Ph.D. Thesis

INFLUENCE OF VARIOUS SUBSTANCES AND DIFFERENT TECHNOLOGICAL PROCEDURES ON SOME PARAMETERS OF TABLETS AND CRYSTALS

PÉTER KÁSA, Jr., D.Pharm.

DEPARTMENT OF PHARMACEUTICAL TECHNOLOGY
UNIVERSITY OF SZEGED
SZEGED, HUNGARY

2001

Contents

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on following publications that in the text are referred by their Roman numerals I-XIII and can be found in the Annex.

I. Deák, D., Pintye-Hódi, K., Szabó-Révész, P., **Kása, P. Jr.**, Erős, I. and Muskó, Zs.: Use of different cellulose derivatives for the preparation of tablets with a high active agent content. S.T.P. Pharma Sci., 9, 525-529 (1999).

II. Deák, D., Pintye-Hódi, K., Szabó-Révész, P., **Kása, P. Jr.**, Erős, I. and Muskó Zs.: Influence of the granulating process on the parameters of tablets. Hung. Ind. J. Chem., 28, 117-120 (2000).

III. Göcző, H., Szabó-Révész, P., Farkas, B., Hasznos-Nezdei, M., Serwanis, S.F., Pintye-Hódi, K., **Kása, P. Jr.**, Erős, I., Antal I. and Marton, S.: Development of spherical crystals of acetylsalicylic acid for direct tablet-making. Chem. Pharm. Bull (Tokyo) 48, 1877-1881 (2000).

IV. **Kása, P.**, Pintye-Hódi, K., Szabó-Révész, P., Miseta, M., Selmeczi, B., Traue J. and Wenzel, U.: The compressibility of nitrazepam crystals. (Untersuchung der Komprimierbarkeit von Nitrazepamkristallen) Pharmazie 43, 556-557 (1988).

V. **Kása, P.**, Pintye-Hódi, K., Szabó-Révész, P., Miseta, M., Selmeczi, B., Traue J. and Wenzel, U.: Direct compression nitrazepam tablets (Untersuchung von direktverpreβen Nitrazepamtabletten). Pharmazie 43, 780-781 (1988).

VI. **Kása, P.**, Pintye-Hódi, K., Szabó-Révész, P., Miseta, M., Selmeczi, B., Traue J. and Wenzel, U.: Zur Komprimierbarkeit von Tolbutamidkristallen. Pharmazie 44, 47-48 (1989).

VII. Muskó, Zs., Pintye-Hódi, K., Szabó-Révész, P., **Kása, P. Jr.**, Erős, I. and Deák, D.: Study of the influence of polymer coating films on drug release. Hung. J. Ind. Chem., 28, 111-115 (2000).

VIII. Serwanis, F.S., Szabó-Révész, P., Pintye-Hódi, K., **Kása P. Jr.** and Erős, I.: Surface treatment of acetylsalicylic acid with water soluble lubricants in a fluid bed coater by the Wurster method. Hung. J. Ind. Chem., 27, 197-201 (1999).

IX. Shourbaji, M., Pintye-Hódi, K., Novák, Cs., Madarász, J., Szabó-Révész, P., **Kása, P. Jr.**, Erős, I. and Gál, S.: Morphological, thermoanalytical and crystallographic study of different sulphadimidine crystals. Hung. J. Ind. Chem., 27, 221-226 (1999).

X. Siaan, M., Pintye-Hódi, K., Szabó-Révész, P., **Kása, P. Jr.** and Erős, I.: Morphological and flowability study of some drugs: phenobarbitone and α-methyldopa. Hung. J. Ind. Chem., 27, 209-213 (1999).

XI. Siaan, M., Pintye-Hódi, K., Szabó-Révész, P., **Kása, P. Jr.** and Erős, I.: Study of the influence of some materials on the rearrangement of Avicel® PH 301 and 302. Pharmazie 53, 424-426 (1998).

XII. Sourbaji, M., Pintye-Hódi, K., Novák, C.S., Szabó-Révész, P., **Kása, P. Jr.** and Erős, I.: A study of sulfadimidine-b-cyclodextrin mixtures. J. Incl. Phenom. Macro Chem., 37, 299-307 (2000).

XIII. Szabó-Révész, P., Göcző, H., Pintye-Hódi, K., **Kása, P. Jr.** and Erős, I., Hasznos-Nezdei, M. and Farkas, B. Development of spherical crystal agglomerates of an aspartic acid salt for direct tablet making. Powder Technol., 114, 118-124 (2001).

1. INTRODUCTION

The preparations most widely used at present in the pharmaceutical industry are solid dosage forms, such as tablets, pellets, granules or coated tablets ("dragées"). All of these dosage forms must be easily administered, and have long physical and chemical stability. These forms, and especially tablets, are more popular among patients than dosage forms such as suspensions and emulsions.

To prepare such dosage forms, various materials are used in different amounts. The preparation methods applied for tablets mostly depend on the properties of the active agents, but in some cases the properties of the auxiliary materials are decisive. If the material properties allow, the easiest and cheapest method is direct processing, but in some cases this method is not possible. In the preparation of solid dosage forms, the physical characteristics of the active agents and raw materials may cause different problems. However, there are many technological possibilities (direct compression [1-8], granulation [9-13], pelletization [14-23], etc.) with which such difficulties can be overcome. Additional problems may be the unfavourable taste or odour of the effective materials.

The production of high-quality tablets requires a tablet mixture with excellent properties as regards homogeneity, flowability [24-36] and compactibility [37-51]. When the powder mixture does not possess these properties, it has to be preprocessed, or direct compression can be used. Direct compression is possible when the mixture itself has good tabletting properties. The mixture has to flow easily and furnish good binding during compaction. Unfortunately, most tablet mixtures lack these properties and a granulation or pelletization step is necessary.

This thesis summarizes some of our research efforts aimed at satisfying the above-mentioned criteria.

2. LITERATURE SURVEY

2.1. Tablet preparation by direct compression

A number of methods are available for tablet making. Until the late 1950s, the vast majority of tablets produced in the world were manufactured by a process requiring granulation of the powder constituents prior to 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 tablet making) [52-60].

A powder mixture intended for direct compression should possess adequate fluidity and compressibility. These features may be influenced by the powder rheological properties of drugs. However, many materials have unsuitable flow properties and compressibility. These materials require wet granulation or pellet preparation prior to tabletting.

The greatest advantages as compared with other preparation forms, are the time and cost savings. However, the physical limitations of the drug and the physical properties of other raw materials become more critical and must be controlled more precisely.

The advantages of direct compression are follows:

- the number of preparation steps is reduced, which means lower needs for time and equipment;
- the lower need for equipment means that fewer operators are required;
- less material is lost;
- heat- and water-sensitive materials can be applied safely;
- the process is advantageous at low active material contents;
- the disintegration time of preparations is relatively short;
- the bioavailability is uniform because the dissolution of the active material is good.

Unfortunately, there are only a few materials that can be processed in direct tabletting, e.g. such as inorganic salts as sodium chloride. This preparation method can be used only with solid binders because most drugs require the addition of a direct compression vehicle to aid compression [61-65].

Although, the use of this technique, seems quite simple, it depends on the habit of the particles (size, form, surface, etc.) and hence on [66-71]:

- the flowability of the crystals, consistent with the production rates of modern compression technologies;
- the bulk density of the powder, so that the correct amount of drug into a die cavity;
- the compressibility of the powder.

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

- the use of alternative drug crystals, which have good flowability and compressibility properties;
- direct tablet making with "good" excipients which promote direct compression.

The first of these possibilities recently came into the forefront of interest in connection with the habit of crystals (form, surface, etc.).

As concerns the use of "good" excipients, dry binders and lubricants are very important because they can influence the direct compressibility of powder mixtures significantly.

The most important dry binder is microcrystalline cellulose, which was introduced as a direct compression tabletting agent in the early 1960s and is nowadays used as a filler too in tablet-making. Some authors deal with the availability of microcrystalline cellulose for direct compression [72-89].

Microcrystalline cellulose is the most compressible of all compression fillers and has the highest dilution potential. It is widely used because microcrystalline cellulose displays valuable plastic deformation properties. Hydrogen bonds between groups on adjacent cellulose molecules account almost exclusively for the strength and cohesiveness.

Cellulose can bind together to form interlocking layers that produce solid bridges. Microcrystalline cellulose has extremely low coefficients of static and dynamic friction and therefore has no lubricant requirements. Microcrystalline cellulose generally withstands lubricant addition, without a significant softening effect at a high concentration (greater than 0.75%) of alkali metal stearate.

If lubricants are used, and the blending time is long, tablets containing microcrystalline cellulose will be soft. Hard compacts of microcrystalline cellulose disintegrate rapidly due to the rapid passage of water into the compact and the instantaneous rupture of hydroxy bonds. The effect of microcrystalline cellulose is due to the high water uptake capacity of cellulose. It is important that tablets contain a disintegration agent with a high swelling force, so that the tablets disintegrate perfectly. Experience indicates that the disintegrative effect of microcrystalline cellulose depends on the compression force and the solubility of active agents.

The first family of microcrystalline cellulose was Avicel® (FMC Corp., Philadelphia, USA) with different registered names [89, 90].

2.2. Preparation of low-dose tablets

In the preparation of low-dose tablets, the main effect that determining the tabletting process is that of the auxiliary materials. Of course, it is not possible to neglect the physical properties of the active agent, but these are not considerable. Powder mixtures intended for direct compression should possess adequate fluidity and compressibility. These may be influenced by the powder rheological properties of the drugs.

The most important factors are the size and the shape of the fillers, the disintegrants and the solid binders.

In general, different microcrystalline celluloses are used as solid binders for direct tabletting. They can increase the cohesion between the particles, and therefore provide the tablets with satisfactory hardness. Many papers have been published on the application of cellulose derivatives [72-89]. They exhibit surface activity and can promote the dissolution of the drug from the tablet.

2.3. Preparation of high-dose tablets

The preparation of tablets with a high active agent content is particularly difficult. The aim is not to increase the weight of the tablets during tablet making. The smallest possible amount of excipients must be applied.

However, the physical limitations of the drug and the physical properties of other raw materials become more critical and must be controlled more precisely [91, 92]. In the preparation of high-dose tablets, the shape and particle size of the active agents are very important.

Powder mixtures intended for direct compression should possess adequate fluidity and compressibility. These may be influenced by the powder rheological properties of the drugs. From the aspect of direct tabletting, testing of the rheological parameters of drugs is also important.

2.4. Granule preparation

Many materials have unsuitable flow properties and compressibility. These materials require wet granulation prior to tabletting. During this process, the quality of the granules is affected by the granulating fluid. Furthermore, the parameters of the granules influence the quality of the resulting tablets.

One possibility for wet granulation is the kneading process [11-12, 37, 61, 83, 93-100]. After homogenization of the components, the powder mixture is kneaded with a granulating solution. The wet mass is passed through a sieve, and the granules are dried.

Another possibility for wet granulation is the fluidization process. In a fluid bed apparatus, the particles are floated upwards from below by the introduction of air at high pressure. The granulating solution is sprayed in from above. The particles can stick together and fluid bridges can be formed, which will become solid bridges during drying.

2.5. Pellet preparation

Pellets are built-up granulates. Pelletization is a procedure of agglomeration in which small particles are transformed into larger spherical units with good flowability. A pellet is therefore an agglomerate with nearly spherical symmetry and a diameter usually of 0.5-1.5 mm.

The latter, however, can vary with the production technology [36, 101, 102]. As compared with classical granules, pellets not only differ in shape, but also have a more compact texture, resulting in better flow characteristics. In the interior of grains with higher porosity and looser structure, bridges of solid particles form point-to-point bonds, resulting in a lower mechanical stability than that of pellets.

In their use, pellets are similar to granulate. They can be:

A separate dosage form, to make substances with a bad taste or a sticky consistency easier to take.

An intermediate in tabletting, with the aim of improving the flowability of materials that can not be tabletted directly. The pellets produced involve larger and more flowable particles with lower specific surface and adhesion than those of the particles of the original powder mixture.

Capsule fillings, due to their good morphology and appropriate stability.

Pellets can be produced by technologies based on:

- moving the solid component;
- compacting;
- drop formation.

If the solid component is moved, the powder mixture is kept in motion while the granulating fluid is being sprayed on the surface of the particles. The particles aggregate and the fluid bridges are transformed into firm binding bridges by the concurrent drying. Forms of apparatus producing pellets by this method include:

Rotating drum: In the drum, the powdered raw material is kept in continuous movement. The granulating fluid is applied to the particle surface by spraying.

Pelleting disk: The powder material is fed onto the surface of a disk with a low perpendicular rim rotating in a slightly tilted plane. The granulating fluid is applied by spraying. Granules that have reached a definite size will gather on the lower part of the disk and can be collected.

Centrifugal granulators are open devices. The mixture is fed onto a disk rotating at high rate in a barrel. The granulating fluid is constantly sprayed onto the disk, whereby a pelletizing powder can also be applied. With the temperature chosen correctly, the procedure can be continuous.

Fluidizing apparatus: A most up-to-date and preferred method. The mixture to be granulated is suspended (fluidized) in an air stream of appropriate speed and temperature, and sprayed with the liquid granulating agent. For pelletizing, roto-fluidizing machines are suitable. These are self-contained devices with a rotating disk at the bottom, to which the powder mixture is introduced.

Pelletizing in a dragée pan: The powder material is forced to rotate constantly within the pan. The fluid is applied by spraying.

Compaction is performed by extrusion and spheroidization. In this compound process, the powder mixture and the granulating fluid are kneaded into a wet mass, which is then passed through a perforated plate containing holes of appropriate size. The oblong grains obtained, extrudates, are spheroidized in a second step [103-105].

Pelletization with drop formation can be performed by spray-drying or spray-freezing. In spray-drying, the substance to be granulated is suspended in the granulating fluid and is atomized in a high-speed hot and dry air stream, where it is quickly formed into small isometric particles and dried. In spray-freezing, the melt of the material to be grained is sprayed. The spray drops quickly form isometric solid particles.

In consequence of their good physical and powder rheological properties, pellets have diverse fields of use. They can be applied in the same way as traditional granulates, but their better morphological and mechanical characteristics make them preferred intermediates. With their good flowability, pellets are equally suitable for tabletting and capsule filling.

Additionally, their spherical shape, smooth surface and mechanical stability make them suitable for coating.

3. AIMS OF THE STUDY

The present study was designed to investigate **a)** the influence of various procedures on tablet formation and the effects of different substances on the parameters of the tablets, **b)** the properties of various crystals used for tablet formation, and **c)** pellets and kneaded products.

The detailed aims were:

Ad a:

1. To study the various technological procedures, the morphological characteristics, the physical parameters, the flowability and the dissolution rates of different substances used for metronidazole tablet preparation.
2. To demonstrate the effect of the granulating method on the parameters of the tablets.
3. To reveal the effects of direct compression, various dry binders (Avicel® and Heweten 12®) and other adjuvants on the physical parameters and the texture of the tablets.
4. To demonstrate the influence of some materials on the rearrangement of Avicel PH 301® and Avicel PH 302® (important substances for tablet preparation) during direct compression.

Ad b:

1. To establish how the crystallization procedure and surface treatment can modify the various parameters and the morphology of acetylsalicylic acid crystals (ASA), the dissolution rate, the flowability, the compactibility and the tablettability.
2. To develop spherical crystal agglomerates of an aspartic acid (AA) salt for direct tablet making.
3. To study the compressibility of the nitrazepam crystals.
4. To reveal the morphological structure and the flowability of phenobarbitone and α-methyldopa.
5. To compare the morphological properties of sulfadimidine samples obtained from various batches.
6. To study the compactibility and compressibility of tolbutamide crystals and the texture of the compressed material prepared under several pressure forces, with the use of

X-ray diffractograms to detect whether the structure of the crystals changes during compressing.

Ad c:

1. To demonstrate the influence of a polymer coating on drug liberation from pellets.
2. To reveal the morphology and the dissolution rate of a physical mixture and a kneaded product containing sulfadimidine and β-cyclodextrin. The answer to this question is important because of the low solubility of sulfadimidine.

4. MATERIALS AND METHODS

4.1. MATERIALS

Some of the most important substances used for the experiments are listed below, together with their chemical properties.

4.1.1. Active ingredients

Nitrazepam (Nitrazepamum, Ph.Hg.VII) was used to study the tablettability properties when the concentration of effective material in the tablets was low. The tablettability of nitrazepam has been investigated by several authors in the literature.

Tolbutamide (Tolbutamidum, Ph.Hg.VII) served as a model material to investigate the effects of a high content of effective material in the tablet. The data in the literature indicate that tolbutamide has different polymorphic variations.

α-Methyldopa (EGIS Pharmaceuticals Ltd., Budapest, Hungary). It has been established that variation of the crystallization conditions can result in differences in the crystal morphology, which influence the flow properties and tablet making. The direct compression of α-methyldopa is especially advantageous because of its discolouring in presence of water [106]. No polymorphism is observed and the crystals to belong in the monoclinic system [107].

Phenobarbitone (Ph. Eur. 3rd) (Alkaloida, Tiszavasvári, Hungary)

This drug was selected because it is difficult to compress directly.

Metronidazole (Ph. Eur. 3rd)

Metronidazole is a drug that is frequently used in the treatment of various anaerobic infections. It is well absorbed following oral administration. The drug is useful in prophylaxis in obstetric and gynaecological interventions, colorectal surgery and appendectomy [108,

109]. The simple oral dose is generally 250 mg, and the tablets have a high active agent content. It has been discussed in various papers [110-117].

Aspartic acid salt (Merck, Darmstadt, Germany)

White odourless crystals with an acidic taste.

4.1.2. Auxiliaries

These substances were applied for tablet or pellet formation using direct tabletting procedures and pellet formation.

Avicel PH-101® (A101) (FMC Corp., Philadelphia, USA). This was selected as a reference adjuvant because of its similarity to the materials under investigation. It is widely used in direct tabletting and also because it is well known in the literature.

Avicel PH-301® (A301) **and Avicel PH-302®** (A302) are high-density Avicel® products recently introduced to improve the flowability of Avicel®, to allow thinner tablets, to furnish a better tablet weight uniformity, etc.

Heweten 12® (VEB Freiberger Papierfabrik, Germany). This was used in all materials that have hydrolytic sensitivity or water solubility. It gives a good disintegration time in direct tabletting. The morphological properties are similar to those of Avicel®.

Vitacel A 300® (Rettenmaier & Söhne GmbH & Co., Ellwangen-Holzmühle, Germany). This is a microfine cellulose. The manufacturer states that the number of glucose units per macromolecule is ca. 1000. Cellulose-like materials are highly useful as filler materials and as binding substances in direct tabletting.

4.2. METHODS

4.2.1. Tablet preparation

Tabletting was carried out with a Korsch EKO eccentric tablet machine (E. Korsch Maschinenfabrik, Germany) mounted with strain gauges, and a displacement transducer was applied.

4.2.2. Granule and pellet formation

For the preparation of pellets, a centrifugal granulator (Freund CF-360, Japan) was used. Granulation was performed with a fluid bed apparatus (Strea-1, Niro-Aeromatic AG, Switzerland).

4.2.3. Morphological investigations

The structural properties of the active agents and the auxiliary materials were investigated with Tesla BS300 (Tesla, Brno, Czech Republic) and Hitachi S-2400 (Hitachi Scientific Instruments Ltd., Tokyo, Japan) scanning electron microscopes (SEMs). A Polaron sputter coating apparatus (Polaron Equipment Ltd., Greenhill, UK) was applied to induce electric conductivity on the surface of the sample. The air pressure was 1.3-13 mPa.

4.2.4. Particle size analysis

For the testing of particle size, sieve analysis (according to Ph.Hg.VII) and an image analysis system were used.

A sample of a few milligrams was dispersed in liquid paraffin for deaggregation, and the suspension was then distributed on a slide and tested with a Laborlux S light microscope and a Quantimet 500 (Q500MC) image processing and analysing system (Leica Cambridge Ltd., Cambridge, UK).

Particle length, breadth and roundness were measured for more than 500 particles each. The obtained data were treated statistically by using the Statgraphics package.

The roundness is a shape factor which provides information on the circularity of the particles It is calculated by the software according to the following formula:

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

4.2.5. Homogenization

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

4.2.6. Mass by volume

This was tested with an ASTM apparatus (ASTM D 392-38) according to Ph.Hg.VII [118].

4.2.7. Flow properties

The flow properties were tested with an ASTM apparatus (ASTM D 392-38) according to Ph.Hg.VII and also with powder testing equipment (PTG-1) (Pharma Test GmbH, Germany) were used. Both the flow time and the angle of repose were tested.

4.2.8. Compactibility and compressibility tests

Calculations were based on loose and tapped densities. A tap density volumeter (Stampfvolumeter 2003, J. Engelsmann AG Apparatebau, Germany) was used for determinations in accordance with the literature [119].

4.2.9. Powder rheology and particle size

Bulk density determination

Bulk density was determined with the ASTM-D apparatus, official in Ph.Hg.VII.

Flowability tests

The flowability tests were also performed with the ASTM-D device and with the PTG-1. The flow-out time of a specified amount of the material, and the slope angle of the flowed- out bulk were measured. Depending on the slope angle, materials can be categorized in different groups **(Table 1).**

Table 1. Relationship of flowability and slope

Slope angle (°)	Flowability
<25	Excellent
25-30	Good
30-40	Modest
>40	Very poor

The influence of the flow on the compressibility was tested with an Engelsmann Stampfvolumeter according to the DIN (German Industrial Standards). In the test, a loose bulk of powder is exposed to a compacting effect under standard conditions, resulting in a volume reduction. With the mass given, the initial (loose) and final (tapped) densities can be calculated [120]. From these, Hausner's factor *(Hf)* can be obtained, which is an indicator of the density increase under the influence of the impacts: $Hf = \frac{\rho_l}{\rho_t}$,

where ρ_l and ρ_t are the densities in the loose and the compact state, respectively. According to the literature, $Hf \approx 1$ is advantageous for direct tablet compressing. If $Hf > 1.5$, the material is better granulated first.

Carr's index (%) can be calculated similarly: $\text{Carr's index} = \frac{\rho_t - \rho_l}{\rho_t}$.

A low Carr's index means a better flowability and space-filling efficiency, resulting in a higher compressibility. According to the literature, the following groups can be defined **(Table 2)** [119, 121].

Table 2. Flowability groups based on Carr's index

Carr's index %	Flowability
5-15	Excellent
12-16	Good
18-21	Fair to passable
23-35	Poor
33-38	Very poor
>40	Extremely poor

Carr's index can be calculated according to the equation [122]

$$\text{Carr's index \%} = \frac{\text{tapped density - loose density}}{\text{tapped density}} \cdot 100$$

5. RESULTS AND DISCUSSION

5.1. The formation and properties of tablets

It is well known that the morphological characteristics, the physical parameters, the flowability and the rates of dissolution of various substances can be altered during the various technological procedures and methods available for tablet preparation. With the application of different materials (metronidazole, nitrazepam and Avicel®), the variables mentioned above were studied and the results obtained are described below.

5.1.1. Metronidazole and different cellulose derivatives used for tablet preparation

Metronidazole has been used for many years in various formulae for the treatment of different illnesses. For the bioavailability of a drug, it is important to know which formula is the best. Among others, our aim in this investigation was to study the morphological characteristics, the flowability and the dissolution rates for better tablet preparation (I).

The result of a morphological SEM study of metronidazole crystals are demonstrated in Figs 1 and 2.

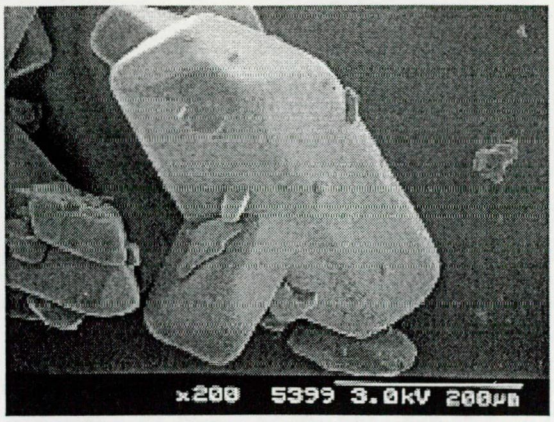

Fig. 1. Metronidazole consists of heterodisperse, stubby columnar crystals.

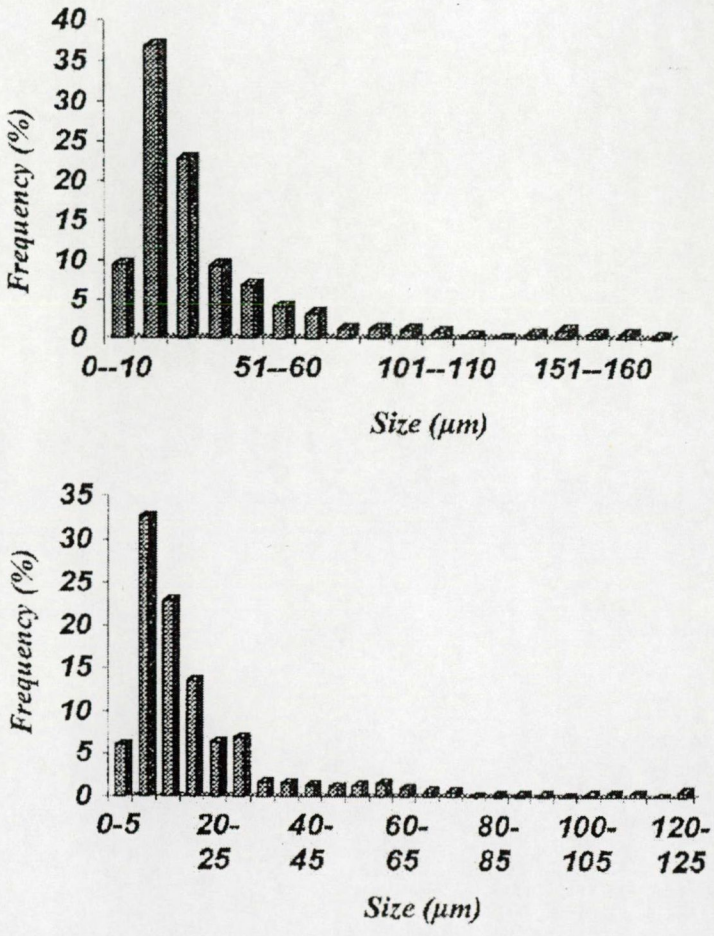

Fig. 2. Particle size distribution of metronidazole crystals by length (top) and breadth (bottom). Most crystals had a length in the range 10-30 µm, and a breadth in the range 5-20 µm.

In accordance with the roundness value, this crystal shape results in unsuitable flow properties. Various cellulose derivatives (hydroxyethyl cellulose, hydroxypropyl cellulose and methylcellulose) were therefore used as binders. The physical parameters of tablets are presented in **Table 3**.

Table 3: Physical parameters of tablets

Samples	Average mass (mg)	Uniformity of mass (mg)	Friability (%)	Breaking hardness (N)	Disintegration time (s)
S 1					
10 kN	307.9	± 2.9	2.27	29.5	598
15 kN	311.5	± 3.3	2.73	31.5	380
S 2					
10 kN	313.6	±2.5	0.83	107.2	156
15 kN	312.6	± 2.8	0.80	112.7	190
S 3					
10 kN	296.1	± 4.0	2.31	22.2	92
15 kN	295.4	± 6.9	2.18	23.5	92
S 4					
10 kN	295.0	± 4.9	2.03	24.7	140
15 kN	297.0	± 3.4	1.77	27.1	106

In all cases, the uniformity of mass was within a limited range, according to Ph. Hg.VII. It can be seen that the value was best for S2, which was prepared by using hydroxypropyl cellulose (Klucel LF®). The hardness of the tablets was likewise most satisfactory with Klucel LF®.

A small increase in hardness was observed at higher pressure levels, but only with the tablets prepared by using Klucel LF®. This was in accordance with the friability results. The disintegration time was longest for tablets prepared by using hydroxyethyl cellulose (Cellosize®). The disintegration time of the tablets compressed at 10 kN was longer. However, when the pressure was increased, the granule particles underwent a higher degree of breaking, and the polymer film also broke, resulting in a shorter disintegration time. The disintegration of other tablets occurred after almost the same period (1.5-3.0 min). An increase in pressure generally had no influence on the parameters of the tablets.

The dissolution of the drug was very rapid (100% within 10-20 min), except for the tablets prepared by using Cellosize® (Fig. 3).

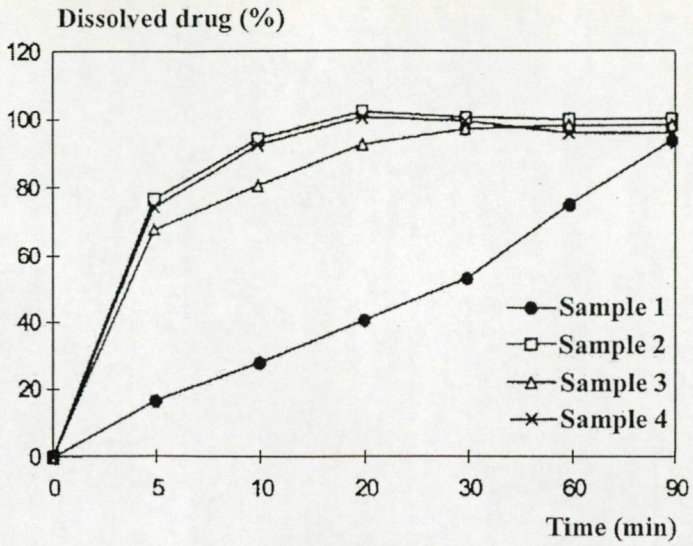

Fig. 3. Rate of dissolution of metronidazole from tablets. Pressure: 10 kN.

Overall, it can be concluded that the best physical parameters and most rapid dissolution were achieved with the tablets prepared by using Klucel LF® at 10 kN. The reason for this lies in the particle size and shape.

In another set of experiments **the effects of the granulating method on the parameters of the tablets** were studied (II).

The shape of the granules was demonstrated by SEM. The conventional granule consists of larger particles, whereas, the fluid granule consists of smaller particles (Fig. 4). As Fig. 4 shows, granules lead to better powder rheological parameters.

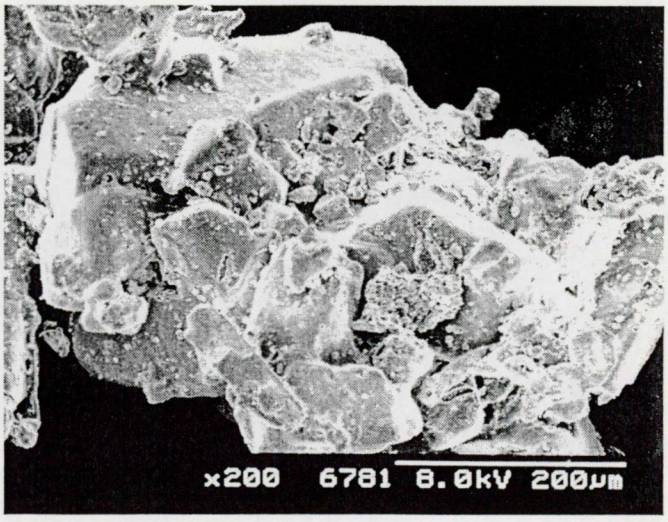

Fig. 4. Granule shape

The results with the granulating method are described in detail in II. It emerged that the flow properties of the crystals were unsuitable, and wet granulation should be preferred as the tablet manufacturing method. The physical parameters of the tablets and the rate of dissolution of the drug were also tested.

The results permit the conclusion that the granulation process influences the parameters of tablets.

5.1.2. Nitrazepam and different binders applied for tablet preparation by direct compression

The aim of this study was to study the effects of direct compression, various dry binders and other adjuvants on the physical parameters and the texture of the tablets. The results of this study are described in detail in V. Here, only the most important findings will be summarized.

With the help of SEM, it was revealed that the texture of the tablets was altered differently when A101 (Fig. 5) and Heweten® were applied in nitrazepam tablet formation.

Fig. 5. SEM photo demonstrating the upper surface of a tablet prepared from nitrazepam and A101.

When the dissolution rate was studied with nitrazepam, A101 and other auxiliaries (N/A1, N/A2, N/A3 and N/A4), it was demonstrated that the best rate could be obtained with N/A4 (Fig. 6).

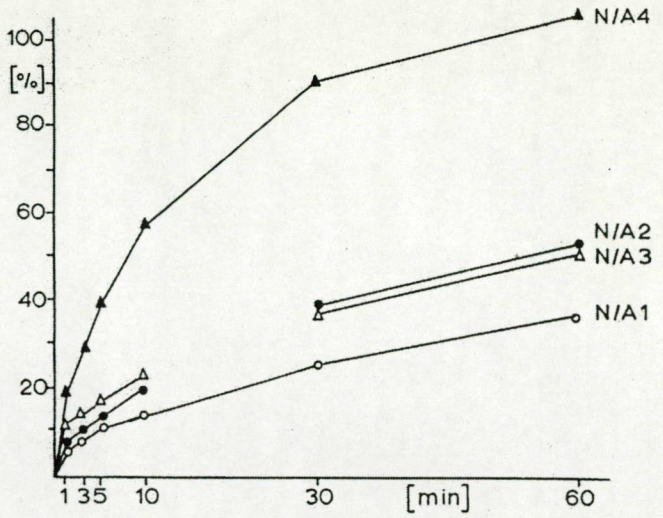

Fig. 6. The rate of dissolution of nitrazepam in the presence of A101.

When Heweten was used for nitrazepam tablet preparation (N/H1, N/H2 and N/H3), the dissolution rate was lower than that with A101 (Fig. 7.).

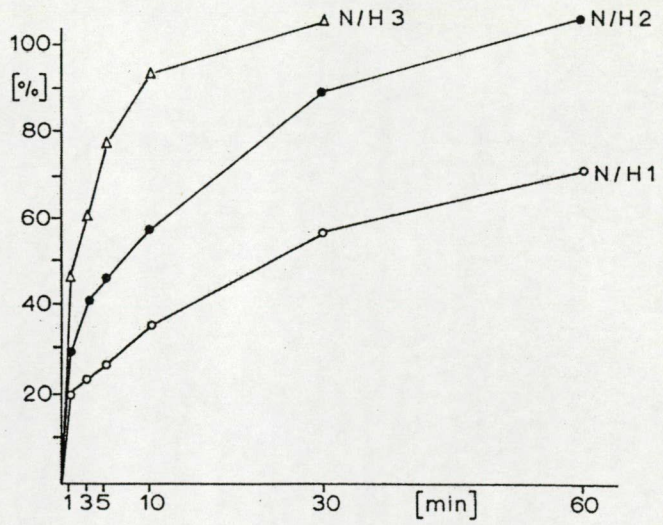

Fig. 7. The best dissolution rate was obtained with N/H3.

The results show that the use of A101 leads to slow dissolution, and the use of Heweten 12® to fast dissolution.

5.1.3. A301 and A302 properties during compression

We earlier described the advantages of direct compression and the rearrangement of A301 and A302 [123]. These microcrystalline celluloses are used as dry binders to decrease the friction work between the die wall and the side of the tablet. Furthermore, in most cases diluents (fillers) (e.g. different starches or sugars) are used to prepare the tablets. Disintegrants (e.g. starches) are generally found too in a tablet composition [120, 124, 125]. These components influence the rearrangement of the particles of the powder mixture in the first phase of the compression [126].

The specific aim in this study was to demonstrate the influence of some materials on the rearrangement of A301 and A302 during direct compression (XI).

We tested the density and compactibility of powder mixtures. The results show that the moisture contents of A301 and A302 were decreased by sorbit (A301S and A302S). However, on the addition of corn starch to this mixture (A30lSS; A302SS), the moisture contents again rose to about 3.0%. The moisture content of phenobarbitone and α-methyldopa [bulk substances (Ph; Md) and with 0.5% of magnesium stearate (Ph+ and Md+)] were low, but increased a little on the addition of A301 or A302 (A30lPh; A302Ph; A30lMd; A302Md). Magnesium stearate (0.5%) had no influence on the densities of A301 (A301+) and A302 (A302+). However, the densities changed when the mixtures contained sorbit (A301S; A302S) or sorbit plus corn starch (A30lSS; A302SS).

It can be concluded that the compactibilities of A301 and A302 may be corrected by the addition of sorbit.

The densities of the mixtures containing active agents and A301 or A302 (A30lPh; A30lMd; A302Ph; A302Md) were higher than those of A301 and A302 alone, but the Hausner ratio and Carr's index remained almost the same.

It is well known that the compactibility behaviour is very important during compression. It depends on the rearrangement of the particles. The rearrangement constants were calculated according to the literature [123]. The data are presented in **Table 4**.

The results of regression analysis show that the exponential model reflects the rearrangement for the studied materials. It can be seen that the excipients and the active agents influence the rearrangement of A301 and A302. Analysis of the data reveals that the different ingredients have different effects on the rearrangement, but there is practically no difference between the mixtures containing A301 and A302.

Table 4: Regression analysis of compactibility test

Material	Linear model $y = 1 + kn$ ($p < 0.05$)			Exponential model $y = \exp(1 + kn)$ ($p < 0.05$)		
	r	k	F-ratio	r	k	F-ratio
A301	0.626	10049	3.219	0.982	0.2276	135.06
A302	0.748	3236.6	6.356	0.989	0.2216	220.80
A301+	0.644	2776.6	3.544	0.982	0.2056	135.65
A302+	0.644	14888	3.535	0.973	0.2368	87.52
A301S	0.704	113.33	6.885	0.994	0.0894	586.51
A302S	0.684	414.6	6.146	0.981	0.0965	178.27
A301SS	0.495	10665.2	5.516	0.987	0.1130	627.08
A302SS	0.543	7655.4	5.593	0.976	0.1186	216.47
Ph	0.699	27516	16.290	0.978	0.1177	382.38
Ph+	0.570	106267	8.654	0.979	0.1072	417.09
A301Ph	0.661	26755	13.220	0.984	0.1147	514.46
A302Ph	0.681	11911	12.090	0.981	0.1575	355.68
Md	0.610	230382	9.491	0.996	0.1580	1814.08
Md+	0.597	23539	8.289	0.993	0.1636	1095.91
A301Md	0.659	9686.38	10.74	0.987	0.1533	540.41
A302Md	0.691	8553.12	13.71	0.979	0.1227	349.53

Finally, it can be stated that the studied materials have a positive influence on the rearrangement of A301 and A302, and these mixtures exhibit a good compactibility.

5.2. Crystal structure changes during processing

The crystal structure, morphology, size and crystal quality can affect the chemical reactivity, bulk powder flow, rheology and stability of suspensions, and other mechanical and physical properties of a substance. For pharmaceutical applications, an appropriate choice of crystal form can enhance the bioavailability of the drug. Data obtained from an investigation of the properties of various crystals for tablet making are presented below.

5.2.1. ASA crystals

The purpose of this experiment was to learn which crystallization procedure is the best for the crystal habit (form, surface, size, etc.) of ASA and how the surface treatment can modify the various parameters (morphology, dissolution rate, flowability, compactibility and tablettability) of the crystals (III).

The results of this experiment indicated that that only the typical spherical crystallization technological procedure leading to spherical crystals of ASA can be

recommended because this can result in excellent flow properties, favourable compactibility and tablettability values.

The next questions to be answered were how the surface coating can modify the flowability, the compactibility, the dissolution rate and the tablettability of ASA.

Commercial, unlubricated ASA crystals are tetragonal prism-shaped, with uneven and fragmented edges. About 50% of the particles measured between 0.63 and 0.8 mm.

The coating process was studied with 0.5 or 1% of Lutrol F68 and 0.5% 1% of Carbowax 6000 in the fluid bed coater. The Strea-1 Aerocoater with the Wurster method facilitated the intensive motion of the crystals in the product column. The parameters of the surface treatment of the ASA crystals were the same in all cases.

After evaporation of the solvent (a water and alcohol mixture), a thin film coat adhered to the surface of the ASA crystals, due to the film-forming properties of Lutrol F68 and Carbowax 6000.

The **compactibility** and cohesivity properties of the unlubricated and lubricated ASA crystals were also investigated. Both parameters are very important in tablet making. The unlubricated ASA crystals exhibited good compactibility (VIII).

The **cohesivity** values give information on the flow properties of the crystals. The coating process influenced the flowability of the crystals favourably, except for the ASA crystals coated with 1% of Lutrol F68. This can be ascribed to the change in the ASA particle size during the coating process.

We studied the effects of the lubricants involved on the **tablettability** of ASA crystals. Strong friction between the side of the tablet and the die wall was experienced during the pressing of unlubricated ASA crystals. This was indicated among others by an unpleasant noise from the machine. Signs of adhesion to the punches were observed on the surface of the tablets with increase of the pressure force. Nevertheless, the tablets prepared from unlubricated ASA crystals had a very good breaking hardness.

Table 5: Parameters of tablets with unlubricated and lubricated ASA crystals

Sample	Pressure force, kN	Weight variation, R.S.D.	Breaking hardness, N	Disintegration time, s
Unlubricated ASA	5	0.933	167.0	32
	10	0.792	200.0	63
ASA+Lutrol F68 0.5%	5	0.957	129.8	13
	10	1.926	200.0	43
ASA+Lutrol F68 1%	5	1.220	112.0	14
	10	0.980	161.4	49
ASA+Carbowax 6000 0.5%	5	1.107	135.0	13
	10	0.901	194.8	32
ASA+Carbowax 6000 1%	5	1.100	139.4	19
	10	0.840	198.5	80

(R. S. D. Relative Standard Deviation)

In the last step, the lubricant coats were studied with regard to the rates of dissolution of ASA crystals from tablets. The values of $t_{63.2\%}$ for the lubricated tablets indicate a longer dissolution time than that for the unlubricated tablets. Moreover, the wetting of the lubricants can not be effective because of the decreasing crystal surface during compressing. Although the disintegration time of the tablets compressed from lubricated ASA crystals was shorter (wetting effect) than that of the tablets prepared from unlubricated crystals, larger crystal aggregates with a small surface underwent only disintegration, instead of perfect disaggregation **(Table 5)**.

From the results presented in these experiments, it can be inferred that the Strea-1 fluid bed coater with the Wurster column can be suggested for the surface treatment of crystals with water-soluble lubricants. The process is fast and well reproducible. 0.5% of either of the water-soluble lubricants (Lutrol F68 or Carbowax 6000) was sufficient to decrease the electrostatic charge. This amount was also sufficient to cover the surface irregularities (edges) of the crystals. The lubricant coat improved the flow properties and the tablettability of the ASA crystals. The wetting of the coats was effective as concerns the rate of ASA dissolution and the tablet disintegration time. It can be stated that both Lutrol F68 and Carbowax 6000 resulted in good parameters, but 1% of Lutrol F68 can not be recommended for use in a coating process.

5.2.2. AA salt crystallization for direct tablet making

The aim of this investigation was to develop spherical crystal agglomerates of an AA salt for direct tablet making (XIII).

The investigated crystals and crystal agglomerates were found to have different particle sizes. The control (commercial) AA salt consists of single, very small crystals and agglomerated crystals with an unfavourable habit for direct compressing (Fig. 8).

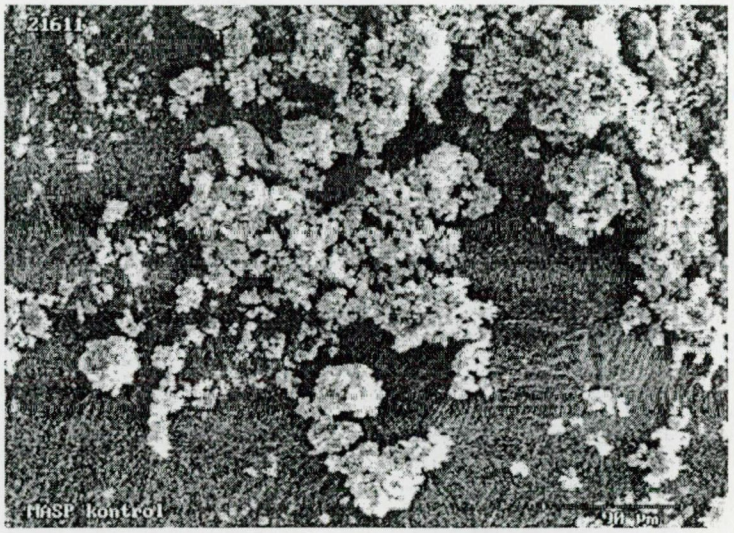

Fig. 8. Control (commercial) aspartic acid salt crystals.

The size of 91% of the crystals was less than 71 μm. The structure, surface, size and particle size distribution of the crystal agglomerates were determined via the parameters of the crystallization process. In the same way, samples A and B (AA salt crystal agglomerates) were crystallized by salting-out combined with cooling, using the traditional mechanical stirring method. Sample A consisted of smaller particles than those of sample B (Fig. 9) because of the slower initial cooling and the higher stirring rate. The spherical crystal agglomerates of sample B had a closed "cauliflower-like" structure with a relatively large particle size (62% of the particles were larger than 250 μm).

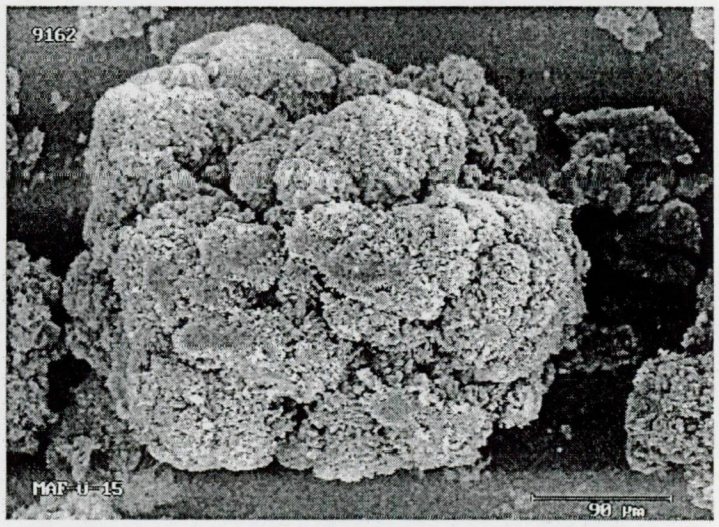

Fig. 9. Crystal structure of sample B with "cauliflower-like" appearance.

In fact, it was revealed that a higher initial cooling rate and a lower stirring rate are very favourable in the building-up of crystal agglomerates with a closed structure.

The particle size distribution of sample C (produced in a recirculation process) was situated between those of sample A and sample B. The agglomerates of sample C had a small specific surface, a small micropore volume and a small average pore diameter.

The different macro- and micromorphologies of samples A, B and C did not involve modification of the inner crystal structure of the agglomerates. This was documented by thermoanalytical investigations (for the details see in XIII).

It is very important that the deformability of the AA (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.

Both the traditional mechanical stirring crystallization and the recirculation process are suitable for the development of spherical crystal agglomerates of an AA salt. Samples A, B and C had 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.

5.2.3. Nitrazepam crystals

Nitrazepam is a safe long-acting benzodiazepine safe hypnotic and possibly the most commonly used soporific since 1966 [127].

The physical characteristics of this "life-saving" substance are still not fully understood; the purpose of this research was therefore to reveal the compressibility of nitrazepam crystals.

To establish new characteristics of this substance, SEM was used. The results showed that, when the crystals were subjected to direct compression, the morphology underwent some structural alterations (IV).

While the normal structure of nitrazepam crystals is to be seen in Fig. 10, the compressed surface of the nitrazepam tablet is demonstrated in Fig. 11.

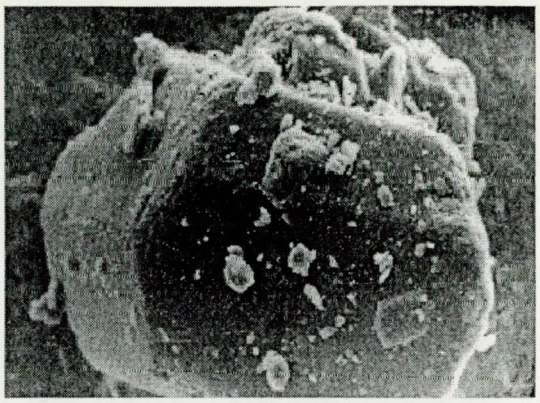

Fig. 10. Normal structure of nitrazepam crystal.

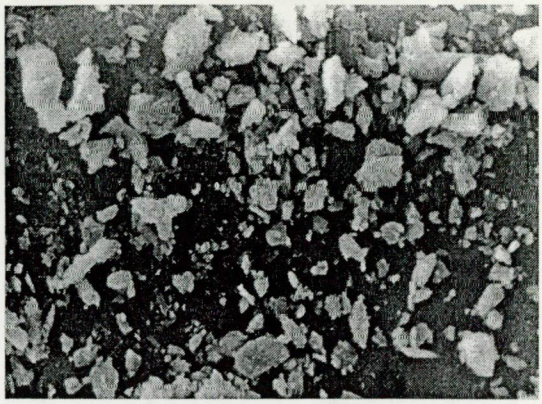

Fig. 11. Upper surface of nitrazepam tablet.

Direct compression resulted in small crystals growing on the surface of nitrazepam tablets.

5.2.4. Phenobarbitone and α-methyldopa crystals

Before tablet making, preformulation tests have to be performed. Among these, a very important role is played by the powder rheological properties of drugs and other additives. In this part of this thesis, the morphological and powder rheological parameters of phenobarbitone and α-methyldopa will be described (X).

The habits of the crystals were investigated by SEM, and the particle size distribution was tested with an image analysis system. The rearrangement factor (k), the compactibility and the cohesiveness of the crystals were calculated from the loose and tapped volumes of the drugs.

From the micrographs of phenobarbitone, it can be seen that there are different habits and crystal sizes, with many columnar crystals and many crystal aggregates in the sample. Two forms can be observed at higher magnification. One of them involves larger column-like crystals, but it can be seen that the recrystallization is not faultless. Some small crystals are visible on the larger smooth crystal surface. The other is the aggregate presented in Fig. 12, which is built up from many small crystals. Phenobarbitone crystals have a large rough surface.

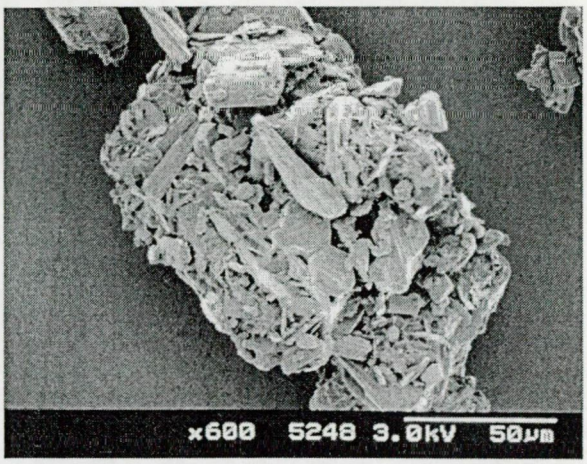

Fig. 12. SEM reveals the aggregated form of phenobarbitone. Many small crystals are evident.
Scale bar = 50 µm.

The sample of α-methyldopa proved to be heterodisperse. Among the well-grown crystals, numerous small particles could be observed. At higher magnification, the well-grown crystals are columnar in shape with a rough surface and the ends of some columns are planar, while others have moderately sharp ends (Fig. 13).

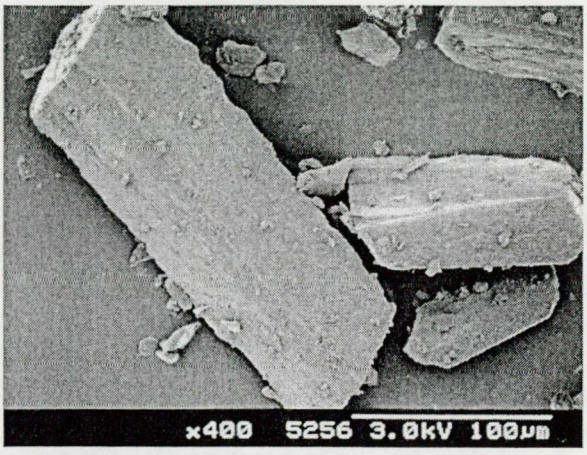

Fig. 13 The appearance of α-methyldopa crystals. Scale bar = 100 µm.

The results of particle size analysis showed that α-methyldopa has larger length and breadth values than those of phenobarbitone, but the roundness values are almost the same.

The roundness influences the flowability of the materials, so it is an important parameter. When this value is near 1, it means that the shape of the particle is spherical. The shape can be observed in the SEM pictures, but the degree of sphericity can be obtained only from this parameter.

When the particles are very small, their kinetic energy is also small, and those particles that have already fallen into the die are unable to move. If bigger particles fall into the die,

their greater energies allow them to rearrange the lower layers into more efficient packing arrangements and the mean weight of the compact thereby increases [128].

It can be stated that the habits (shape, surface, particle size and particle size distribution) of the tested drugs differ. This difference influences the flow and rearrangement behaviour of the crystals in the die.

The degree of cohesiveness plays an important role in tablet making. Thus, the compactibility and cohesiveness of these materials were evaluated according to the Kawakita equation. The results are shown in **Table 6.**

Table 6: Compactibility and cohesiveness values by Kawakita model

Materials	Correlation coefficient (r) ($p < 0.05$)	Compactibility ($1/a$)	Cohesiveness ($1/b$)
Phenobarbitone	0.9964	4.4600	16.8811
α-Methyldopa	0.9926	3.7703	22.9383

It can be stated that the compactibility constant (1/a) of phenobarbitone is higher and its cohesiveness (1/b) is smaller than that of α-methyldopa.

From these results, it can be concluded that phenobarbitone has smaller length and breadth values than those of α-methyldopa. Differences can also be seen in the particle size distribution and the shape and surface of the drug crystals. These properties influence the flowability of the crystals, and the rearrangement of the particles in the die during compression. The habit and particle size of phenobarbitone are favourable for rearrangement of the crystals in the first phase of compression. This means that the powder rheological properties of phenobarbitone are better than those of α-methyldopa. The effect of direct compression is widespread, so these properties should be taken into consideration before direct compression. It can also be concluded that the powder rheological parameters of phenobarbitone are better than those of α-methyldopa.

5.2.5. Sulfadimidine crystals

The commercial products of sulfadimidine exhibit various morphologies that influence the preparation of the solid dosage forms. The powder mixture must have adequate flowability and compactibility during direct compression and capsule filling. These properties are influenced by the morphological parameters of the particles, and are additionally important in the preparation of granules as concerns the distribution of the drug particles.

The aim of the present work was to compare the morphological properties of sulfadimidine samples obtained from three different batches (IX).

The crystals in the three sulfadimidine samples displayed different structural properties. Sulfadimidine 1 consisted of thin tabular crystals with a rough surface. Some very small crystal particles could be seen on their surfaces (Fig. 14). Sulfadimidine 2 consisted of smaller, but stubby crystals with an irregular shape (Fig. 15). Sulfadimidine 3 was comprised of larger, thicker crystals with a smooth surface (Fig. 16); some of them had a columnar, and others a tabular form.

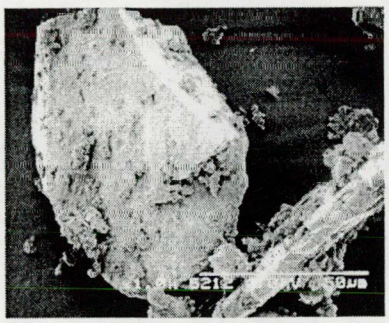

Fig. 14. Sulfadimidine 1 crystals (SEM).

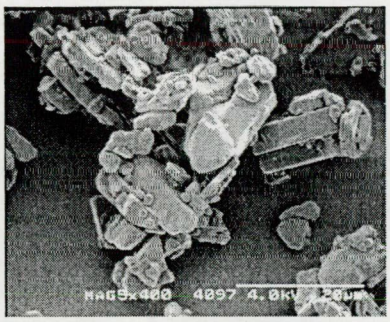

Fig. 15. Sulfadimidine 2 crystals (SEM).

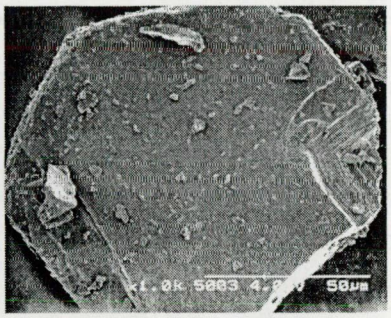

Fig. 16. Sulfadimidine 3 crystals (SEM).

The particle sizes and the distributions of the particle size in the three samples also differed. The sulfadimidine 1 sample was homodisperse: 63% and 75% of the crystals measured under 10 μm in length and breadth, respectively. Most crystals of sulfadimidine 2 were less than 30 μm in length and 20 μm in breadth. Sulfadimidine 3 was heterodisperse: 92% and 82% of the particles were less than 60 μm in length and breadth, respectively.

From the aspect of direct compression or capsule filling, sulfadimidine 1 and sulfadimidine 2 were unsuitable, because the particles were too small. Particles smaller than 10 μm generally have van der Waals attractive forces that are greater than the force of gravity and consequently the material is cohesive [129]. In this case, the adhesion between the particles is too high. The flow properties of such samples are generally not suitable and the rearrangement of the particles in the die cavity or capsule is not uniform. In this respect, the best sample was sulfadimidine 3. For larger particles, the gravitational force, which increases in proportion to the cube of diameter, becomes much greater.

From the morphological SEM observations, were was combined with image analysis of the various sulfadimidine forms, we can infer that the particle size distribution influences

the behaviour of the particles, which is very important in the first phase of the compression. The results permit a choice of the best sample for the preparation of a solid dosage form.

5.2.6. Tolbutamide crystals

Tolbutamide, an antidiabetic agent, is a typical pharmaceutical substance which exhibits polymorphism, the tendency of a substance to crystallize in different crystalline states. Each of the polymorphs, the solid forms of the same compound, display different physicochemical properties and as bioavailability, and the pharmaceutical industry is confronted by this behaviour.

Our aim in this investigation was to study the compactibility and compressibility of tolbutamide crystals and the texture of the compressed material prepared at several pressures was also examined. X-ray diffractograms were made to detect whether the structure of the crystals changed during compressing (VI).

Tolbutamide crystals have an oblong form with rounded ends (Fig. 17). High magnification clearly reveals small needle-shaped crystals adhering to the surface. The average size is 28.7x60.6 μm. The main size of the particles is less than 80 μm.

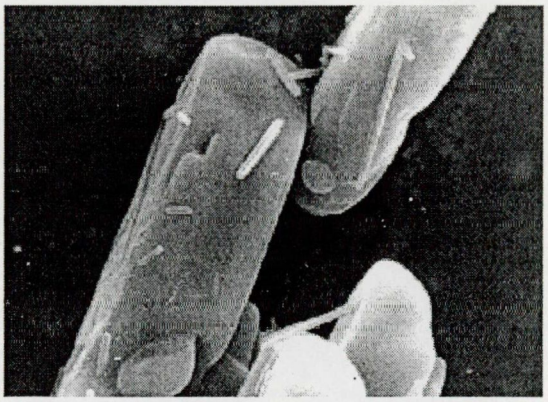

Fig. 17. The SEM appearance of the tolbutamide crystal. Note the needle shape of the crystals.

X-ray diffraction was performed to detect whether the structure of the crystals changed during compressing (Fig. 18). It is clearly demonstrated that 5 kN caused a significant alteration in the crystal structure; however, when the pressure was increased to 10 kN, no further alteration could be detected. These results permit insight into the behaviour of the tolbutamide crystal structure during compression.

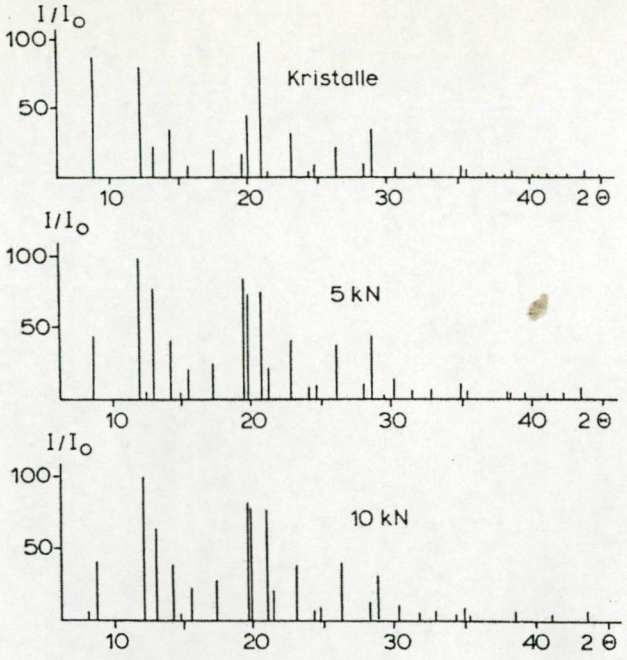

Fig. 18. X-ray diffractogram of tolbutamide crystals grown under different pressure forces.

5.3. Pellets and kneaded products

The aim of the investigation of the pellets was to study the influence of a polymer coating on the drug liberation (VII).

Polymethacrylates (Eudragit and Eastacryl) and ethyl cellulose (Surelease) in different quantities were used as coating materials. The coating process was carried out in a fluid bed apparatus with a Wurster column. The surface of uncoated and coated pellets was investigated by SEM.

The results of the SEM studies revealed that a suitable and uniform coating film is formed on the approximately spherical pellet surface (Figs 19 and 20).

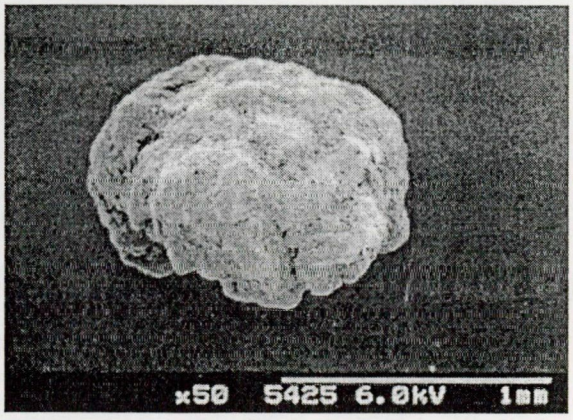

Fig. 19. The surface of the uncoated pellet is rough and several and various micropores can be revealed.

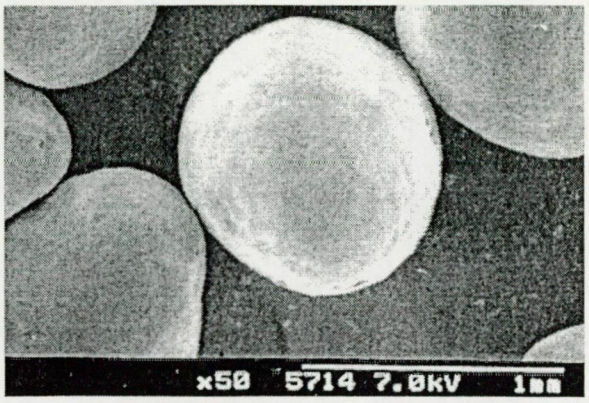

Fig. 20. Surface of a coated pellet. Note the disappearance of the prominences and the recesses, and the smooth appearance of the pellet surface.

The results of the dissolution tests demonstrated the influence of the nature and quantity of the coating material on the liberation of the drug (Figs 21a, 21b and 21c).

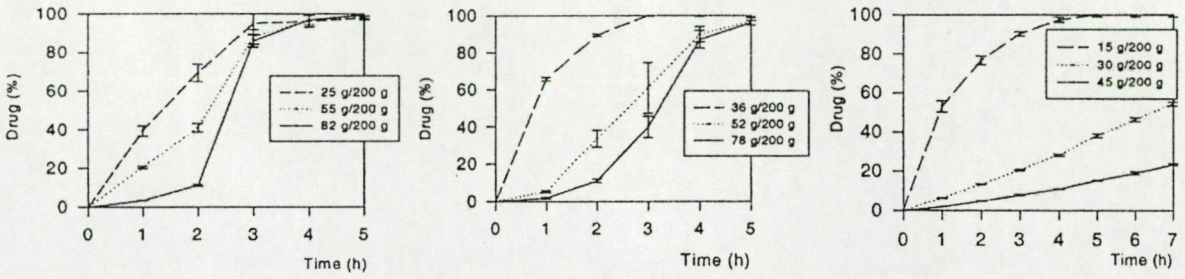

Fig. 21. Drug dissolution from coated pellets: a) coating material Eudragit 100-55; b) coating material Eastacryl 30D; c) coating material Surelease.

It can be seen that the polymethacrylate films (Eudragit and Eastacryl) with the smallest dry material content proved to be protective films. Increase of the dry material content in the coating dispersion ensured a slow drug release. The dissolution profile exhibited a sigmoid shape at higher dry film coating material content. A slow liberation could be seen in the gastric juice, but at higher pH values the total drug dissolved within 5 h.

From these results it can be concluded that a lower Surelease quantity was sufficient to attain a slow release from the coated pellet. As indicated by the characteristic dissolution time, the agent was most rapidly liberated to 63.2% from pellets coated with Eudragit film. A comparison of Eudragit vs. Eastacryl coatings of identical thickness revealed a close similarity in $t_{63.2\%}$. This is not really surprising because the two substances are both polymethacrylate derivatives. Surelease, on the other hand, differs from the previous two in

chemical structure and in properties. Surelease films of the same thickness liberated the active agent much more slowly than did polymethacrylate film.

The next experiment was designed to reveal the morphology and the dissolution rate of a physical mixture and a kneaded product containing sulfadimidine and β-cyclodextrin. A more detailed description of the results is to be found in Annex (XII).

The SEM investigation revealed the morphology of the typical sulfadimidine crystals of many different sizes in their original form in the physical mixture (Fig. 22). On the other hand many small adhered crystals were observed in the sulfadimidine-β-cyclodextrin kneaded product (Fig. 23).

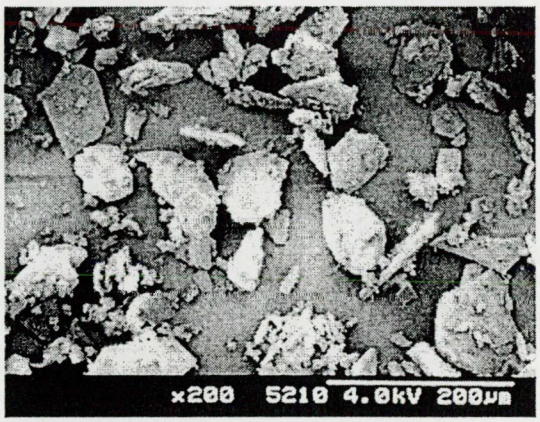

Fig. 22. The appearance of the sulfadimidine crystal is demonstrated by SEM.

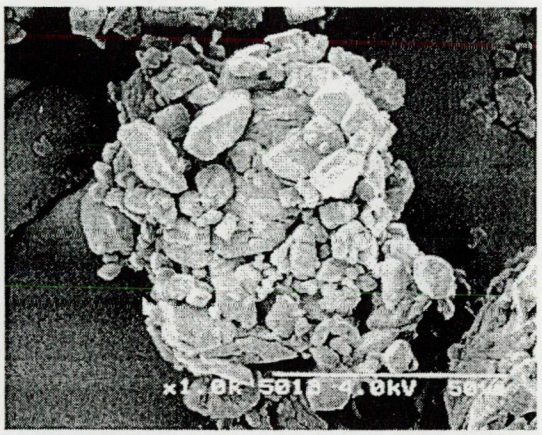

Fig. 23. The appearance of the sulfadimidine-β-cyclodextrin kneaded product, shown by SEM.

Dissolution. The rate of dissolution of sulfadimidine is very poor, as can be seen on (Fig. 24).

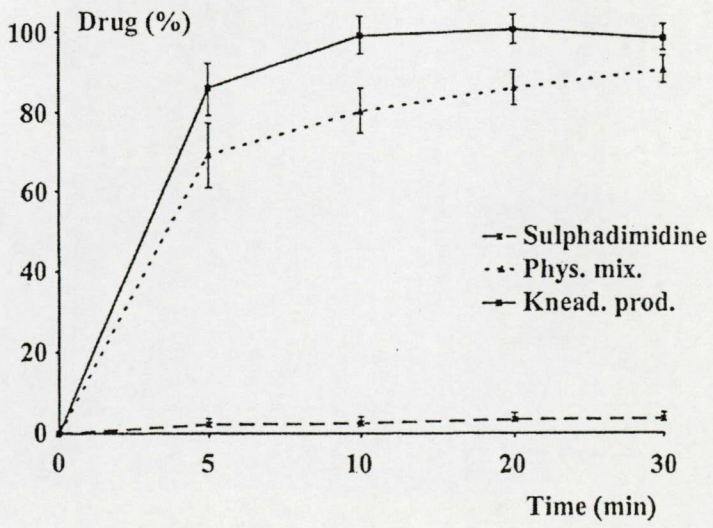

Fig. 24. Rates of dissolution of sulfadimidine, the physical mixture and the kneaded product.

Only about 4% of the drug dissolved during 30 min. The rates of dissolution of sulfadimidine products containing β-cyclodextrin were much higher than that of the bulk substance. As concerns the two products, the dissolution of the kneaded product was faster. About 80% of the drug dissolved from the physical mixture during 30 min, whereas less than 10 min was sufficient for the total mass of the drug to dissolve from the kneaded product.

From the results, it can be inferred that β-cyclodextrin influenced the rate of dissolution of sulfadimidine. The accelerating effect of β-cyclodextrin on the dissolution rate is connected with the regular distribution of the active agent, and the better solubility of β-cyclodextrin and the small crystals adhering to the surface. The better solubility of the kneaded product can be explained by the formation of granule particles, in which crystals of sulfadimidine and β-cyclodextrin are present together. Overall, therefore, the application of β-cyclodextrin is of advantage as concerns the process of sulfadimidine dissolution.

6. SUMMARY AND CONCLUSIONS

6.1. Results on the formation and properties of tablets

1. It was shown that the best physical parameters and highest rates of dissolution of metronidazole tablets can be obtained with the use of hydroxypropyl cellulose (Klucel LF®) at 10 kN.
2. We revealed that the wet granulation process influenced the parameters of tablets.
3. We demonstrated that Avicel® and Heweten 12® not only influenced the tablet formation when direct compression was applied, but also affected their dissolution rates.
4. It was also revealed that the compactibilities of A301 and A302 may be corrected by the addition of sorbit. The mixtures studied have good compactibility and a positive influence on the rearrangement of A301 and A302.

Conclusion: *From the results, it can be concluded that not only the drug substance, but also the various auxiliaries and the different techniques used for tablet formation may affect the properties of a tablet.*

6.2. Results on crystal structure changes during processing

1. The results on ASA crystals indicated that only the typical spherical crystallization technological procedure and surface-treated ASA can be recommended for tablet preparation. These crystals may posses excellent flow properties and favourable compactibility.
2. With the development of spherical crystal agglomerates for AA salt, it was revealed that a higher initial cooling rate and a lower stirring rate are very favourable in the building-up of crystal agglomerates for direct tablet making.
3. The physical characteristics of "life-saving" nitrazepam crystals was demonstrated by SEM. The morphological results indicate that the direct compression of the substance resulted in recrystallization on the surface of the tablet.
4. It was found that the habits of phenobarbitone and α-methyldopa crystals were different, as were the particle sizes and the particle size distributions. It was also established that the powder rheological parameters of phenobarbitone are better than those of α-methyldopa.
5. When sulfadimidine crystals from various batches were investigated, we demonstrated that the particle size may be different and their distribution may influence the behaviour of the particles, which is very important in the first phase of the compression.
6. It was clearly demonstrated that 5 kN caused a significant alteration in the structure of tolbutamide crystals, but no further alteration could be detected when the pressure was increased to 10 kN.

Conclusion: *This work has shown that not only the technological procedures (direct compression), but also other parameters (cooling rate, stirring rate), may exert important effects on both the structure and the behaviour of the crystals.*

6.3. Results on pellets and kneaded products

1. The results showed that a suitable and uniform polymer coating film can be formed on the surface of spherical pellets. Moreover, it was established that a drug may be liberated most rapidly from pellets coated with Eudragit film. Surelease films of the same thickness liberated the active agent much more slowly than did polymethacrylate film.

2. The results reveal that β-cyclodextrin influenced the rate of dissolution of sulfadimidine. The better solubility of the kneaded product can be explained by the formation of granule particles, in which crystals of sulfadimidine and β-cyclodextrin are present together. Overall, the application of β-cyclodextrin is of advantage as concerns the process of sulfadimidine dissolution.

Conclusion: *From the results presented, it can be concluded that a spherical pellet can be coated uniformly and the various polymethacrylate films used for coating differently affect the release of an active agent from the pellet. From the investigation of sulfadimidine, it may be concluded that the low solubility of this drug can be improved by the addition of β-cyclodextrin to the active substance.*

7. REFERENCES

1. Duvall, R.N., Koshy, K.T., Dashiell, R.E.: *J. Pharm. Sci.* **54**(8) 1196-200 (1965)
2. Kwan, K.C., Milosovich, G.: *J. Pharm. Sci.* **55**(3) 340-3 (1966)
3. Batuyios, N.H.: *J. Pharm. Sci.* **55**(7) 727-30 (1966)
4. Ridgway, K., Lazarou, C., Thorpe, E.E.: *J. Pharm. Pharmacol.* **23** 214S-215S (1971)
5. Enezian, G.M.: *Pharm. Acta Helv.* **47**(6) 321-63 (1972)
6. Delattre, L., Gillard, J., Jaminet, F., Roland, M.: *J. Pharm. Belg.* **30**(1) 23-38 (1975)
7. Bertulli, A., Bianchini, R., D'ercole, C., Dondi, G., Gatti, G.: *Boll. Chim. Farm.* **115**(8) 547-69 (1976)
8. Graf, E., Nada, A.: *Arch. Pharm.* **319**(9) 808-14 (1986)
9. Marlowe, E., Shangraw, R.F.: *J. Pharm. Sci.* **56**(4) 498-504 (1967)
10. Selkirk, A.B., Ganderton, D.: *J. Pharm. Pharmacol.* Suppl. 86S+ (1970)
11. Zoglio, M.A., Huber, H.E., Koehne, G., Chan, P.L., Carstensen, J.T.: *J. Pharm. Sci.* **65**(8) 1205-8 (1976)
12. Sekulovic, D., Birmancevic, M.: *Pharmazie* **41**(4) 293-4 (1986)
13. Maejima, T., Osawa, T., Nakajima, K., Kobayashi, M.: *Chem. Pharm. Bull.* **46**(3) 531-3 (1998)
14. Torrado, S., Torrado, S., Agis, A., Jimenez, M.E., Cadorniga, R.: *Pharmazie* **50**(2) 141-3 (1995)
15. Beten, D.B., Amighi, K., Moes, A.J.: *Pharm. Res.* **12**(9) 1269-72 (1995)
16. Hileman, G.A., Upadrashta, S.M., Neau, S.H.: *Pharm. Dev. Technol.* **2**(1) 43-52 (1997)
17. Gazzaniga, A., Sangalli, M.E., Bruni, G., Zema, L., Vecchio, C., Giordano, F.: *Drug. Dev. Ind. Pharm.* **24**(9) 869-73 (1998)
18. Fekete, R., Zelko, R., Marton, S., Racz I.: *Drug. Dev. Ind. Pharm.* **24**(11) 1073-6 (1998)
19. Vecchio, C., Fabiani, F., Sangalli, M.E., Zema, L., Gazzaniga, A.: *Drug. Dev. Ind. Pharm.* **24**(3) 269-74 (1998)
20. Thoma, K., Ziegler, I.: *Drug. Dev. Ind. Pharm.* **24**(5) 401-11, 413-22 (1998)
21. Kleinebudde, P., Schroder, M., Schultz, P., Muller, B.W., Waaler, T., Nymo, L.: *Pharm. Dev. Technol.* 4(3) 397-404 (1999)
22. Kristensen, J., Schaefer, T., Kleinebudde, P.: *Pharm. Dev. Technol.* **5**(2) 247-56 (2000)
23. Kristensen, J., Schaefer, T., Kleinebudde, P.: *AAPS PharmSci.* **2**(3) E24 (2000)
24. Asker, A.F., Saied, K.M., Abdel-Khalek, M.M.: *Pharmazie* **30**(6) 373-6 (1975)
25. York P.: *J. Pharm. Sci.* **64**(7) 1216-21 (1975)

26. Asker, A.F., Saied, K.M., Abdel-Khalek, M.M.: Pharmazie. **30**(7) 463-5 (1975)

27. Onyekweli, A.O., Pilpel, N.: *J. Pharm. Pharmacol.* **32**(2) 120-5 (1980)

28. Parrott, E.L.: *J. Pharm. Sci.* **70**(3) 288-91 (1981)

29. Nyqvist, H., Brodin, A.: *Acta Pharm. Suec.* **19**(2) 81-90 (1982)

30. Lerk, C.F., Andreae, A.C., de Boer, A.H., Bolhuis, G.K., Zuurman, K., de Hoog, P., Kussendrager, K., van Leverink, J.: *J. Pharm. Pharmacol.* **35**(11) 747-8 (1983)

31. Sanghvi, P.P., Collins, C.C., Shukla, A.J.: *Pharm. Res.* **10**(11) 1597-603 (1993)

32. Hiestand, E.N.: *J. Pharm. Sci.* **86**(9) 985-90 (1997)

33. Tsai, T., Wu, J.S., Ho, H.O., Sheu, M.T.: *J. Pharm. Sci.* **87**(1) 117-22 (1998)

34. Tomozawa, H., Momonaga, M., Uemura, T., Yazawa, H.: *Drug. Dev. Ind. Pharm.* **24**(9) 857-61 (1998)

35. Wu, J., Ho, H., Sheu, M.: *Eur. J. Pharm. Biopharm.* **51**(1) 63-9 (2001)

36. Rashid, H.A., Heinamaki, J., Antikainen, O., Yliruusi, J.: *Eur. J. Pharm. Biopharm.* **51**(3) 227-34 (2001)

37. Ho, T., Hersey, J.A.: *J. Pharm. Pharmacol.* **32**(3) 160-6 (1980)

38. Bos, C.E., Bolhuis, G.K., Van Doorne, H., Lerk, C.F.: *Pharm. Weekbl. Sci.* **9**(5) 274-82 (1987)

39. Blattner, D., Kolb, M., Leuenberger, H.: *Pharm. Res.* **7**(2) 113-7 (1990)

40. Ishino, R., Yoshino, H., Hirakawa, Y., Noda, K.: *Chem. Pharm. Bull.* **38**(7) 1987-92 (1990)

41. Wikberg, M., Alderborn, G.: *Pharm. Res.* **10**(1) 88-94 (1993)

42. Juppo, A.M., Kervinen, L., Yliruusi, J., Kristoffersson, E.: *J. Pharm. Pharmacol.* **47**(7) 543-9 (1995)

43. Yang, L., Venkatesh, G., Fassihi, R.: *J. Pharm. Sci.* **85**(10) 1085-90 (1996)

44. Joiris, E., Di Martino, P., Berneron, C., Guyot-Hermann, A.M., Guyot, J.C.: Pharm. Res. **15**(7) 1122-30 (1998)

45. Miyamoto, Y., Ryu, A., Sugawara, S., Miyajima, M., Matsui, M., Takayama, K., Nagai, T.: *Chem. Pharm. Bull.* (Tokyo). **46**(9) 1432-7 (1998)

46. Takeuchi, H., Yasuji, T., Hino, T., Yamamoto, H., Kawashima, Y.: *Pharm. Res.* **16**(8) 1193-8 (1999)

47. Barra, J., Falson-Rieg, F., Doelker, E.: *Pharm. Res.* **16**(9) 1449-55 (1999)

48. Horisawa, E., Danjo, K., Sunada, H.: *Drug. Dev. Ind. Pharm.* **26**(6) 583-93 (2000)

49. Murakami, H., Yoneyama, T., Nakajima, K., Kobayashi, M.: *Int. J. Pharm.* **216**(1-2) 159-64 (2001)

50. Mattsson, S., Nystrom, C.: *Drug. Dev. Ind. Pharm.* **27**(3) 181-94 (2001)

51. de Lourdes Garzon, M., Villafuerte, L.: *Int. J. Pharm.* **231**(1) 33-41 (2002)

52. Führer, C.: *Dtsch. Apoth. Ztg.* **105**(34) 1150-3 (1965)

53. Nürnberg, E., Krebs, K.G.: *Pharm. Weekbl.* **104**(26) 671-8 (1969)

54. van Waert, J.H.: *Pharm. Weekbl.* **107**(49) 783-91 (1972)

55. Asker, A.F., Saied, K.M., Abdel-Khalek, M.M.: *Pharmazie* **30**(3) 181-5 (1975)

56. Asker, A.F., Saied, K.M., Abdel-Khalek, M.M.: *Pharmazie* **30**(4) 236-8 (1975)

57. Moldenhauer, H., Kala, H., Zessin, G., Dittgen, M.: *Pharmazie* **35**(11) 714-26 (1980)

58. Franz, R.M., Banker, G.S., Buck, J.R., Peck, G.E.: *J. Pharm. Sci.* **69**(6) 621-8 (1980)

59. Berta, E., Hódi, K., Révész, P., Miseta, M., Selmeczi, B.: *Acta Pharm. Hung.* **64**(1) 26-9 (1994)

60. Picker, K.M.: *Eur. J. Pharm. Biopharm.* **48**(1) 27-36 (1999)

61. Jaiyeoba, K.T., Spring, M.S.: *J. Pharm. Pharmacol.* **32**(1) 1-5 (1980)

62. Gorodnichev, V.I., El-Banna, H.M., Andreev, B.V.: *Pharmazie* **36**(4) 270-3 (1981)

63. Zelko, R., Kiekens, F., Antal, I., Bihari, E., Rácz, I.: *Acta. Pharm. Hung.* **68**(2) 123-6 (1998)

64. Skinner, G.W., Harcum, W.W., Barnum, P.E., Guo, J.H.: *Drug. Dev. Ind. Pharm.* **25**(10) 1121-8 (1999)

65. Planinsek, O., Pisek, R., Trojak, A., Srcic, S.: *Int. J. Pharm.* **207**(1-2) 77-88 (2000)

66. Shotton, E., Obiorah, B.A.: *J. Pharm. Pharmacol.* **25** Suppl 37P-43P (1973)

67. Fairbrother, J.E., Grant, D.J.: *J. Pharm. Pharmacol.* **30** Suppl 19P (1978)

68. Garekani, H.A., Ford, J.L., Rubinstein, M.H., Rajabi-Siahboomi, A.R.: *Int. J. Pharm.* **187**(1) 77-89 (1999)

69. Garekani, H.A., Ford, J.L., Rubinstein, M.H., Rajabi-Siahboomi, A.R.: *Int. J. Pharm.* **208**(1-2) 87-99 (2000)

70. Di Martino, P., Scoppa, M., Joiris, E., Palmieri, G.F., Andres, C., Pourcelot, Y., Martelli, S.: *Int. J. Pharm.* **213**(1-2) 209-21 (2001)

71. Tiwary, A.K.: *Drug. Dev. Ind. Pharm.* **27**(7) 699-709 (2001)

72. Chalmers, A.A., Elworthy, P.H.: *J. Pharm. Pharmacol.* **28**(3) 234-8 (1976)

73. Shotton, E., Leonard, G.S.: *J. Pharm. Sci.* **65**(8) 1170-4 (1976)

74. Marshall, K., Sixsmith, D.: *J. Pharm. Pharmacol.* **28**(10) 770-1 (1976)

75. Sixsmith, D.: *J. Pharm. Pharmacol.* **29**(2) 82-5 (1977)

76. David, S.T., Augsburger, L.L.: *J. Pharm. Sci.* **66**(2) 155-9 (1977)

77. Lerk, C.F., Bolhuis, G.K., de Boer, A.H.: *J. Pharm. Sci.* **68**(2) 205-11 (1979)

78. Rippie, E.G., Danielson, D.W.: *J. Pharm. Sci.* **70**(5) 476-82 (1981)

79. Bi, Y., Sunada, H., Yonezawa, Y., Danjo, K., Otsuka, A., Iida, K.: *Chem. Pharm. Bull.* (Tokyo). **44**(11) 2121-7 (1996)

80. Akande, O.F., Rubinstein, M.H., Ford, J.L.: *J. Pharm. Sci.* **86**(8) 900-7 (1997)

81. Rashid, H.A., Heinamaki, J., Antikainen, O., Yliruusi, J.: *Drug. Dev. Ind. Pharm.* **25**(5) 605-11 (1999)

82. Obae, K., Iijima, H., Imada, K.: *Int. J. Pharm.* **182**(2) 155-64 (1999)

83. Opota, D., Prinderre, P., Kaloustian, J., Joachim, G., Piccerelle, P., Ebba, F., Reynier, J.P., Joachim, J.: *Drug. Dev. Ind. Pharm.* **25**(6) 795-9 (1999)

84. Suzuki, T., Nakagami, H.: *Eur. J. Pharm. Biopharm.* **47**(3) 225-30 (1999)

85. Westermarck, S., Juppo, A.M., Kervinen, L., Yliruusi, J.: *Eur. J. Pharm. Biopharm.* **48**(3) 199-206 (1999)

86. Edge, S., Steele, D.F., Chen, A., Tobyn, M.J., Staniforth, J.N.: *Int. J. Pharm.* **200**(1) 67-72 (2000)

87. Kolter, K., Flick, D.: *Drug. Dev. Ind. Pharm.* **26**(11) 1159-65 (2000)

88. Ishikawa, T., Mukai, B., Shiraishi, S., Utoguchi, N., Fujii, M., Matsumoto, M., Watanabe, Y.: *Chem. Pharm. Bull.* (Tokyo). **49**(2) 134-9 (2001)

89. Huttenracuh, R., Schmeiss, U.: *Pharmazie* **23**(9) 473-9 (1968)

90. Goodhart, F.W., Draper, J.R., Ninger, F.C.: *J. Pharm. Sci.* **59**(4) 540-7 (1970)

91. Menon, A., Ritschel, W.A., Sakr, A.: *J. Pharm. Sci.* **83**(2) 239-45 (1994)

92. Te Wierik, G.H., Eissens, A.C., Bergsma, J., Arends-Scholte, A.W., Bolhuis, G.K.: *Int. J. Pharm.* **157**(2) 181-187 (1997)

93. Chowhan, Z.T.: *J. Pharm. Sci.* **69**(1) 1-4 (1980)

94. Ghanta, S.R., Srinivas, R., Rhodes, C.T.: *Pharm. Acta Helv.* **61**(7) 191-7 (1986)

95. Johnson, J.R., Wang, L.H., Gordon, M.S., Chowhan, Z.T.: *J. Pharm. Sci.* **80**(5) 469-71 (1991)

96. Miyamoto, Y., Ryu, A., Sugawara, S., Miyajima, M., Ogawa, S., Matsui, M., Takayama, K., Nagai, T.: *Drug. Dev. Ind. Pharm.* **24**(11) 1055-65 (1998)

97. Faure, A., Grimsey, I.M., Rowe, R.C., York, P., Cliff, M.J.: *J. Pharm. Sci.* **88**(2) 191-5 (1999)

98. Faure, A., Grimsey, I.M., Rowe, R.C., York, P., Cliff, M.J.: *J. Pharm. Pharmacol.* **50**(12) 1431-2 (1998)

99. Gotthardt, S., Knoch, A., Lee, G.: *Eur. J. Pharm. Biopharm.* **48**(3) 189-97 (1999)

100. Miwa, A., Yajima, T., Itai, S.: *Int. J. Pharm.* **195**(1-2) 81-92 (2000)

101. Kása, P., Hódi, K., Révész, P., Erős, I.: *Acta Pharm. Hung.* **70**(2) 41-4 (2000)

102. Tomer, G., Podczeck, F., Newton, J.M.: *Int. J. Pharm.* **231**(1) 107-19 (2002)

103 Kleinebudde, P., Solvberg, A.J., Linder, H.: *Int. J. Pharm.* **119**(1) (1995)

104. Goskonda, S.R., Hileman, G.A., Upadrastha, S.M.: *Int. J. Pharm.* **111**(1) (1994)

105. Nürnberg, E., Wunderlich, J.: Pharm. Technol. Eur. **11**(41) (1999)

106. Reynolds, J.E.F.: Martindale. The Extra Pharmacopoeia, Thirty-first Edition, Royal Pharmaceutical Society, London, 1989, pp. 151-154

107. Szász Gy.: Pharmaceutical Chemistry, Vol. 2., Medicina Könyvkiadó, Budapest, p. 779, 1983

108 Mutschler, E., Derendorf, H.: Drug actions, Medpharm Scientific Publishers, Stuttgart, 1995, pp. 546

109 Knoll, J.: Gyógyszertan. Egyetemi tankönyv. Medicina, Budapest, 1993, pp. 782

110. USP XXIII, The United States Pharmacopoeia, United States Pharmacopoeial Convention Inc., Twinbrook Parkway, Rockwille, MD., 1995, pp. 1019

111. Index Nominum. International Drug Directory, Edited by Swiss Pharmaceutical Society, Medpharm Scientific Publishers, Stuttgart, 1992, pp. 752

112. Rote Liste. Bundesverband der Pharmazeutischen Industrial E. V., 1996, 46077

113. Reynolds, J.E.F.: Martindale. The Extra Pharmacopoeia, Thirty-first Edition, Royal Pharmaceutical Society, London, 1996, pp. 621

114. Alfonso, R.G.: Remington's Pharmaceutical Sciences, 17th edition, Mack Publishing Company, Easton, Pennsylvania, 1985, pp. 1222

115. British Pharmacopoeia 1998. Vol. I., Crown Copyright, London, 1998, pp. 893

116. Deutsches Arzneibuch. 10. Ausgabe. Band 3. Deutscher Apotheker Verlag, Stuttgart, 1991

117. European Pharmacopoeia, Second edition, Maisonneuve S. A., Saint-Ruffine, France, 1995, pp. 675

118. Pharmacopoeia Hungarica Ed. VII., Vol. I, Medicina Könyvkiadó, Budapest, 1986

119. Wells, J.I.: Pharmaceutical preformulation – The physicochemical properties of drugs. Ellis Horwood Ltd., Chichester, 1998. pp 209

120. Aulton, M.E.: Pharmaceutics, the science of dosage form design. Churchill Livingstone, Edinburgh, 1991, pp. 307, 308 and 653, 654

121. Jones, M.T.: *Pharm. Ind.*, **39**(469) (1977)

122. Carr, R.L.: *Chem. Eng.*, **72**(163) (1965)

123. Siaan, M., Pintye-Hódi, K., Szabó-Révész, P., Kása, P. Jr., Erős, I.: Pharmazie, **52**, 564 (1997)

124. Lieberman, H.A., Lachman, L.: Pharmaceutical Dosage Forms: Tablets Vol. 1, Marcel Dekker Inc., New York and Basel 1990

125. Rubinstein, M.H.: Pharmaceutical Technology, Tableting Technology, Vol. 1, Ellis Horwood Ltd., Chichester, 1987

126. Carstensen, J.T.: Solid Pharmaceutics: Mechanical Properties and Rate Phenomena, Academic Press, New York-London-Toronto-Sidney-San Francisco, 1980

127. Matthew, H., Proudfoot, A.T., Aitken, R.C., Raeburn, J.A., Wright, N.: Br. Med. J. 3(661):23-5 (1969)

128. Watt, P.R.: Tablet machine instrumentation in pharmaceutics: Principles and practice, Ellis Horwood Ltd., Chichester, pp. 342-343, 1988

129. Washington, C.: Particle Size Analysis in Pharmaceutics and other Industries. Theory and Practice, Ellis Horwood Limited Publishers, Chichester, pp. 9-40, 1992

ACKNOWLEDGEMENTS

The present study was carried out at the Department of Pharmaceutical Technology University of Szeged.

First of all I wish to express my sincere thanks to **Professor István Erős**, Head of the Department, for providing me with the opportunity to work in his Department. I am grateful to him for guiding me with his invaluable advice and inspiring me to work in an accurate way. I greatly appreciate his continuous help during the preparation of my thesis and for providing the excellent facilities for this study. I owe my warm gratitude to him for his criticism, encouragement and numerous discussions during my Ph.D. work.

I am greatly indebted to **Professor Béla Selmeczi** for his support during the time when he was the Head of the Department.

I am very grateful to my supervisor **Dr. Klára Pintye-Hódi** for her help, for kindly providing her laboratories, and for sharing her knowledge and for providing me with useful advice.

I am grateful to **Dr. Erzsébet Mihalik**, Head of the Department of Botanics, for her invaluable help with the scanning electron microscopy.

Furthermore, I express my kindest thanks to **Professor Mihály Kata** and the research group in the technology laboratory for their friendliness and for interesting discussions during years in the laboratory.

I thank **Dr. Piroska Szabó-Révész** and all my co-authors for their collaboration in this work.

I thank all members of the Department for their help and friendship.

I owe my thanks to my family for their support, encouragement and understanding attitude during these years.

ANNEX

LIST OF OTHER *IN EXTENSO* PUBLICATIONS

1. Askrabic, M., Rajic, D.S., Tasic, L., Djuric, S., **Kása, P.** and Pintye-Hódi, K.: Etodolac and solid dispersion with beta-cyclodextrin. Drug Dev. Ind. Pharm., 23, 1123-1129 (1997)
2. Deák, D., Pintye-Hódi, K., Szabó-Révesz, P., **Kása, P. Jr.**, Erős, I. and Muskó, Zs. Mathematical evaluation of the dissolution of metronidazole from tablets. Pharmazie 55, 394-395 (2000)
3. Jónas, E., Pintye-Hódi, K., Szabó-Révész, P. and **Kása, P.**: Water uptake kinetics and swelling force of some disintegrants. Pharmazie 51, 605-606 (1996)
4. **Kása, P.,** Hódi, K., Révész, P and Erős, I.: Preparation of pellets with a centrifugal granulator. Acta Pharm. Hung., 70, 41-44 (2000)
5. **Kása, P. Jr.**, Papp, H., Pákáski, M., Kovács, I. and Kása, P. Sr.: Amyloid β1-42 induces reduction of vesicular acetylcholine transporter and synaptophysin-immunoreactive axon varicosities in in vitro tissue cultures, as revealed by image analysis. Clin. Neurosci., 51, 55-56 (1998)
6. Kása, P., Papp, H., **Kása, P. Jr.**, and Török, I.: Donepezil dose-dependently inhibits acetylcholinesterase activity in various areas and in the presynaptic cholinergic and the postsynaptic cholinoceptive enzyme-positive structures in the human and rat brain. Neuroscience 101, 89-100 (2000)
7. Milicaskrabic, J., Rajic, D.S., Tasic, L., Djuric, S., **Kása, P.**, Pintye-Hódi, K.: Etodolac and Solid Dispersion with Beta-Cyclodextrin, Drug Dev. Ind. Pharm. 1997, Vol 23, Iss 11. pp 1123-1129
8. Muskó, Zs., Pintye-Hódi, K., Szabó-Révész, P., **Kása, P. Jr.**, Erős, I. and Deák, D.: Measurement of film thickness on the surface of coated pellets and its influence on drug dissolution rate. Pharmazie. 55, 465-466 (2000)
9. Pákáski, M., Farkas, Z., **Kása, P. Jr.**, Forgon, M., Papp, H., Zarándi, M., Penke, B., Kása, P. Sr.: Vulnerability of small GABAergic neurons to human beta-amyloid pentapeptide. Brain Res. 796, 239-246 (1998)
10. Rakonczay, Z., Kovács, I., Török, I., **Kása, P. Jr.**, and Kása, P. Sr.: Search for selective inhibitors for the different molecular forms of acetylcholinesterase. Clin. Neurosci., 51, 15-16 (1998)

11. Serwanis, S.F., Szabó-Révész, P., Pintye-Hódi, K., **Kása, P.**, Erős I.: Study of flowability and compactibility of some types of Vivapur. Pharmazie 53, 881-882 (1998)
12. Serwanis, S.F., Szabó-Révész, P., Pintye-Hódi, K., **Kása, P.**, Erős I.: Surface Treatment of acetylsalicylic acid with Lubricants by the Wurster method, Chem. Pharm. Bull (Tokyo), 47: (6) 772-776 JUN 1999
13. Siaan, M., Pintye-Hódi, K., Szabó-Révész, P., **Kása, P. Jr.** and Erős, I.: Study of the rearrangement of some types of Avicel®. Pharmazie 52, 564-564 (1997)
14. Siaan, M., Pintye-Hódi, K., Szabó-Révész, P., **Kása, P.**, Erős, I.: Influence of avicel PH-301 on the compressibility of alpha-methyldopa and phenobarbitone in direct compression, Drug Dev. Ind. Pharm., 26: (9) 1013-1018 2000
15. Szabó-Révész, P., Bognár, K., Pintye-Hódi, K., **Kása, P. Jr.** and Erős, I.: The use of Ludipress® in view of disintegration time and release of tablets. Pharmazie 51, 125-126 (1996)
16. Tasic, L., Pintye-Hódi, K., Stupar, M., **Kása, P.** and Szabó-Révész, P.: Compression of paracetamol solid dispersion tablets. Pharmazie 53, 206-207 (1998)

Cumulative impact factor of *in extenso* publications: **18.237**