Ph.D. Thesis

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Preparation and study of tablets with a high active agent content

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PUBLICATIONS RELATED TO THE SUBJECT OF THE THESIS

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1. **D. Deák**, K. Pintye-Hódi, P. Szabó-Révész, P. Kása jr, I. Erős and Zs. Muskó: Use of different cellulose derivatives for the preparation of tablets with a high active agent content. S.T.P. Pharma Sciences, 9, 525-529 (1999)
2. **D. Deák**, K. Pintye-Hódi, P. Szabó-Révész, P. Kása jr, I. Erős and Zs. Muskó: Mathematical evaluation of the dissolution of metronidazole from tablets. Pharmazie, 55, 394-395 (2000)
3. **D. Deák**, K. Pintye-Hódi, P. Szabó-Révész, P. Kása jr, I. Erős and Zs. Muskó: Influence of the granulating process on the parameters of tablets. Hung. J. Ind. Chem., 28, 117-120 (2000)
4. Zs. Muskó, K. Pintye-Hódi, P. Szabó-Révész, P. Kása jr, I. Erős and **D. Deák**: Measurement of film thickness on the surface of coated pellets and its influence on drug dissolution rate. Pharmazie, 55, 465-466 (2000)
5. Zs. Muskó, K. Pintye-Hódi, P. Szabó-Révész, P. Kása jr, I. Erős and **D. Deák**: Study of the influence of polymer coating films on drug release. Hung. J. Ind. Chem., 28, 111-115 (2000)

ABSTRACTS:

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RATIONALE

Solid dosage forms play a major role in the practice of medication. Research on the factors influencing the manufacturing of solid forms of medicines are therefore of great importance. In the process of tablet making, for example, the chemical and physical properties of the active agent must be taken into consideration. The natures and amounts of auxiliary materials and the procedures applied must be chosen in accordance with the characteristics of the active component so that the latter undergoes no unwanted alterations during manufacturing.

A number of methods are available in tablet making. One possibility is direct compression. A powder mixture intended for direct compression should be of adequate fluidity and compressibility [1]. These features can be influenced by the powder flow properties of drugs. Numerous materials, however, have unsuitable flow properties and compressibility and hence require wet granulation prior to tabletting. During this process, the quality of the granules is influenced by the granulating fluid. Furthermore, the parameters of the granules influence the quality of the resulting tablets. The preparation of tablets with a high active agent content is particularly difficult. The aim here is not to increase the weight of the tablets during tablet making. The only way to achieve this is to use the smallest amount of excipients.

Kneading is one means of wet granulation. After homogenization of the components, the powder mixture is kneaded with a granulating solution. The wet mass is then passed through a sieve and the granules are dried [2-5].

Wet granulation can also be performed by 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 in this way stick together; fluid bridges are formed, which will become solid bridges during drying [6-10].

The model substance chosen for the present experimental work was metronidazole. Its oral therapeutic dose is 250 mg; metronidazole tablets therefore belong among tablets with a high active agent content. The aim of my work was to produce a tablet with optimal parameters by using a variety of auxiliaries. The morphology of the agent was studied and the particle size distribution, powder flowability and water absorption of the granulates produced were determined. I also investigated the physical parameters of the tablets made, and additionally the extent and rate of drug liberation from the tablets, including a mathematical description of the drug liberation process.

I. INTRODUCTION

In pharmaceutical production, granulation is primarily a preparatory step of tabletting, permitting alteration of the characteristics of powders unfavourable for tablet compression. For compression, good flowability, adequate particle size distribution, optimal compactibility and nearly isodimensional particle shape are of great importance.

In **dry granulation**, the components are dry-mixed and then compressed, a process called briqueting. The briquets are then chopped in a suitable device and particles of the desired size are separated by a sieve. The four steps of dry granulation are homogenization, compression, chopping and sieving. It is important in the chopping of the briquets to obtain granules in the determined size range and no excessive amount of dust [11].

In **wet granulation,** the powder mixture containing the active agent is wetted with a solution containing a binding agent. During the procedure, fluid bridges are formed between the particles. In the course of the subsequent drying, the solvent evaporates and solid bridges are formed in parallel with the reduction of the surface and the agglomeration of the particles. [2].

In conventional granulation **(granulation by kneading)**, the prepared powder mixture is homogenized and subsequently aggregated with the granulation fluid. The wet mass obtained is dispersed through a sieve or a perforated plate. The process can be achieved in practice with the Z-arm kneading machines, oscillating granulators, etc.

Fluidization granulation [12] involves wetting, granule formation and drying in one apparatus. The granulation step itself is achieved in the lower, conical part of the apparatus, called the bulk container. The particles are kept moving by the compressed air introduced into the device. Powder particles move upwards with the air stream in the column and meet the droplets of the sprayed binding agent. The surface of the particles is thus partially moistened. Fluid bridges are formed between the particles, which are transformed into solid bridges by the simultaneous drying. This is the way the granulate is built up. In the procedure, care must be taken with materials that tend to adhere or aggregate or have bad wetting properties, because they are floated unevenly, resulting in over-moistened clumps. Granulates obtained by fluidization usually have a smaller particle size and a more homogeneous size distribution than those produced by the traditional methods. The fine powder content of the granules is lower. The units obtained are nearly spherical and their surface is a little rough. Such particles are tabletted with no problem.

In **rotational or vortex granulation** [13], the dust mixture is first homogenized in the vortex apparatus. The granulating fluid is then applied by spraying. The moistened dust particles agglomerate due to the swirling rotation and in this way the granules are gradually built up. The process can be continued until the desired particle size is achieved.

Vacuum granulation [14] allows the performance of five steps (homogenization, kneading, granulation, drying and regranulation) in one device. Homogenization is followed by applying the granulation fluid. The wetted particles adhere to each other: granules are formed. At the same time, chopper knives perform the regranulation.

Tablets as solid dosage forms must have a declared active agent content, an appropriate disintegration time, the necessary mechanical resistance, appropriate drug liberation, an attractive appearance, etc. **Tablet production** involves not only the active constituents, but usually a variety of auxiliary substances, as the number of agents compressible to tablets without addition of an auxiliary is limited [15-17]. In the application of auxiliaries, the primary requirement is to obtain tablets with uniform mass, adequate mechanical resistance, and properties corresponding to a good biological utilization of the drug. The auxiliaries can be fillers, binders, adsorptives, moisture stabilizers, disintegrants, hydrophilizers and dissolution retardants. Glidants, lubricants, antiadhesives, antistatics, sweetenings and colorings are also used [18-30].

Tablets are manufactured in tabletting machines. The main parts of these are the upper and lower punches, the die, the feeder and the filling funnel. The adequately prepared powder mixture or granulate is introduced into the cavity of the die. During compression, the evenly increasing force exerted by the upper punch (or both punches) constrains the particles to undergo plastic or elastic deformation. During the compression, the particles first slide along each other and fill up the space available, and are then deformed, resulting in ready pressing, i.e. the tablets are held together by direct and indirect (electrostatic, etc.) bonds [31,32].

Flowability can be defined as the ease of flow of the powder mass as a whole [33]. Numerous factors affect the flow properties of powders, e.g. particle shape and size, size distribution, surface roughness of the particles and compacting properties [34]. Several methods can be used to investigate flow properties. The angle of repose has been widely used [35] as a flow parameter.

Angle of repose (°)	Flow properties
<25	very good (excellent)
25-30	good
30-40	fair to passable
>40	very poor

Values of 40-45° are often taken as the dividing line between poor flow and good flow [33]. The experimental conditions applied during testing have a great influence on the results [36]. Measurement of the time required for a certain amount of powder mass to flow through a funnel is another method widely utilized [35] to describe powder flow. Numerous findings, however, show that this time or flow rate is usually not correlated with the flow of powder in the tabletting process [37]. Flowability can also be measured by using a recording powder flowmeter [38] or tensile testers and shear cells [36].

The results from the tapping test are likewise widely employed [35, 38, 39] as flow parameters. The shape, size, size distribution and surface roughness of the particles, and the amplitude and frequency of beats directed towards the powder bed, affect the density of the powder during the tapping test [37, 40].

Carr`s index [41] can be calculated according to the equation :

$$Carr's\ index\ (\%) = \frac{tapped\ density - loose\ density}{tapped\ density} \times 100 \qquad (1)$$

Carr`s index characterizes the flow property as follows [42, 43] :

Carr`s index	Flow description
5-15	excellent
12-16	good
18-21	fair to passable
23-35	poor
33-38	very poor
>40	extremely poor

Hausner demonstrated that a ratio between the tapped density and the loose density of approximately 1.2 was characteristic of powders with low interparticle friction, such as coarse

spheres, while a ratio of more than 1.6 corresponded to more cohesive and less free-flowing powders, such as flakes. The Hausner ratio is calculated as follows [1]:

$$Hausner\ factor = \frac{tapped\ density}{loose\ density} \tag{2}$$

The rearrangement constant is another parameter for compactibility evaluation. Here, the first step during the formation of a tablet is filling, and the next is rearrangement. If this is insufficiently fast, a "hole" can form in the tablet and this can lead to lamination or capping. These phases influence the compactibility [44]. The extent of particle rearrangement is a function of the surface structure, particle size and shape. The force applied must overcome the interparticle friction and cohesion before slippage and rearrangement of the particles can take place [45]. The rearrangement constant (k) can be calculated from the loose and tapped volume data according to Takkiedin [46] :

$$\frac{V_n - V_\infty}{V_0 - V_\infty} = (1 + kn)^{-0.25} \tag{3}$$

where n = number of taps,

V_n = powder volume after n taps,

V_0 = initial powder volume,

V_∞ = final powder volume.

The rearrangement constant (k) is the slope of the curve from linear and exponential regression analysis.

Some authors [35, 47] have applied the Kawakita equation to tap density measurements by using the formula

$$\frac{N}{C} = \frac{N}{a} + \frac{1}{ab} \tag{4}$$

where N is a tapping number, $1/a$ is a constant related to the volume reduction, called the compactibility, and $1/b$ is another constant, related to cohesion and called the cohesiveness [39, 48].

The ability of a powder mass to reduce in volume when compressed does not ensure the formation of a tablet [49]. For the industrial-scale production of tablets, it is much more important to obtain tablets with adequate strength rather than adequate deformation and volume reduction mechanisms [50].

Postcompression parameters are widely used to evaluate the compactibility and compressibility of a variety of pharmaceutical materials by measuring tablet mass variation and the mechanical strength, which can be described by several means, including the crushing strength [51], the axial or radial tensile strength [52], the breaking hardness [53] and the friability [54, 55]. The disintegration time [56, 57] and the dissolution time [57, 58] are also very important parameters to evaluate tablet quality.

One of the most important postcompression parameters is the breaking hardness. During breaking hardness determination, a vertically or horizontally fixed tablet is exposed to a gradually increasing load along its diameter. A shear effect develops in the tablet, which results in splitting in the mid-line, i.e. the tablet breaks [42, 59-61].

Various methods and instruments are applied for the measurement of breaking strength, but most literature reports merely present hardness values and do not describe the deformation process leading to breaking. Schweiger and Zimmermann described a tensile strength tester and methods for measurement of the tensile strength of powders [62]. During the past few years, a number of hardness testers have become available, with which the breaking curves of tablets can be recorded.

In the present work, the process of breaking of metronidazole tablets was studied by means of a modified breaking hardness tester. The tester is connected to a computer via an interface. The breaking process can be analysed by means of appropriate software, which yields not only the hardness value, but also the work necessary for breaking. Accordingly, it is possible to investigate the deformability of the tablets.

The hardness of tablets obtained by wet granulation is also influenced by the properties of the macromolecular film formed by the binding agent used, and therefore the deformability of the film must be taken into consideration. This has a decisive role in the elastic recovery phase of the compression. If the film is of adequate elasticity, it will not break and retains its stability-increasing role. A film of lower elasticity will break apart, however, which can affect the hardness of the tablet. The formation and study of free films have been extensively described in the literature [63-76].

Free films are obtained in several ways. Numerous authors have used casting or spray application on a Teflon surface. Others have developed casting on a mercury surface, or sprayed the coating agent on a rotating disk, from which the film was released by use of an appropriate knife.

It is very important to study the rate of drug dissolution from tablets and to evaluate the results mathematically. There are many papers on the mathematical evaluation of drug liberation [77, 78]. The results concerning the rate of dissolution of metronidazole were evaluated by means of the Rosin-Rammler-Sperling-Bennett-Weibull (RRSBW) distribution, and the characteristic dissolution time ($t_{63.2\%}$) was determined after linearized regression and transformation by Langenbucher according to the following equation [79-86]:

$$M = M_0\left\{1-\exp\left[-\frac{(t-T)^{\beta}}{a}\right]\right\} \tag{5}$$

where M is the amount of material dissolved after time t, M_0 is the amount of initial material (maximum), T is the delay time, β is a shape parameter and a is a time parameter.

$\beta = 1$ means first-order kinetics in the dissolution process. $\beta < 1$ means that fast liberation can be observed at the beginning of the process, followed by a slower release of active agent. If $\beta > 1$, a sigmoidal curve can be seen, indicating that a slow release is followed by faster dissolution.

Linearized regression from parameters β and a without T gives

$$\ln\ln\frac{M_0}{M_0-M} = \beta\cdot\ln t - \ln a \tag{6}$$

where β is the slope and $\ln a$ is the intercept.

After the transformation according to Langenbucher, we obtain

$$\ln a = \beta \ln t_{63.2\%}, \qquad t_{63.2\%} = 10^{-a/b} \tag{7}$$

where $t_{63.2\%}$ (min) is the characteristic dissolution time.

II. MATERIALS AND METHODS

1. Materials

Metronidazole (Ph. Eur. 3rd) is a drug frequently used in the treatment of various anaerobic infections. It is well absorbed following oral administration. The drug is a useful prophylactic in obstetrical and gynaecological interventions, colorectal surgery and appendectomy [87, 88]. Its single oral dose is generally 250 mg, and the tablets have a high active agent content. The drug and its actions (doses) have been discussed in various papers [89-96].

Microcrystalline cellulose (Avicel PH 101; FMC Corp., Philadelphia, USA) is water-insoluble, has a high binding capability and facilitates the compression of other excipients [97]. It exhibits a low Young's modulus [98] and may be classified as ductile rather than brittle [99, 100].

Povidone® K-30 (ISP, Belgium) is used in a variety of pharmaceutical formulations, primarily in solid dosage forms. In tabletting, Povidone solutions are used as binders in wet granulation processes. They may also be used as coating agents. As a binder, tablet diluent or coating agent, its useful concentration is 0.5-5.0%(w/w). It is very hygroscopic, significant amounts of moisture being absorbed at low relative humidity. The dynamic viscosity of aqueous Povidone solutions depends on both the concentration and the molecular weight of the polymer employed [101-105].

Cross-linked povidone (Kollidon® CL; BASF AG, Germany) is a fine granular powder with good flow characteristics. It is a superdisintegrant, used in the tabletting process in a concentration of 2-5%(w/w). The disintegration effect is due to the large capillary activity. Its water-uptake ability is fairly high [106, 107]. The resulting swelling pressure force breaks up the tablets.

Magnesium stearate (Ph. Eur. 3rd) 0.5%(w/w) was applied as a lubricant in the present work. This material was chosen because it is probably the most widely used lubricant [108] and is known to have excellent lubricating and good anti-adherent properties. However, it exhibits little glidant action [109].

Cellulose ethers [Hydroxyethyl cellulose (Cellulose WP 4400 L; Union Carbide Belgium N.V.); Hydroxypropyl cellulose (Klucel LF; Hercules Inc., USA); Hydroxypropyl methylcellulose (Pharmacoat 603; ShinEtsu Chemical Co., Ltd., Japan) or Methylhydroxy ethylcellulose (Tylose MH 1000 P; Hoechst AG., Germany)] are used as binders in tablet making involving wet granulation [110-112]. Increases in the molecular mass and degree of substitution increase the viscosity of their aqueous solutions. These solutions belong among the non-Newtonian fluids [113]. Their water uptake is good and they can retain the water. This ability can be utilized very well to ensure the optimum moisture content of tablets [114-116]. They display surface activity and can promote the dissolution of the drug from the tablets [117, 118]. They can also be used as coating materials [119-121]. They can increase the cohesion between the particles and provide the tablets with a good hardness.

Starches [Corn starch (Ph. Eur. 3rd) and Wheat starch (Roquette, France)] are used as excipients primarily in oral solid dosage formulations, where they are utilized as binders, diluents and disintegrants. In tablet formulations, freshly prepared starch mucilage is used at a concentration of 5-25%(w/w) in the granulation prior to tabletting as a binder. Starch is one of the most commonly used tablet disintegrants at concentrations of 3-15%(w/w) [122-126].

2. Methods

2.1. Processes

2.1.1. Homogenization

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

Blending of dry granules with an external phase (magnesium stearate) was performed at 50 rpm for 2 min with a Turbula mixer (Willy A. Bachofen Maschinenfabrik, Basel, Switzerland).

2.1.2. Granulation

Two methods were used: conventional granulation and fluid bed granulation.

In conventional granulation, the ingredients of the granules were blended in a high-speed mixer (Keripar, Tatabánya, Hungary) for 2 min. After addition of the binder solution, agitation was continued for 45 s, the period depending on the consistency of the mass. The wet mass was passed through a sieve with a mesh size of 1.2 mm. The granules were dried at room temperature to a moisture content of about 1.0% [127].

In some of the experiments, granulation was performed by means of a fluid-bed apparatus (Strea-1, Niro-Aeromatic AG., Switzerland) with the following parameters:

atomizing pressure:	2.0 bar,
blow-out pressure:	4.5-5.0 bar,
drying temperature:	60 °C,
outlet temperature:	40 °C,
peripump speed:	30-40 rpm (10-12 ml/min),
nozzle:	0.8 mm,
duration of process:	30-40 min.

2.1.3. Tabletting

Tabletting was carried out with a Korsch EK0 instrumented eccentric tablet machine (E. Korsch Maschinenfabrik, Berlin, Germany) equipped with strain gauges. A displacement transducer was applied.

Tabletting parameters:

punches:	flat, simple, 10 mm in diameter,
pressure force:	10±2 kN and 15±2 kN,
relative air humidity:	25-35%,
air temperature:	24-27 °C,
rate of pressing:	36 tablets/min,
compressed quantity:	500 tablets,
temperature of the table of the tabletting machine:	
at the start of compression:	25.0-27.6 °C,
at the end of compression:	26.1-28.5 °C,
temperature of the tablet:	30-32 °C.

2.2. Test methods

2.2.1. Morphological investigations

2.2.1.1. Particle shape and surface structure

Metronidazole crystals and granules and the texture of the tablets were investigated. A Hitachi S2400 scanning electron microscope (SEM) (Hitachi Scientific Instruments Ltd., Tokyo, Japan) was used. A polaron sputter coating apparatus (Polaron Equipment Ltd., Greenhill, UK) was applied to create electric conductivity on the surface of the sample. The air pressure was 1.3-13.0 mPa [128].

2.2.1.2. Particle size analysis and distribution

The above-mentioned materials were investigated. A sample of a few milligrams was dispersed in liquid paraffin for deaggregation, and the suspension was then spread on a slide and tested by means of 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

(shape parameter) were measured for more than 500 particles each. The obtained data were processed statistically by using the Statgraphics package.

2.2.2. Process of polymer film deformation

The deformation characteristics of the coating films were studied on free films.

In my experimental work, 20 g of the granulating solution used for the aggregation was cast in a 150 mm diameter Petri dish. The dishes were placed on a horizontal surface to ensure an even film thickness in every case. The dry films obtained after evaporation of the solvent were kept at 70% relative humidity during 24 hours until investigation.

The thickness of the films was measured, after 24 hours, by using a screw micrometer (Mitutoyo, Japan; n=20).

The breaking strength and the deformation process were studied with a modified breaking hardness tester (Chinoin Chemical and Pharmaceutical Works Ltd., Budapest, Hungary; see under Breaking process). In the test, a piece of the film was fixed in a ring-shaped holder. The process of breaking induced by the vertical downward pressure force was observed and the force needed to break the film was measured.

2.2.3. Water uptake determination

The Enslin number (g/ml) was determined with a glass sieve and a pipette with 0.01 ml accuracy.

2.2.4. Moisture content

The moisture contents of granules were measured before tabletting. This was performed gravimetrically, through water removal with an infrared lamp mounted on a quick dryer (Szerves Vegyipari Vállalat, Budapest, Hungary) [128]. A 10 g sample (W_1) was accurately weighed, placed under the infrared lamp at 60 °C, and weighed every 10 min until constant weight (W_2) was attained. The moisture content (MC) was then calculated:

$$MC\% = \frac{(W_1 - W_2)}{W_1} \cdot 100 \qquad (8)$$

2.2.5. Compactibility and rearrangement constant

The compactibility and the rearrangement constant were tested with a Stampfvolumeter 2003 (J. Engelsman AG Apparatebau, Ludwigshafen, Germany) according to a method described in the literature [128]. The Hausner ratio and Carr's index were obtained. Carr's index was expressed in % and considered as the compressibility index related to flowability [43].

The rearrangement constant (k) was calculated from the loose and tapped volume data according to Takieddin [46]. Linear and exponential regression analysis was subsequently performed, the slope of the curve being the rearrangement constant.

The Kawakita equations were also applied to the data obtained from the tapping test. The volume reduction, compactibility and cohesiveness of the investigated materials were evaluated in this manner. Tapping tests were performed with 0-200 taps at 10-tap intervals, using the above-mentioned tap density volumeter.

2.2.6. Test of granule flowability

Mass by volume

This was tested with an ASTM apparatus (ASTM D 392-28) according to Ph. Hg. VII and with a PTG-1 apparatus (Pharma Test GmbH, Germany).

Flow properties

A powder testing apparatus (PTG-1; Pharma Test GmbH, Germany) was used to test the flow time and the angle of repose.

2.2.7. Postcompression tests on tablets

Geometrical dimension measurements

The thickness (h) and diameter (D) of the tablets were measured shortly after ejection, and remeasured after 24 hours, using a screw micrometer (Mitutoyo Corp., Japan; n=20).

The percentage elastic recovery ($ER\%$) was calculated by using the equation

$$ER\% = \frac{(h_{24} - h)}{h} \cdot 100 \qquad (9)$$

where h and h_{24} are the heights of the tablet immediately after ejection and after 24 hours, respectively [129].

Uniformity of mass

The tablets were weighed on an analytical balance, with an accuracy of 0.1 mg, and the weight variation was calculated (n=30 for the tablets).

Breaking hardness

The breaking hardness of the tablets was measured 24 hours after ejection on a Heberlein apparatus (Heberlein & Co. AG., Switzerland).

Breaking process

The breaking process was carried out with a modified breaking hardness tester (Chinoin, Chemical and Pharmaceutical Works Ltd., Budapest, Hungary). Its technical parameters:

range of measurement:	0-200 N,
reading:	$3_{1/2}$ digits,
forward rate of pressing jaw:	20 mm/min,
recording output:	0-500 mV,
sensor:	Unicell Load Cell (MIKI) 20 kg,
accuracy of equipment:	0.5±0.1 digit,
operating voltage:	220 V at 50 Hz.

The tablets were positioned vertically.

Friability

Tablet friability was tested with a Roche friabilator (Erweka Apparatebau GmbH, Heusenstamm, Germany). Three lots of 10 tablets were weighed before and after treatment at 100 rpm. The results were recorded as the percentage loss from the initial mass.

Disintegration time

The disintegration time was determined for 20 individual tablets, using an Erweka VZ4 disintegration tester (Erweka Apparatebau GmbH, Heusenstamm, Germany). The disintegration medium was distilled water at 37±1 °C.

Dissolution rate

The rate of dissolution of metronidazole was studied with a rotary basket method.

Conditions:

apparatus:	Pharma Test PTWII, equipped with a rotary basket (Pharma Test GmbH, Germany),
dissolution medium:	900 ml artifical gastric juice (pH = 1.2 ± 0.1),
temperature:	37 ± 0.5 °C,
rotation speed:	50 rpm,
sampling time:	5, 10, 20, 30, 60 and 120 min,
number of tablets:	6,
measurement:	at 277 nm with a UV spectrophotometer (Spectromom 195D, MOM, Budapest, Hungary).

III. RESULTS AND DISCUSSION

1. Preformulation evaluation

1.1. Morphological investigations

The results of the morphological studies of metronidazole crystals are to be seen in Fig. 1. It may be stated that metronidazole consists of heterodisperse, stubby columnar crystals. Most of the crystals had a length in the range 10-30 μm and a breadth in the range 5-20 μm (Figs 2 and 3). In accordance with the roundness values (Table 1), such a crystal shape results in unsuitable flow properties.

Table 1 – Analysis of particle size of metronidazole crystals

	Length (mm)	Breadth (mm)	Roundness
Average	31.279	18.416	1.427
Std.	30.624	19.211	0.333
Minimum	4.154	17.780	1.049
Maximum	280.000	168.235	3.688

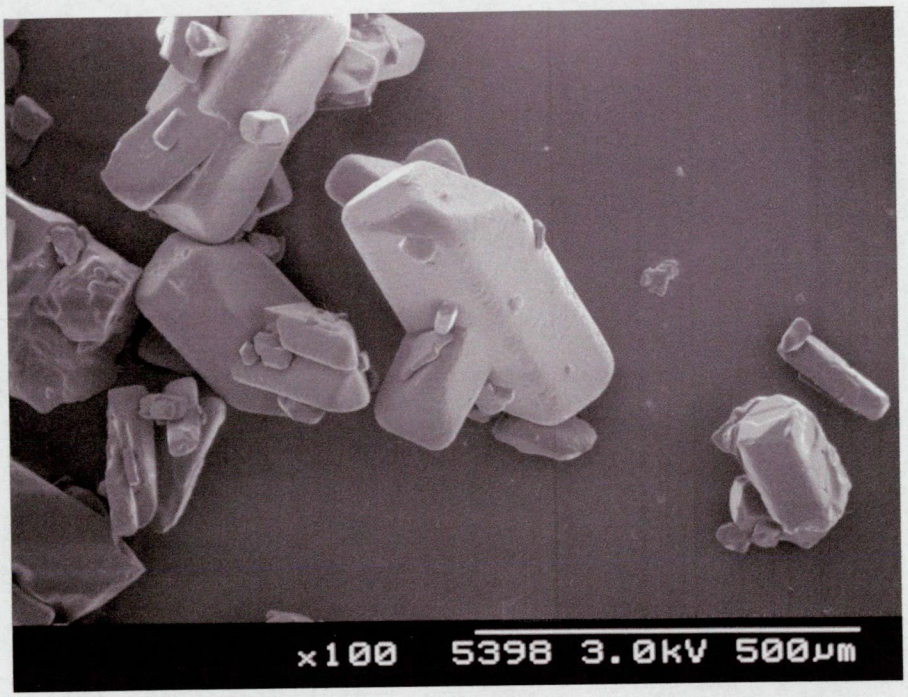
The roundness is a shape factor providing information on the sphericity of the particles. It is calculated by the image analysis software according to the following formula:

$$Roundness = \frac{(perimeter)^2}{4\pi \cdot area \cdot 1.064} \qquad (10)$$

The perimeter is calculated from the horizontal and vertical projections with an allowance for the number of corners. The adjustment factor of 1.064 corrects the perimeter for the effect of the corners produced by the digitizing of the image [130].

Several papers are to be found on the determination of the shape factor [131, 132]. The shape factor influences the flowability of the materials, and is therefore an important parameter. If its value is close to 1, the particles are close to spherical. The shape can be observed from the SEM images, but the degree of sphericity can be obtained only by calculating this parameter.

Fig. 1 Metronidazole crystals (SEM)



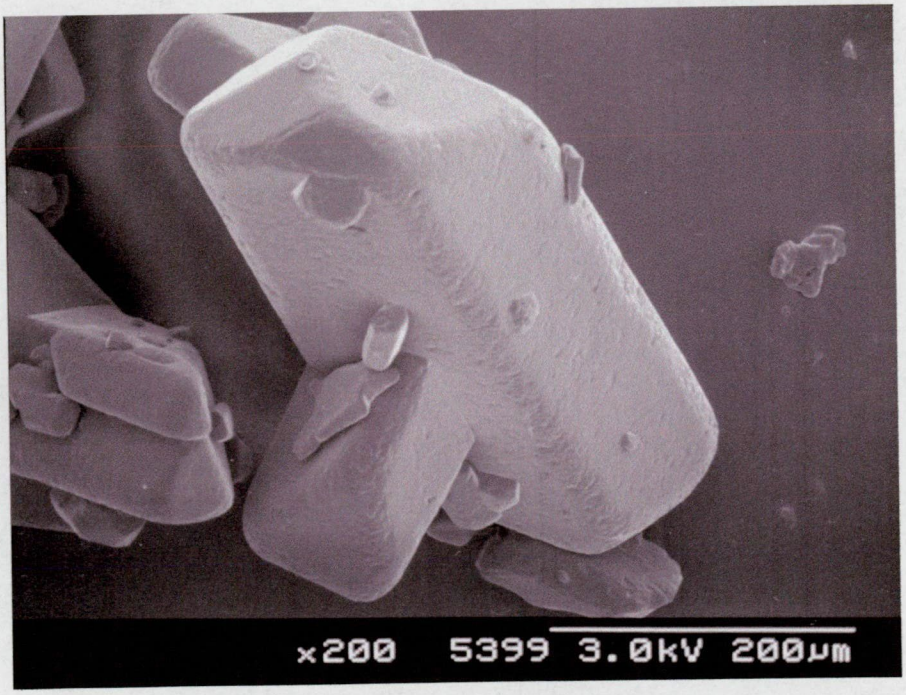


Fig. 2

Particle size distribution of metronidazole crystals by length

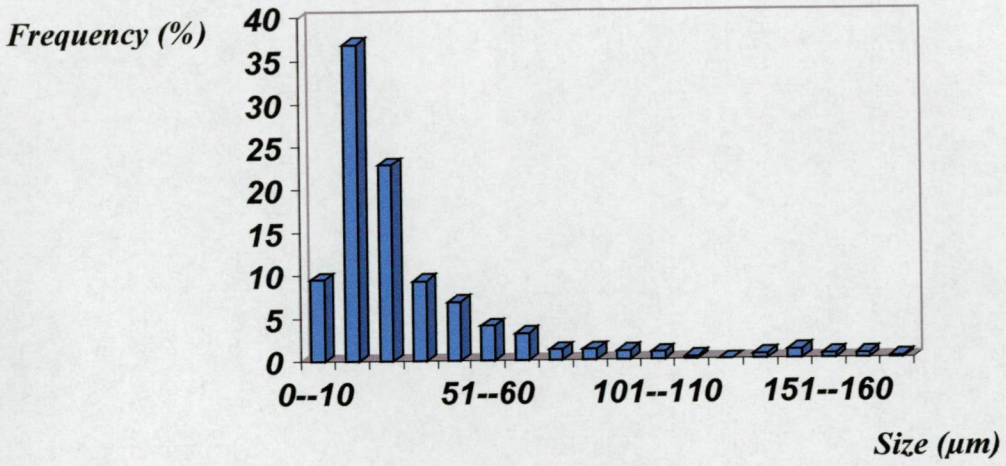
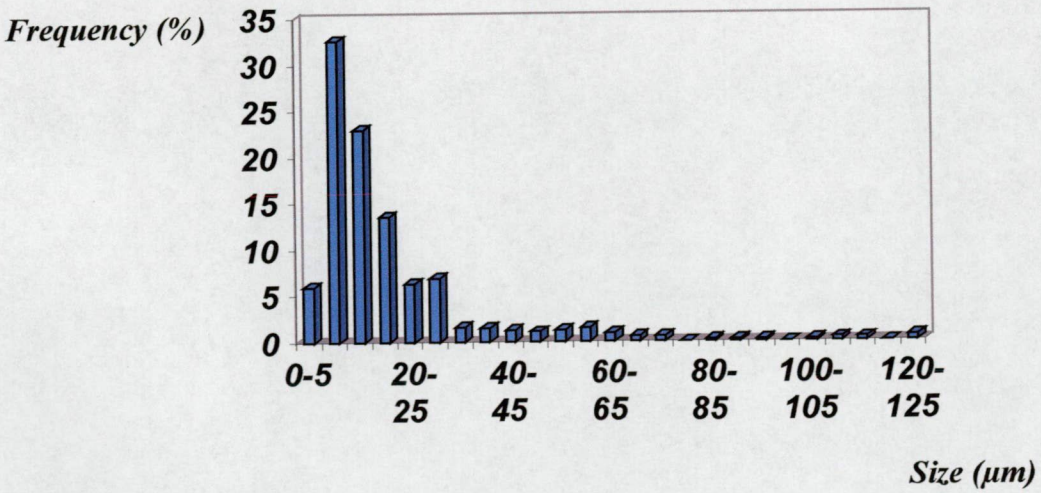


Fig. 3

Particle size distribution of metronidazole crystals by breadth



1.2. Process of polymer film deformation

The investigation of films involved determination of the thickness of the films formed from different granulating fluids, study of the deformation process and measurement of the breaking strain force. All films had similar force - time curves (Fig. 4). The initial linear change in the force indicated elastic behaviour. The force then became constant, in spite of the increasing load, due to the viscoelastic character of the film caused by the rearrangement of the binding points between macromolecules. This was followed by a linear increase section, again indicating elasticity. At a given limit, the force suddenly dropped back to zero and the film broke apart. This time course, of course, is influenced by the film thickness, so that all deformation tests were preceded by thickness measurement. The outcome of these tests is summarized in Table 2.

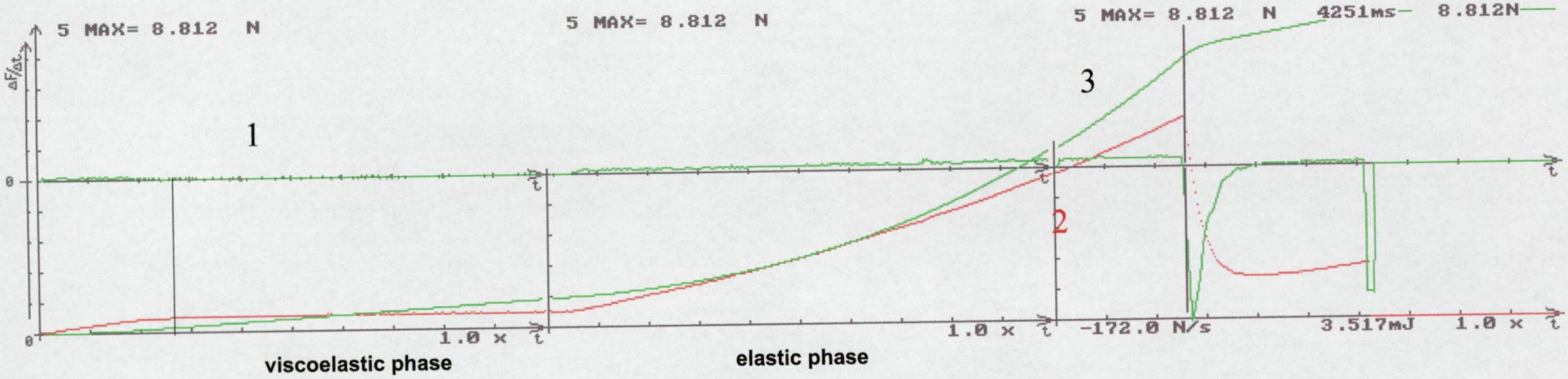
Table 2 - Parameters of the process of deformation of free films

Polymers	Thickness (mm)	Breaking force (N)	Time of visco-elastic phase (s)	Time of elastic phase (s)	Time of breaking (s)
Klucel LF(10%)	0.117	13.20	1.63	10.05	11.68
Cellosize WP 4400 L (1%)	0.028	13.10	1.64	10.59	12.23
Pharmacoat 603 (2%)	0.022	13.21	1.61	6.88	8.49
Tylose MH 1000 P (2%)	0.025	8.81	1.20	3.05	4.25

It may be seen that Klucel LF films, made of 10% mucilage, proved to be the thickest. In spite of the differences in thickness, the breaking force was the same for films made of Klucel LF, Cellosize WP 4400 L or Pharmacoat 603. In contrast, the ultimate stress of Tylose MH 1000 P films was lower (Fig. 4). The length of the viscoelastic segment was identical for all three films, but the subsequent elastic segment was shorter for the film of Pharmacoat 603, so that this film failed earlier. For Klucel LF and Cellosize WP 4400 L films, the elastic deformation lasted equally long; in spite of the difference in thickness, therefore, the elasticity of these films was sufficient, i.e. they show sufficient elastic recovery after being compressed. All the same, there was a difference in the hardness of the tablets, indicating that the film thickness can be of importance in the formation of appropriate binding forces.

Fig. 4

Deformation process of Tylose-film



1. differential curve; 2. deformation curve; 3. integral curve

2. Influence of Povidone K-30 on the properties of granules and tablets

Different Povidone products are very frequently used in tablet making. Therefore, for the first part of the experimental work, Povidone K-30 was chosen from among the numerous binding agents described in the literature. With the use of this binder, granulates were manufactured traditionally by kneading and by means of the fluid-bed granulator Strea-1 (see next point). I tried to optimize the physico-chemical characteristics of the tablets produced by altering the natures and amounts of the binders and other auxiliary components.

The compositions of the tablets are presented in Table 3.

Table 3 - Compositions of the tablets

Components	Prep. 1 (mg)	Prep. 2 (mg)	Prep. 3 (mg)	Prep. 4 (mg)	Prep. 5 (mg)	Prep. 6 (mg)	Prep. 7 (mg)	Prep. 8 (mg)	Prep. 9 (mg)	Prep. 10 (mg)
Metronidazole	250.0	250.0	250.0	250.0	250.0	250.0	250.0	250.0	250.0	250.0
Corn starch	80.0	80.0	—	10.0	—	10.0	—	—	—	—
Wheat starch	—	—	—	—	10.0	—	—	—	—	—
Kollidon CL	—	—	15.0	5.0	5.0	5.0	5.0	5.0	5.0	7.0
Avicel PH 101	10.0	10.0	10.0	10.0	10.0	20.0	20.0	30.0	33.0	33.0
Povidone K-30	23.2	19.7	7.9	7.6	8.4	7.95	8.3	7.7	10.1	10.1
Mg-stearate	2.8	2.3	2.1	2.4	2.6	2.05	2.7	2.3	1.9	1.9
Average mass	366.0	362.0	285.0	285.0	286.0	295.0	286.0	295.0	300.0	302.0

A morphological investigation of the granules produced was performed first. The crystal shape of metronidazole results in unsuitable flow properties (Table 4), but the shape of the granules ensured better flowability (Table 4). The granules produced conventionally consist of large particles (Fig. 5). Adhering crystals can be observed in each granule particle. The flow properties of the active agent and the granules themselves are of primary importance in tabletting, as is the size distribution of the granulate produced (see Table 4 for the results).

The data indicate that it was possible to reduce the flow-out time of the active agent substantially. The values of the angle of repose are acceptable and exhibit a narrow distribution. The angle is the largest for Preparation 7; the interparticle adhesion is thus the strongest here, but it can be reduced by adding a glidant (e.g. Aerosil at 0.2%). As shown by the data, Preparation 3 had the highest bulk density, and hence the best space filling. The Hausner factor and Carr's index were excellent for all preparations and much better than those of the untreated active agent.

Fig. 5 Conventional granule (SEM)

Table 4 - Flow properties of the granules

Preparations	Moisture content (%)	Mass by volume (g/100 ml)	Flowing time (s)	Angle of repose (°)	Hausner factor	Carr`s index (%)
Metronidazole	---	65	23	37.3	1.153	13.334
Preparation 1	3.7	50	12	36.8	1.045	6.842
Preparation 2	0.8	44	10	37.7	1.073	6.833
Preparation 3	0.6	56	9	36.0	1.036	3.498
Preparation 4	0.5	49	12	37.3	1.060	5.670
Preparation 5	0.5	49	12	37.7	1.069	6.498
Preparation 6	1.0	50	10	35.2	1.065	6.173
Preparation 7	0.7	47	11	37.8	1.069	6.499
Preparation 8	1.0	49	9	35.6	1.065	6.168
Preparation 9	0.9	54	9	36.4	1.065	6.166
Preparation 10	1.0	55	10	35.6	1.063	6.003

The particle size distribution (Table 5) showed that the majority (55-70%) of the granules were in the range 0.32-1.20 mm, but it can be seen that use of a binder agent in higher amount resulted in much larger particles (1.2-2.0 mm). In spite of this, the size distribution was suitable for tabletting.

Table 5 - Particle size distribution of the granules

Preparations	Particle size (mm)			
	2.0-1.2 (%)	1.2-0.8 (%)	0.8-0.32 (%)	< 0.32 (%)
Preparation 1	21	20	55	3
Preparation 2	15	20	50	14
Preparation 3	19	61	15	5
Preparation 4	46	20	31	2
Preparation 5	32	17	46	3
Preparation 6	6	22	67	4
Preparation 7	22	31	43	3
Preparation 8	4	17	69	9
Preparation 9	32	14	41	12
Preparation 10	28	17	47	7

The physical parameters of the tablets are displayed in Table 6.

Table 6 - Physical parameters of the tablets

Preparations	Uniformity of mass (mg)		Breaking hardness (N)	Friability (%)	Disintegration time (s)
	Average	SD			
Preparation 1	362.6	2.5	68	1.11	445
Preparation 2	354.4	4.1	40	1.79	49
Preparation 3	284.0	1.6	34	1.97	17
Preparation 4	287.7	3.6	47	1.75	158
Preparation 5	285.6	2.3	34	1.83	28
Preparation 6	289.2	3.4	43	1.45	49
Preparation 7	279.4	6.6	47	1.36	184
Preparation 8	290.2	2.0	38	1.52	65
Preparation 9	307.1	3.3	73	0.97	621
Preparation 10	300.2	3.1	56	1.06	315

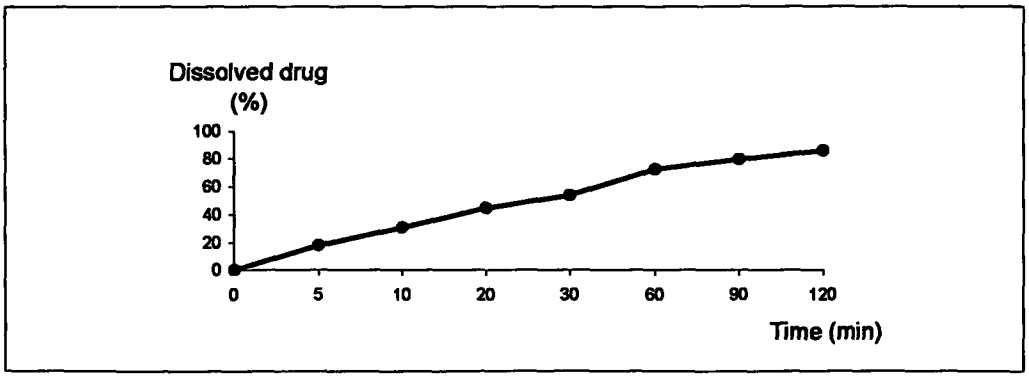
The data reveal that the dosage accuracy was in all cases within the limit set in Ph.Hg.VII [133]. Preparation 3 had the best dosage accuracy. The uniform space filling was probably due to the even spread of the binding agent resulting in more compact and approximately isometric granules. The mechanical resistance of the tablets met the requirements in Ph.Hg.VII in every case. The friability was below 2%. The disintegration time was within 15 min, also meeting Ph.Hg.VII. It is very interesting to observe the changes in the volume of the tablets (Table 7) during 24 hours following compression, which are due to the rearrangement of the binding forces. As may be seen in Table 7, the diameter of the tablets decreased and their height increased in 24 hours.

Table 7 - Geometrical parameters of the tablets

Preparations	Geometry				Change in geometry		Change in volume
	After compression		After 24 hours				
	Diameter (mm)	Thickness (mm)	Diameter (mm)	Thickness (mm)	Diameter (mm)	Thickness (mm)	(mm^3)
Preparation 1	10.0834	3.6879	10.0810	3.6881	-0.0024	0.0002	-0.12
Preparation 2	10.1119	3.5802	10.1105	3.5880	-0.0014	0.0078	0.54
Preparation 3	10.1042	3.0277	10.1023	3.0301	-0.0019	0.0024	0.10
Preparation 4	10.0949	3.0362	10.0920	3.0371	-0.0029	0.0009	-0.07
Preparation 5	10.0932	3.0229	10.0917	3.0305	-0.0015	0.0076	0.53
Preparation 6	10.0968	3.0431	10.0922	3.0451	-0.0046	0.0020	-0.07
Preparation 7	10.0875	2.9409	10.0814	2.9479	-0.0061	0.0070	0.28
Preparation 8	10.0862	3.2536	10.0839	3.2673	-0.0023	0.0137	0.98
Preparation 9	10.0828	3.1767	10.0718	3.1801	-0.0110	0.0034	-0.28
Preparation 10	10.0928	3.1478	10.0911	3.1532	-0.0017	0.0054	0.35

One of the most important postcompression tests was the determination of drug liberation. The longest dissolution time was that for the tablets prepared with the highest amount of binder. The tablets with the best physical parameters were chosen for the drug liberation test. As demonstrated in Fig. 6, only 60-70% of the agent was dissolved within 60 min. The likely explanation is that, although the disintegration of the tablets is fast, the granules set free failed to fall apart rapidly, which could impede appropriate liberation of the pharmacon.

Fig. 6 Dissolution of metronidazole from the tablets (Preparation 9)



3. Influence of the methods on the properties of granules and tablets

New preparations were prepared in order to investigate the effects of the mode of granulation on the properties of the granules and tablets. The compositions were the same (Table 8), but the methods were different. One composition was made by kneading, and the other by fluid-bed granulation.

Table 8 lists the compositions of the tablets. The flow parameters demonstrated that, with the exception of the angle of repose, all the parameters were improved as compared with those of metronidazole alone. The bulk density and flow time were decreased. The angle of repose was increased a little in the case of Preparation 11/B and decreased in the case of Preparation 11/A (Table 9).

Table 8 - Composition of the tablets
Pressure force: 15 kN

Components	Mass (mg)
Metronidazole	250.00
Avicel PH 101	33.00
Kollidon CL	7.00*
Povidone K-30	23.20
Mg-stearate	1.80
Average mass	315.00

*5.00 mg in the internal phase
*2.00 mg in the external phase

Table 9 - Flow properties of the granules

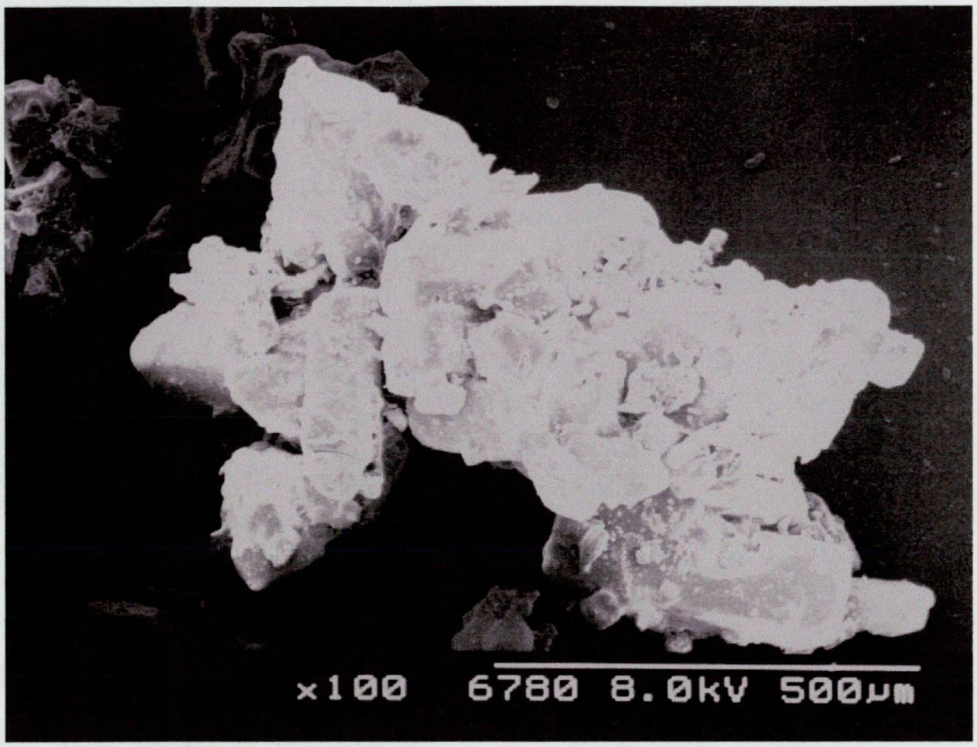
Preparations	Flowing time (s)	Mass by volume (g/100 ml)	Angle of repose (°)	Hausner factor (%)	Carr's index
Metronidazole	23	65	37.3°	1.153	13.334
Preparation 11/A	10	47	33.7°	1.071	6.676
Preparation 11/B	10	37	39.6°	1.048	4.665

A means fluid bed granulation
B means conventional granulation

The reason for this lies in the particle size and shape. The granules prepared by kneading consist of larger particles (Fig. 5) and the fluidization granules of smaller particles (Fig. 7), but the sphericity of the conventional granules is better and therefore so is their flowability. This

parameter can be corrected by the use of a glidant. The value for the material prepared by kneading is suitable, and thus the use of a glidant is not necessary.

Fig. 7 Fluid bed granule (SEM)



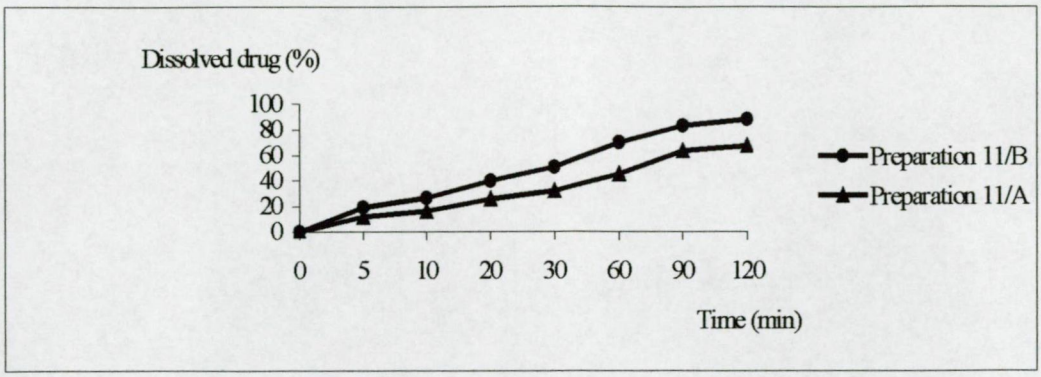
The data on the postcompressional parameters of the tablets are presented in Table 10. The uniformity of mass is in every case within the limits set by Ph.Hg.VII.

Table 10 - Physical parameters of the tablets

Preparations	Uniformity of mass (mg)		Breaking hardness (N)	Dizintegration time (min)	Friability (%)
	Average	SD			
Preparation 11/A	302.4	6.1	80	<15	1.04
Preparation 11/B	313.1	2.0	54	<15	1.16

It can be seen that this value was better for Preparation 11/B, prepared with the Strea-1 fluid-bed apparatus, but the hardness of the tablets was better for Preparation 11/A, prepared by the conventional method, than for Preparation 11/B. This was in accordance with the friability results. The disintegration time of the tablets was too long: more than 15 minutes. It can be observed Fig. 8 that the dissolution of the drug was slow and uniform. It can further be seen that the dissolution curve profiles are the same, but more drug could be dissolved from the Preparation 11/B tablet.

Fig. 8 Dissolution of metronidazole from the tablets



Several papers and monographs deal with the mathematical description of drug liberation [77, 78].

The dissolution process was evaluated mathematically via the RRSBW distribution, and the characteristic dissolution time ($t_{63.2\%}$) was determined after linearized regression and transformation according to Langenbucher. Regression analysis was carried out with the Statgraphics package (© STSC, Inc. and Statistical Graphics Co., USA); the confidence limit was 95%.

The results are presented in Table 11. The data show that the characteristic dissolution time was shorter for the Preparation 11/B tablet, due to its lower hardness. The solid bridges can break more easily and the drug can be released more quickly. On the basis of the shape parameter (β), it can be concluded that an exponential process is involved, i.e. a fast drug release is followed by a slow saturating process.

Table 11 - Mathematical evaluation of drug release

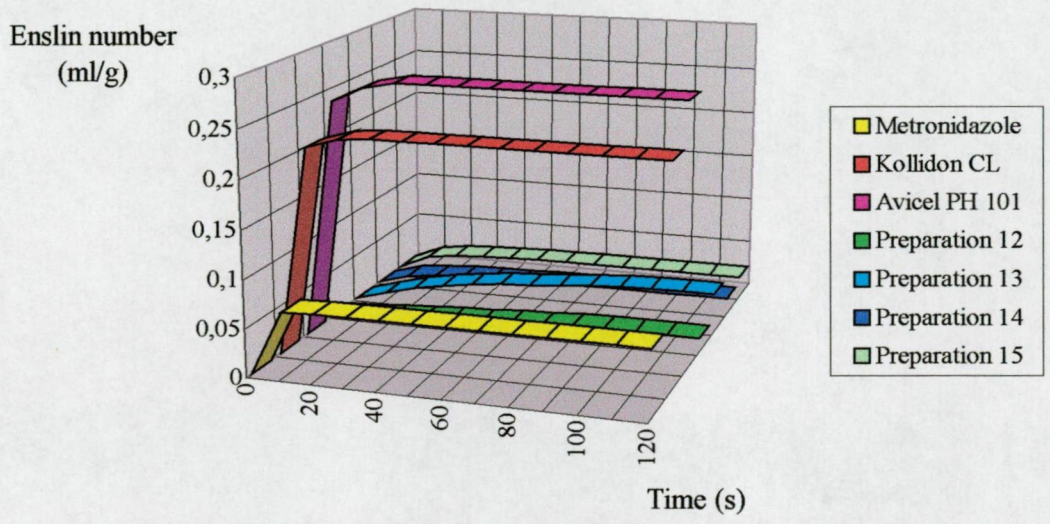
Peparations	$t_{63.2\%}$ (min)	Slope (β)	Intercept (ln a)	Correlation coeffitient (R) $p<0.05$
Preparation 11/A	106.95	0.7080	-3.3084	0.9949
Preparation 11/B	45.63	0.7441	-2.8429	0.9977

The data indicate that the same amount of binder resulted in harder tablets with a slower drug release following kneading granulation. This means that the two methods require different binder contents.

4. Influence of cellulose derivatives on the properties of granules and tablets

In wet granulation, the adequate wetting of the powder mixture is crucial, as this influences the uptake of the granulating fluid and hence the formation of a mass of suitable consistency and the binding forces themselves. In my experimental work, the water-absorbing capacities of the drug, the auxiliaries and the granulates produced by using cellulose ethers were determined. Figure 9 reveals that the water uptake of metronidazole is rather poor, and it can be potentially improved by means of additives with a better water-uptake capacity (e.g. Avicel PH 101 or Kollidon CL). Figure 9 also shows the water-absorbing capacities of the different compositions which were suitable for wet granulation.

Fig. 9 Water uptake of materials and granules



The compositions of the tablets are presented in Table 12. The fluid-bed apparatus was used for the preparation of the granules. The flow parameters of these granules are presented in Table 13.

Table 12 - Compositions of the tablets

Components	Preparation 12 (mg)	Preparation 13 (mg)	Preparation 14 (mg)	Preparation 15 (mg)
Metronidazole	250.00	250.00	250.00	250.00
Avicel PH 101	33.00	33.00	33.00	33.00
Kollidon CL	10.00	10.00	10.00	10.00
Cellosize WP 4400 L	4.35	---	---	---
Klucel LF	---	13.2	---	---
Pharmacoat 603	---	---	3.24	---
Tylose MH 1000 P	---	---	---	3.34
Magnesium stearate	2.65	1.8	1.76	1.66
Average mass	300.00	308.00	298.00	298.00

Table 13 - Rheological parameters of the granules

Preparations	Flowing time (s)	Angle of repose (°)	Mass by volume (g/100 ml)	Hausner factor	Carr's index (%)
Metronidazole	23	37.3	65.0	1.1538	13.3342
Preparation 12	11	40.6	36.0	1.0525	4.9913
Preparation 13	11	41.6	28.3	1.0528	5.0172
Preparation 14	14	39.1	38.0	1.0951	8.6858
Preparation 15	11	38.6	41.3	1.0416	4.0000

The flowability of the granules was influenced by the binder used (Table 13). Except for the angle of repose, all the parameters were improved as compared with those of metronidazole alone. The mass by volume and the flow-out time were decreased. The values of the angle of repose were not changed, or even increased a little, but this can be corrected by the application of a glidant before tabletting.

The Hausner factor and Carr's index, calculated from the loose and the tapped density according to the literature, revealed excellent compactibility and compressibility after granulation.

The actual arrangement of the granulate bulk is characterized by the arrangement factor k (Table 14).

Table 14 - The rearrangement constant

Preparations	Linear model (y=ax+b)			Exponential model (y=exp[1+kn])		
	R	k	F	R	k	F
Metronidazole	0.367	1193.780	5.21	0.963	0.102	233.43
Preparation 12	0.777	12.820	10.45	0.952	0.140	59.76
Preparation 13	0.468	3.390	5.28	0.909	0.075	60.15
Preparation 14	0.578	3.140	5.48	0.967	0.096	116.58
Preparation 15	0.789	3.739	11.21	0.977	0.077	127.63

The values of the correlation coefficient showed that the rearrangement followed an exponential model. For a linear model, the correlation (R) was very low, but for an exponential model it was near 1. The Table also demonstrates that Preparation 12 had the highest k, i.e. the best rearrangement.

A number of experimental parameters were followed during the tabletting step. Of these, the considerable temperature increase for the ready tablets (30-32 °C) is of particular importance. The friction during compression results in sintering and partial melting, together with hot spots. This in turn can influence the texture of the tablets, possibly affecting the physical parameters of the tablets and the liberation of the drug [134, 135]. Figure 10 depicts the hot spots induced by the compression. In Fig. 11, they are presented at higher magnification.

The physico-chemical parameters of the tablets tested are presented in Table 15.

Table 15 - Physical parameters of the tablets

Preparations	Average mass (mg)	Uniformity of mass (mg)	Friability (%)	Breaking hardness (N)	Disintegration time (s)
Preparation 12					
10 kN	307.9	±2.9	2.27	29.5	598
15 kN	311.5	±3.3	2.73	31.5	380
Preparation 13					
10 kN	313.6	±2.5	0.83	107.2	156
15 kN	312.6	±2.8	0.80	112.7	190
Preparation 14					
10 kN	296.1	±4.0	2.31	22.2	92
15 kN	295.4	±6.9	2.18	23.5	92
Preparation 15					
10 kN	295.0	±4.9	2.03	24.7	140
15 kN	297.0	±3.4	1.77	27.1	106

Fig. 10 "Hot spots" on the surface of the tablet (SEM, Preparation 12)

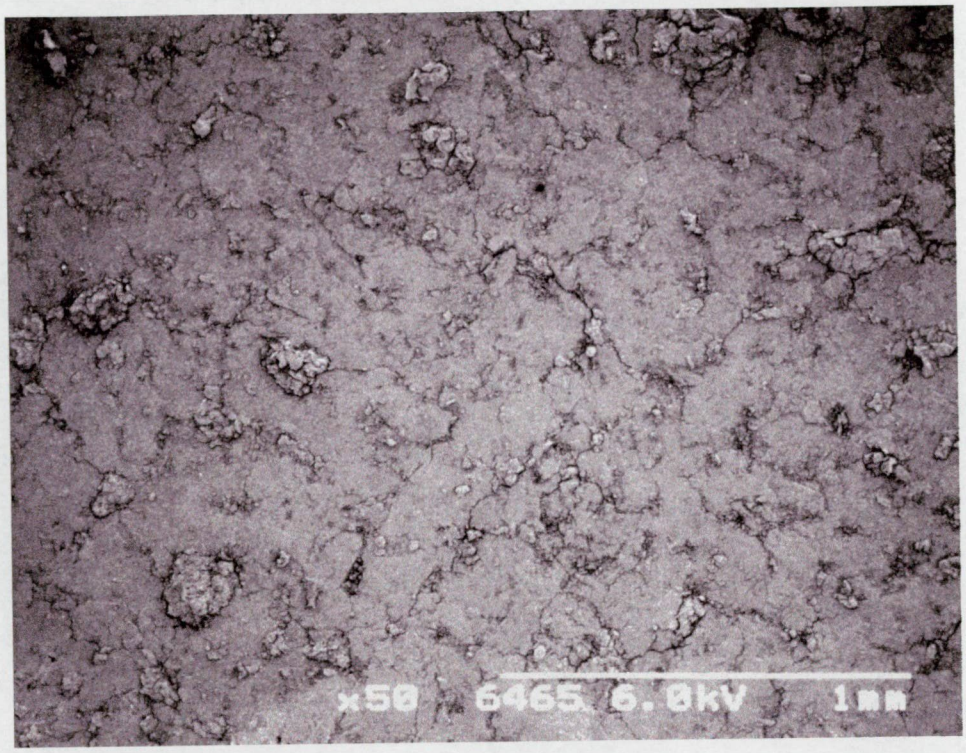
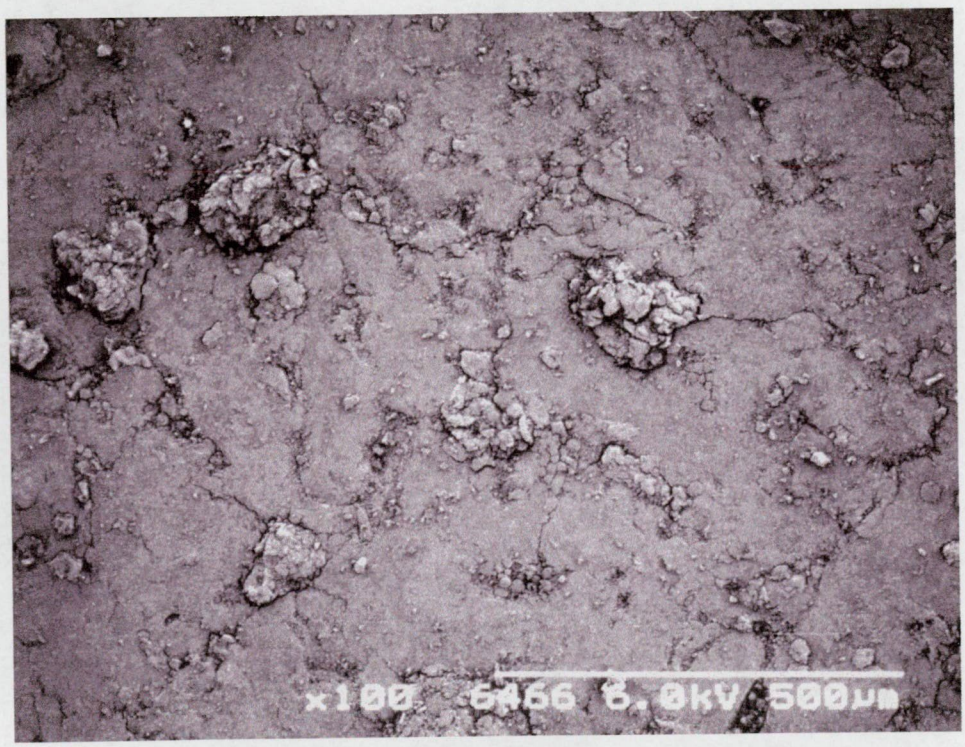


Fig. 11 "Hot spots" on the surface of the tablet (SEM, Preparation 12) at higher magnification



It can be seen from the data that the uniformity of mass was in every case within the limits given by Ph.Hg.VII. It is clear that this value was best for Preparation 13, prepared with hydroxypropyl cellulose (Klucel LF), and the hardness of these tablets was also the best. For other tablets, the hardness was too low. A small increase in hardness was observed at higher pressure force only for the tablets prepared with hydroxypropyl cellulose (Klucel LF). This was in accordance with the friability results.

The tablets prepared with hydroxyethyl cellulose (Cellosize WP 4400 L) had the longest disintegration time. The disintegration time of the tablets compressed at 10 kN was longer. With increase of the pressure force, however, the granule particles underwent a higher degree of breakage, and the polymer film also broke, resulting in a shorter disintegration time.

The disintegration of the other tablets occurred at almost the same time (1.5-3.0 min). Increase of the pressure force generally had no influence on the parameters of the tablets.

The dissolution of the drug was very fast (100% within 10-20 min), with the exception of the tablets prepared with hydroxyethyl cellulose (Cellosize WP 4400 L) (Figs 12 and 13). The dissolution from this tablet was slow and uniform. Here, the disintegration of the tablet was fast, but that of the granules was probably not. The polymer film formed from the granulating fluid is transformed to a gel, acting as a barrier against the rapid liberation of the active agent and making it prolonged. Furthermore, increase of the pressure force had practically no influence on the rate of dissolution of the drug. In the fast drug release, the surface activity of the binder film is an important factor. It is well known from the literature that the surface activities of aqueous solutions of cellulose derivatives differ [117, 118]. A polymer film is formed from the granulating solution. This film should dissolve during the process of dissolution and the surface activity of this solution influences the dissolution profile. Hydroxyethyl cellulose has the lowest surface activity among the cellulose derivatives used. This is the reason for the decrease in the degree of dissolution.

The results of the mathematical evaluation of the dissolution are presented in Table 16. It can be seen that the characteristic dissolution time was very short for Preparations 13, 14 and 15. From these tablets, 63.2% of the metronidazole was released within 5 min. The correlation coefficient was near to 1. On the basis of the shape parameter (β), it can be supposed that for Preparations 12 and 14 the release of the drug followed first-order kinetics with $\beta = 1$, but in the other cases the dissolution processes were of other exponential types.

Fig. 12

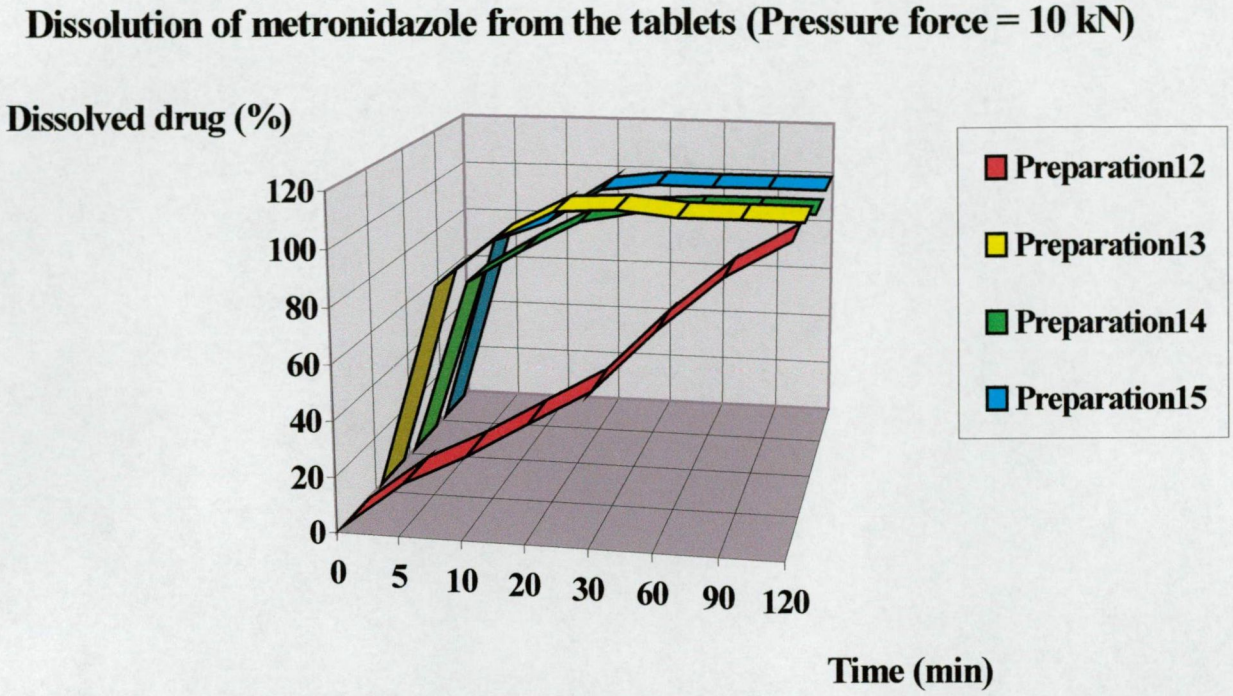

Dissolution of metronidazole from the tablets (Pressure force = 10 kN)
Dissolved drug (%)
120
100
80
60
40
20
0
0
5
10
20
30
60
90
120
Time (min)
Preparation12
Preparation13
Preparation14
Preparation15

Fig. 13

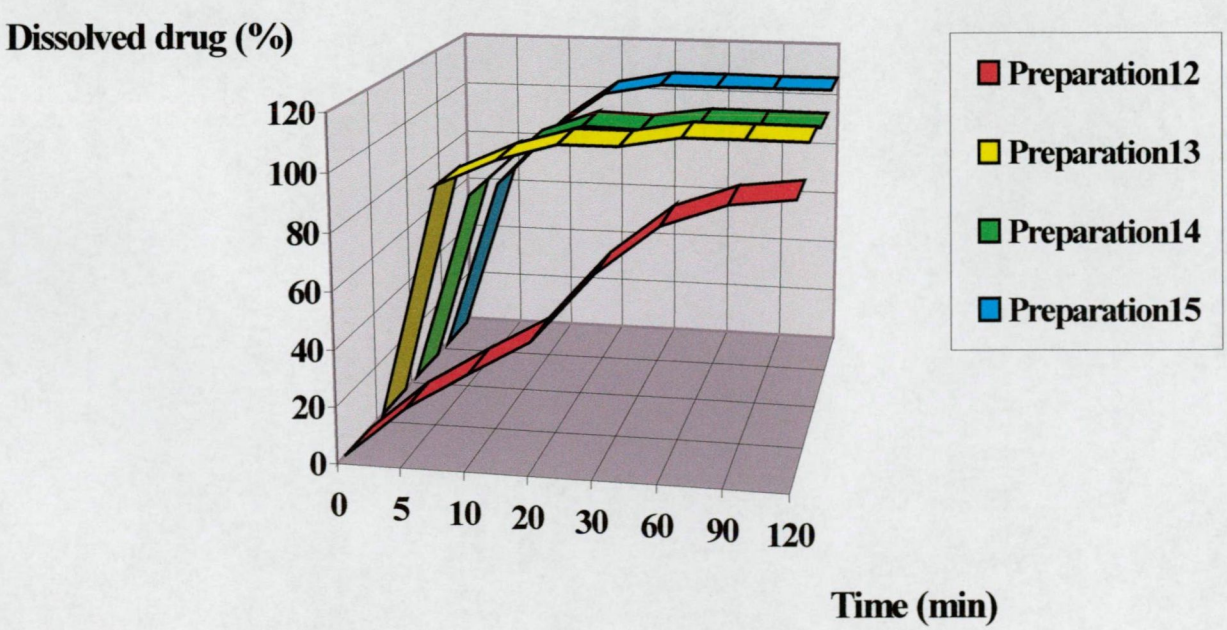

Dissolution of metronidazole from the tablets (Pressure force = 15 kN)
Dissolved drug (%)
120
100
80
60
40
20
0
0
5
10
20
30
60
90
120
Time (min)
Preparation12
Preparation13
Preparation14
Preparation15

Table 16 - Mathematical evaluation of drug release

Preparations	$t_{63,2\%}$ (min)	Slope (β)	Intercept (ln a)	Correlation coefficient (r) $p<0.05$
Preparation 12				
10 kN	26.27	0.9908	-3.2388	0.9941
15 kN	43.74	0.9438	-3.1883	0.9951
Preparation 13				
10 kN	4.03	1.3332	-1.8570	0.9879
15 kN	3.06	1.1238	-1.2561	0.9715
Preparation 14				
10 kN	3.63	1.0435	-1.3458	0.9832
15 kN	4.08	1.0562	-1.4850	0.9988
Preparation 15				
10 kN	4.70	1.3721	-2.1246	0.9196
15 kN	5.13	1.5396	-2.5185	0.9795

The breaking parameters of the tablets are presented in Table 17. It can be observed that an

Table 17 - Breaking parameters of the tablets

Preparations	Breaking force (N)	Breaking work (mJ)	Breaking time (ms)	Breaking factor (mJ/N)
Preparation 12				
10 kN	25.61 (SD=4.82)	2.34 (SD=9.98)	690.0 (SD=6.4)	0.0913
15 kN	24.75 (SD=8.01)	2.10 (SD=10.94)	658.4 (SD=6.8)	0.0848
Preparation 13				
10 kN	121.09 (SD=3.06)	25.48 (SD=6.41)	1483.5 (SD=2.6)	0.2104
15 kN	128.24 (SD=2.17)	28.52 (SD=4.93)	1551.1 (SD=3.5)	0.2223
Preparation 14				
10 kN	19.21 (SD=6.73)	1.63 (SD=12.78)	591.4 (SD=13.3)	0.0848
15 kN	19.48 (SD=9.81)	1.50 (SD=13.20)	558.6 (SD=8.3)	0.0770
Preparation 15				
10 kN	21.96 (SD=4.18)	1.80 (SD=13.88)	608.5 (SD=10.5)	0.0819
15 kN	21.79 (SD=4.69)	1.83 (SD=14.98)	590.3 (SD=8.3)	0.0839

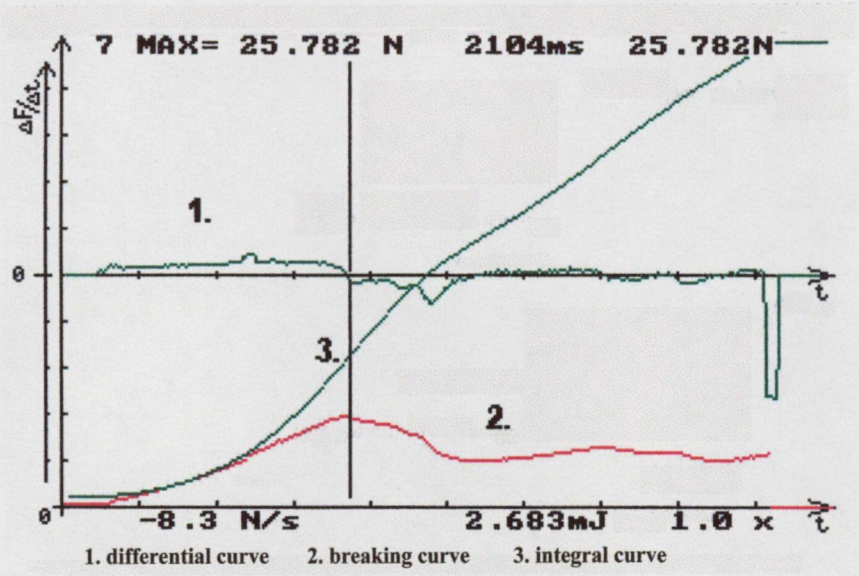
increase of the pressure force generally had no influence on the breaking parameters. Small increases in these parameters were observed at higher pressure force only for the tablets prepared with hydroxypropyl cellulose (Klucel LF). It can be stated that the hardness of these tablets was the best, i.e. the binding forces were higher inside these tablets. The breaking force and the breaking work were therefore higher and the process took a longer time. From these data, a new parameter was calculated: the breaking factor. This is the ratio of the breaking work and the breaking force [60]. The breaking work depends on the slope of the linear section and the time up to the completion of breaking, which results from the elastic behaviour of the tablet. The same breaking hardness can be measured at different slopes. If the elastic deformation of the tablet lasts longer, the slope of the linear section will be lower and the work necessary for breaking can also change. If the resistance of the tablet against the load is less, the breaking work will also be less. This is manifested in the value of the breaking factor. A comparison of the data on the tablets of Preparations 12, 14 and 15, for example, reveals that a lower breaking factor is indicative of a lower breaking work. The differences in the breaking factors of Preparations 12, 14 and 15 are not significant, but the differences between that of Preparation 13 and those of the other Preparations are ($p<0.05$). The breaking factor is thus a characteristic tablet parameter suitable for the comparison of different tablets.

The breaking process is displayed in Figs 14 and 15. Two types of deformation behaviour may be observed. That in Figure 14 illustrates the process of breaking of Preparation 12 tablets. It can be learned from the force - time plot that a small resistance in the initial section is followed by a short linear section. This indicates the elastic deformation of the tablet. The force could not decline sharply at the breaking point, however, because of the plastic deformation of the tablet. The breaking processes of the Preparation 14 and Preparation 15 tablets were very similar.

Figure 15 depicts the other type of breaking process. The tablets were prepared with Klucel LF (Preparation 13). The initial section of the force - time curve was similar to that in Figure 14, but the linear section was longer here, continuing until a certain limit, where the tablet underwent breaking. The break-point was sharp. This force - time curve indicates the elastic deformability of the comprimate.

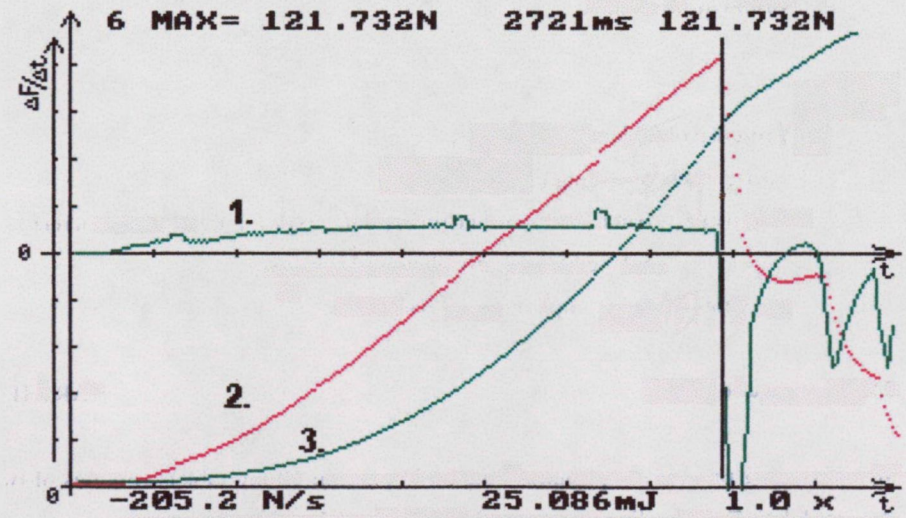
It can be considered that the surface activity of the Klucel LF film promoted the fast dissolution, and its elastic properties ensured the good hardness and breaking behaviour of the tablets.

Fig. 14 **Breaking process of metronidazole tablets**
Pressure force: 10 kN Binding agent: Cellosize



1. differential curve 2. breaking curve 3. integral curve

Fig. 15 **Breaking process of metronidazole tablets**
Pressure force: 10 kN Binding agent: Klucel LF



1. differential curve 2. breaking curve 3. integral curve

5. Effects of the concentration of the granulating solution on the properties of granules and tablets

In the further part of my experimental work, I investigated how the physico-chemical properties of the granulates and tablets are altered by increasing the concentration of the cellulose-ether based granulation fluid.

The compositions of the tablets are presented in Table 18. The granules were prepared in a fluid-bed apparatus (Strea-1). It can be seen from the data that the binder content decreased in the granules prepared with Cellosize WP 4400 L, and it was the same in the case of the granules prepared with Tylose MH 1000 P. However, in the case of granules prepared with Pharmacoat 603, the binder was used in higher amount.

Table 18 - Compositions of the tablets

Components	Preparation 12 (mg)	Preparation 16 (mg)	Preparation 14 (mg)	Preparation 17 (mg)	Preparation 15 (mg)	Preparation 18 (mg)
Metronidazole	250.00	250.00	250.00	250.00	250.00	250.00
Avicel PH 101	33.00	33.00	33.00	33.00	33.00	33.00
Kollidon CL	10.00	10.00	10.00	10.00	10.00	10.00
Binders	Cellosize WP 4400 L (1%)	Cellosize WP 4400 L (2%)	Pharmacoat 603 (2%)	Pharmacoat 603 (4%)	Tylose MH 1000 P (2%)	Tylose MH 1000 P (3%)
	4.35	3.02	3.24	14.5	3.34	3.18
Magnesium stearate	2.65	1.98	1.76	2.5	1.66	1.82
Average mass	300.00	298.00	298.00	310.00	298.00	298.00

The flowability of the granules was tested. The results are presented in Table 19.

Table 19 - Flowability and particle size of the granules

Preparations	Flowing time (s)	Mass by volume (g/100 ml)	Angle of repose (°)	Particle size (%) 2.0-1.2 mm	1.2-0.8 mm	0.8-0.32 mm	<0.32 mm	Hausner factor	Carr's index (%)
Preparation 12	11	36.0	40.6	7	21	56	14	1.05	4.99
Preparation 16	9	43.5	32.9	22	18	39	19	1.07	6.99
Preparation 14	14	38.0	39.1	30	15	43	8	1.09	8.68
Preparation 17	9	41.0	36.0	33	12	44	11	1.09	9.34
Preparation 15	11	41.3	38.6	17	16	49	17	1.04	4.00
Preparation 18	10	43.3	36.6	16	9	46	25	1.08	8.00

It is observed that the flow-out time was reduced by change of the amount of the binder. The values of the angle of repose were in accordance with the former: for a concentrated granulating solution, the angle of repose was less, indicating a reduced adhesion between the granules. In spite of this, there is a need for the use of a glidant in tablet pressing. It can be seen from the mass by volume data that the bulk density, and thus the space-filling, of the granulates varies with the amount of the binder. The sieve analysis revealed that the majority (55-70%) of the granules were invariably in the range 0.32-1.20 μm, which is positive for tabletting.

There were no significant differences in the Hausner factor and Carr's index: these were excellent in all three compositions.

After the compression, the physical parameters of the tablets were tested. The data are given in Table 20.

Table 20 - Physical parameters of the tablets

Binders	Uniformity of mass (mg)	Breaking hardness (N)	Friability (%)	Disintegration time (s)	Uniformity of mass (mg)	Breaking hardness (N)	Friability (%)	Disintegration time (s)
	Pressure force: 10 kN				Pressure force: 15 kN			
Preparation 12	307.9 (s=2.9)	30	2.27	598	311.5 (s=3.3)	32	2.73	380
Preparation 16	295.9 (s=3.0)	32	1.86	655	287.1 (s=4.7)	30	2.89	359
Preparation 14	296.1 (s=4.0)	22	2.31	92	295.4 (s=6.9)	24	2.18	92
Preparation 17	302.7 (s=3.8)	23	1.93	295	299.4 (s=1.5)	33	1.40	460
Preparation 15	295.0 (s=4.9)	25	2.03	140	297.0 (s=3.4)	27	1.77	106
Preparation 18	292.8 (s=2.0)	28	1.91	219	282.1 (s=4.3)	31	1.73	208

The data demonstrate that an increase in the concentration of the binder resulted in no change in the hardness of the tablets. The values of friability are in accordance with this, but the disintegration time generally increased. It can be seen that increase of the concentration of the binder did not influence the mechanical hardness of the tablets.

6. Effects of storage on the characteristics of tablets produced with cellulose derivatives

In the last part of the experiments, the alterations in the tablets containing cellulose derivatives were studied during storage. Tests were performed after storage for 3 and 6 months. The tablets were packed in a polyethylene bag. The post-storage measurement data are shown in Table 21.

Table 21 - Physical parameters of the tablets

Preparations		Uniformity of mass (mg)	Breaking hardness (N)	Friability (%)	Disintegration time (s)	Uniformity of mass (mg)	Breaking hardness (N)	Friability (%)	Disintegration time (s)
		Pressure force: 10 kN				Pressure force: 15 kN			
Preparation 12	After compression	307.96	30	2.27	598	311.51	32	2.73	480
	After 3 months	319.11	31	2.02	387	319.37	34	2.31	490
	After 6 months	320.02	29	2.03	507	318.69	33	2.86	541
Preparation 13	After ejection	313.64	107	0.83	156	312.63	113	0.80	190
	After 3 months	322.98	128	0.72	171	314.52	139	0.73	340
	After 6 months	323.25	106	0.79	113	314.62	116	0.96	226
Preparation 14	After ejection	296.13	22	2.31	92	295.45	24	2.18	92
	After 3 months	295.69	26	2.03	147	293.65	28	2.09	103
	After 6 months	295.08	23	2.37	69	292.58	26	2.85	77
Preparation 15	After ejection	295.01	25	2.03	140	297.01	27	1.77	106
	After 3 months	295.10	27	1.68	136	287.63	31	1.39	80
	After 6 months	296.12	23	2.64	69	288.02	28	2.19	72

The data indicate no significant difference in the mechanical stability of the 3-months-old or 6-months-old tablets relative to those of the fresh tablets. At the same time, it is clear that there was a slight increase in the hardness of the Preparation 13 tablets. This was probably due to the after-hardening processes within the tablets, as the rearrangement of the binding mechanisms in the 3 months subsequent to compression resulted in a more solid inner texture. Table 21 also shows, however, that at 6 months a decrease, albeit minimal, in the hardness was measured. The explanation for this may be that, in spite of the careful storage, the tablets absorbed some water from the environment and therefore lost some mechanical stability.

There was a fair correspondence between the values of friability loss and disintegration time and those of hardness. Table 21 shows that the friability met the requirements of Ph.Hg.VII only in the case of the tablets prepared with hydroxypropyl cellulose (Klucel LF). In contrast, the disintegration time was always below 15 min and hence acceptable.

The above finding is supported by the changes in the tablet volume (Tables 22 and 23). In the

Table 22 - Change in volume (pressure force: 10 kN)

Preparations	Volume after 24 hours (mm^3)	Volume after 3 months (mm^3)	Volume after 6 months (mm^3)	Change in volume (a.24 h.-a.3 m.) (mm^3)	Change in volume (a.24 h.-a.6 m.) (mm^3)	Change in volume (a.24 h.-a.6 m.) (%)
Preparation 12	261.98	263.35	475.20	1.37	213.32	81.38
Preparation 13	265.83	262.61	578.08	-3.22	312.39	117.46
Preparation 14	244.41	246.26	731.53	1.85	487.12	199.30
Preparation 15	246.38	248.79	832.04	2.41	585.66	237.71

Table 23 - Change in volume (pressure force: 15 kN)

Preparations	Volume after 24 hours (mm^3)	Volume after 3 months (mm^3)	Volume after 6 months (mm^3)	Change in volume (a.24 h.-a.3 m.) (mm^3)	Change in volume (a.24 h.-a.6 m.) (mm^3)	Change in volume (a.24 h.-a.6 m.) (%)
Preparation 12	262.57	264.13	331.99	1.56	69.42	26.43
Preparation 13	253.49	253.23	674.42	-0.26	420.93	166.05
Preparation 14	242.66	243.92	773.32	1.26	530.66	218.68
Preparation 15	239.51	242.25	822.32	2.74	582.81	243.33

tablets prepared with hydroxypropyl cellulose, there was a considerable volume reduction after 3 months, which is in accordance with the increase in the hardness. In the other tablets, there was practically no volume change during 3 months. After 6 months, however, there was an excessive increase in the volume, which was manifested in the reduced hardness. This means that the tablets should be stored in a well-closed container, protected from the atmospheric humidity. Storage influenced the rate of dissolution of the active agent from the tablets as well (Tables 24-27).

Tables 24-27 - Drug liberation from the tablets

Preparation 12						
Time (min)	Pressure force: 10 kN			Pressure force: 15 kN		
	After 24 hours	After 3 months	After 6 months	After 24 hours	After 3 months	After 6 months
	Dissolved drug (%)					
0	-	-	-	-	-	-
5	16.60	17.42	13.16	18.33	13.02	13.77
10	27.67	27.63	24.24	31.64	27.58	27.97
20	40.29	43.21	41.95	43.87	48.23	44.92
30	53.01	58.53	57.22	68.20	60.57	57.57
60	74.95	79.66	74.91	85.13	87.13	75.55

Preparation 13						
Time (min)	Pressure force: 10 kN			Pressure force: 15 kN		
	After 24 hours	After 3 months	After 6 months	After 24 hours	After 3 months	After 6 months
	Dissolved drug (%)					
0	-	-	-	-	-	-
5	76.56	80.68	68.68	85.62	67.89	41.49
10	94.19	96.11	91.35	95.22	84.04	83.06
20	100.33	100.27	98.74	100.55	91.39	95.27
30	101.20	101.01	98.75	100.62	94.52	95.33
60	101.51	101.93	98.78	101.46	101.99	96.27

Preparation 14						
Time (min)	Pressure force: 10 kN			Pressure force: 15 kN		
	After 24 hours	After 3 months	After 6 months	After 24 hours	After 3 months	After 6 months
	Dissolved drug (%)					
0	-	-	-	-	-	-
5	67.76	73.21	70.93	71.79	73.67	66.15
10	80.98	85.53	81.53	91.58	88.77	78.11
20	92.46	94.45	83.63	99.07	98.40	78.46
30	96.97	98.71	84.47	99.58	101.51	79.81
60	98.55	101.08	88.69	102.04	102.52	85.65

Preparation 15						
Time (min)	Pressure force: 10 kN			Pressure force: 15 kN		
	After 24 hours	After 3 months	After 6 months	After 24 hours	After 3 months	After 6 months
	Dissolved drug (%)					
0	-	-	-	-	-	-
5	74.71	72.55	54.15	66.37	65.67	67.35
10	82.80	89.97	68.68	88.54	86.15	84.91
20	96.36	100.58	77.76	100.76	93.03	85.47
30	99.31	101.00	86.15	101.91	100.91	87.47
60	100.92	101.52	87.16	102.67	102.28	87.59

The data demonstrate that no change can be seen after 3 months, but the liberation of the drug decreased after 6 months.

IV. SUMMARY

Metronidazole consists of heterodisperse, stubby columnar crystals. Such a crystal shape results in unsuitable flow properties.

In wet granulation, the adequate wetting of the powder mixture is crucial, as this influences the uptake of the granulating fluid and hence the formation of a mass of suitable consistency and of the binding forces themselves.

The water-uptake capacity of metronidazole is rather poor, and must be improved by means of additives with a better water-uptake capacity (Avicel PH 101 or Kollidon CL).

Conventional (kneading) and fluidization methods were used to prepare granules with Povidone K-30. It was found that the same amount of binder resulted in harder tablets with slower drug release ($t_{63.2\%}$ = 45.63 min) when the preparation mode was kneading granulation ($t_{63.2\%}$ = 106.95 min). This means that the two methods require different binder contents.

Different cellulose derivatives with different surface activities were also chosen as binders. It was concluded that the best physical parameters and dissolution were achieved with tablets prepared with the use of hydroxypropyl cellulose at a pressure force of 10 kN.

The tablets should be stored in a well-closed container, protected from the atmospheric humidity.

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