgasp (pressure force: 17 kN)
(space filling of the die cavity of tablet machine: 864 mm^3)

	Mass of tablet (g)	**Mass 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)
Mgasp1	0.475	0.7	89.9 (SD=0.85)	0.75 (SD=0.03)	26.3 (SD=0.86)
Mgasp2	0.639	0.8	93.3 (SD=1.03)	0.58 (SD=0.03)	20.5 (SD=0.57)
Mgasp3	0.484	0.8	90.2 (SD=0.81)	0.67 (SD=0.02)	22.3 (SD=0.46)

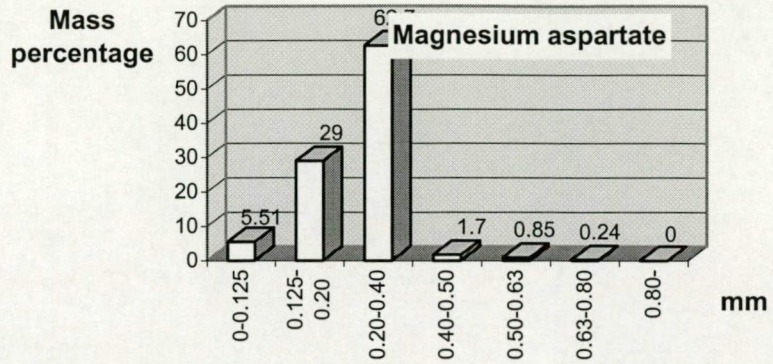
The tablets containing the spherical crystal agglomerates and the control sample differ considerably in the mass of tablet, mass variation (RSD) and tensile strength.

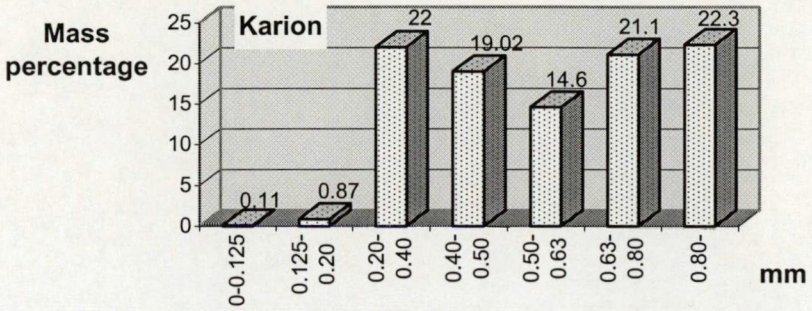
The tablet compression was carried out by maximal space filling of the die cavity of the tablet machine. The difference in the mass of tablet could be explained by the bulk density and the arrangement of the samples in the die cavity. This is reflected by the compressibility values (Pr_{mass}) too. The compressibilities of the spherical crystal agglomerates (Mgaspl, 2 and 3) are better than that of the control product (Table 13). The greater tensile strength and the compressibility value of the tablet containing Mgaspl 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 Mgasp. Mgaspl, 2 and 3 have very good flowability and compressibility, in contrast with the commercial (control) sample. According to the parameters of the tablets (mass, tensile strength, etc.) Mgaspl, 2 and 3 can be used for direct tablet making. However, primarily Mgasp2 can be suggested for the production of tablets with a high active agent content.

5.3. Development of chewable tablets containing Mgasp

The active drug for direct tablet making was produced by a manufacturing process (on a pilot scale) as a result of crystallization process development. The manufactured Mgasp had the same preformulation parameters (flowability, compressibility, etc.) as those of the products developed on a laboratory scale. During the development of the chewable tablet-composition the particle size distribution of the Mgasp and the excipients was the subject of the first preformulating investigation. The investigated materials were found to have different particle sizes (Figs 15a and 15b).





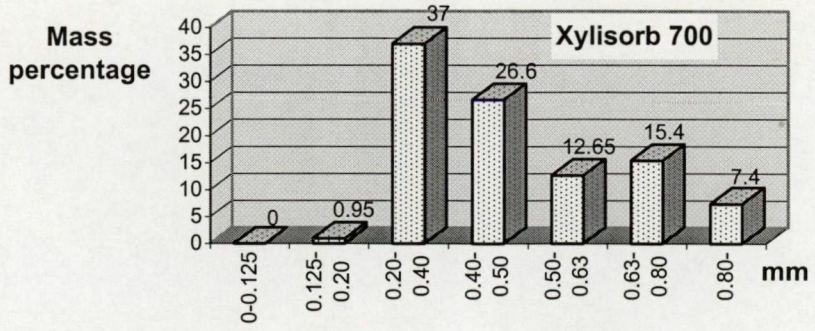
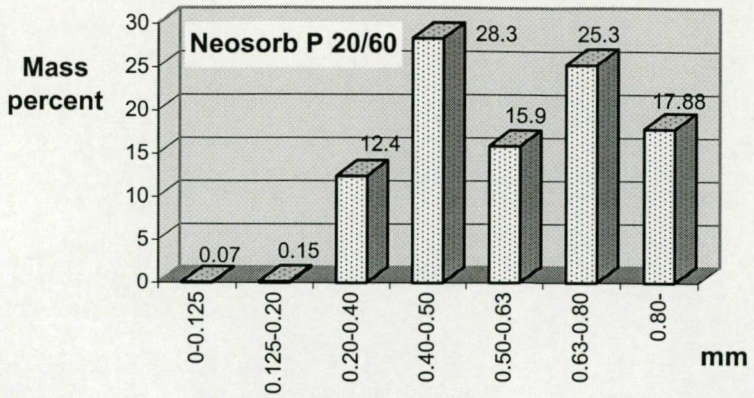
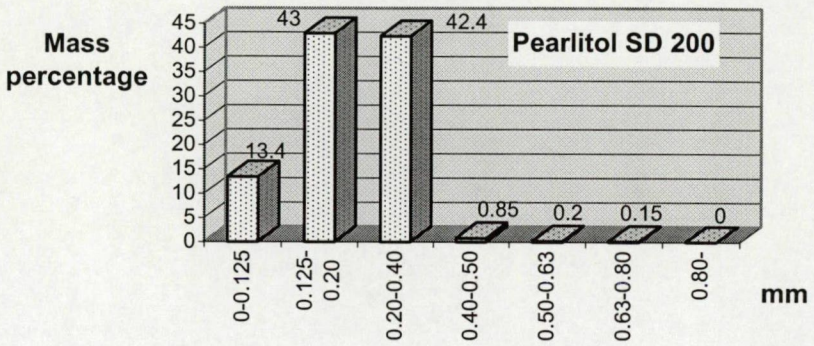


Fig. 15a: Particle size distribution of the applied materials





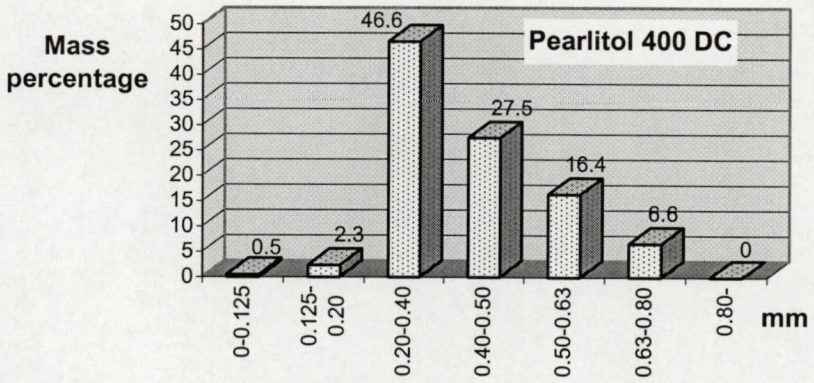


Fig. 15b: Particle size distribution of the applied materials

The particles were more or less spherical in form. 90% of the Mgasp 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 Mgasp, and those of Neosorb and Karion were the most different.

The results of the determination of mass by volume are presented in Table 14. It can be seen that the mass by volume of Xylisorb (73.36 g/100 ml) corresponded most closely to that of Mgasp (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 making. Therefore, these properties influence the constancy of the active agent content (uniformity of content) in the chewable tablets.

The results of Carr index determination of are given in Table 14. The connection between the 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 making.

Table 14: Masses by volume and Carr indices 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

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 large mass by volume, and this caused problems in filling and compression. These problems are reflected in the physical properties of Xylisorb tablets. The physical parameters of the chewable tablets are listed in Table 15.

In respect of mass, mass variation, friability and breaking hardness, the tablets proved of good quality, except those of Xylisorb. Tablets containing Karion exhibited the best hardness, whereas those of Pearlitol 400 DC displayed a very low hardness.

Table 15: Physical parameters of chewable tablets

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

The results of analytical investigations are to be seen in Table 16. For a tablet of 0.50 g, the theoretically measurable magnesium content is 19.72 mg and Table 16 shows the deviations from this theoretical value. The results on the tablets containing Karion indicate deviations in excess of the value set by the U.S. 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 Mgasp, so that the particles of the powder mixture separated during the tabletting process. In consequence of this, the active agent content of Karion tablets was not suitable.

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

Table 16: Results of analytical investigation of chewable tablets

Composition of chewable tablets	Tablet mass (g)	Magnesium content (mg)	Deviation of magnesium content from the theoretical value (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)	0.4910	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

*These values lie outside the range of the magnesium content: 17.75-21.69 mg (theoretical value: 19.72 mg)

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 compression and the formulation of chewable tablets with these compositions. These polyols display better flow, a similar particle size distribution (Pearlitol SD 200) and a similar mass by volume (Neosorb) to those of Mgasp. 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.

6. SUMMARY

Direct compression is the most efficient process used in tablet manufacturing because it is the fastest, simplest, and least expensive tablet-compression procedure. However, although this technique seems quite simple, it requires that different properties of drug materials (free flow and plastic behaviour) should be manifested simultaneously. Many drugs do not exhibit these properties: they have poor flowability and compressibility.

One of the possible solutions may be the spherical agglomeration of drug crystals by spherical crystallization. This possibility 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. The spherical crystallization (agglomeration) technique has recently received great attention and gained considerable importance in the pharmaceutical field. The particle diameter of drug materials produced by spherical crystallization is about 300-500 μm and their form is more or less spherical. The agglomerates exhibit very good flow, high bulk density and high compressibility.

The present research work relates to the improvement of the pharmaceutical technological parameters of drug materials via the spherical crystallization process, the quality of the products and the formulation of chewable tablets with developed active agent.

On the basis of the results of the present research work, the most important findings are as follows:

➪ Many active drugs have poor technological properties, e.g. particle size distribution, flowability and compressibility, and they are therefore not suitable for direct tabletting. Such materials include *acetylsalicylic acid (ASA)* and *magnesium aspartate (Mgasp)*. Spherical crystal agglomeration was used to solve this problem. A non-typical spherical crystallization process was applied in the case of magnesium aspartate (salting-out combined with cooling for Mgasp1 and Mgasp2, and a recirculation process for Mgasp3), and a typical (ASA3) or a non-typical spherical agglomeration (ASA1 and ASA2) technique in the case of acetylsalicylic acid.

➪ Quality control of the products was carried out from various aspects: determination of micro- and macromorphological parameters, recording of diffuse reflectance spectra, thermoanalytical investigations, atomic absorption analysis, and investigation of other technological properties (flowability and compressibility). In the case of magnesium aspartate, all three products have a spherical form (especially Mgasp3) and better technological properties than the commercial (control) material (especially Mgasp2 and Mgasp3). In the case of acetylsalicylic acid, ASA3 has the most spherical form and the best technological results; ASA1 has seed-form crystals and poorer attributes.
The spherical agglomeration technique resulted in crystals with good properties (Mgasp2, Mgasp 3 and ASA3) and successfully produced materials suitable for direct tablet making.

➪ Chewable tablets containing magnesium aspartate were developed with the use of different polyols (Instant Karion, Neosorb P 20/60, Xylisorb 700, Pearlitol SD 200 and Pearlitol 400 DC). The tablets were made from five compositions by direct pressing. After compression, they were investigated. The results indicated that two of the applied vehicles (Pearlitol SD 200 and Neosorb) are suitable in all respects for direct compression in these compositions. In the other cases, modification of the compositions can probably eliminate the problems.

The new relations of the present work are as follows:

➪Successful spherical crystallization of magnesium aspartate and acetylsalicylic acid.
➪Suggestion to the experts of crystallization relating to the quality control of the products.
➪Determination of magnesium contrary to Ph. Eur. 4.
➪Quality control of polyols in connection with the formulation of chewable tablets.

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