Use of different cellulose derivatives for the preparation of tablets with a high active agent content

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Metronidazole tablets were prepared and the morphological and wder rheological parameters of metronidazole were tested. It was ncluded that the flow properties of the crystals were unsuitable, and t granulation was therefore preferred as the tablet manufacturing thod. Different cellulose derivatives (hydroxyethyl cellulose, droxypropyl cellulose, hydroxypropyl methylcellulose, thylhydroxy ethylcellulose) were chosen as binders. Granulation is performed with a fluid bed apparatus, and tableting with an centric tablet machine. The physical parameters of tablets and solution of the drug were tested. It was concluded that the best ysical parameters and dissolution were achieved with tablets epared using hydroxypropyl cellulose (Klucel LF) at 10 kN.

Des comprimés de métronidazole ont été préparés et les paramètres morphologiques étudiés. Les propriétés d'écoulement des cristaux n'étant pas adaptée, la granulation humide a été préférée pour préparer les comprimés. Différents dérivés cellulosiques (hydroxyéthyl cellulose, hydroxypropyl cellulose, hydroxypropyl méthylcellulose, méthylhydroxy éthylcellulose) ont été choisis comme liants. La granulation a été réalisée avec un appareil à lit fluidisé et les comprimés ont été préparés sur une machine à comprimer alternative. Les paramètres physiques des comprimés et la dissolution du principe actif ont été étudiés. Les meilleurs paramètres physiques et la meilleure dissolution ont été obtenus avec des comprimés contenant de l'hydroxypropyl cellulose (Klucel LF) à 10 kN.

y words: Metronidazole — Cellulose derivatives — Morphology — uid bed granulation — Powder rheology — Tableting — Physical rameters — Dissolution.

Mots clefs : Métronidazole — Dérivés cellulosiques — Morphologie — Granulation à lit fluidisé — Rhéologie — Compression — Paramètres physiques — Dissolution.

Several methods are available for tablet making. One ssibility is direct compression. Powder mixtures intended for rect compression should possess adequate fluidity and mpressibility. These may be influenced by the powder eological properties of the drugs. However, numerous aterials have unsuitable flow properties and compressibility. ese materials therefore require wet granulation prior to bleting. During this process, the quality of the granules is fected by a granulating fluid. Further, the quality of the tablets influenced by the parameters of the granules.

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

Metronidazole is a drug that is frequently used for the atment of various anaerobic infections. It is well absorbed llowing oral administration. The drug is useful as prophilaxis the context of obstetric and gynaecological interventions, lorectal surgery and appendectomy [1]. The usual oral dose 250 mg, and the tablets have a high active agent content. It has en discussed in various papers [2-4].

Different cellulose ethers are frequently used as binders in blet making involving wet granulation. They can increase hesion between particles, and therefore provide the tablets th satisfactory hardness. Many papers have been published the application of cellulose derivatives [5-7]. Increases in molecular mass and degree of substitution raise the viscosity their aqueous solutions. These solutions are among the non-Newton fluids [8]. Their water uptake is good and they can retain water. This capacity can be utilized very well to ensure the optimum moisture content of tablets [9-11]. They exhibit surface activity and can promote the dissolution of drug from the tablet [12, 13]. They can also be used as coating materials [14-16].

One option for wet granulation is fluidization. In a fluid bed apparatus, the particles are floated upwards under high air pressure. The granulating solution is sprayed in from above. The particles can adhere and fluid bridges can be formed, which will become solid bridges during drying.

I. EXPERIMENTAL DATA

1. Materials

Metronidazole (Ph. Eur. 3rd). Microcrystalline cellulose (Avicel PH 101) (FMC Corp., United States). Hydroxyethyl cellulose (Cellulose WP 4400 L) (Union Carbide Belgium NV). Hydroxypropyl cellulose (Klucel LF) (Hercules Inc., United States). Hydroxypropyl methylcellulose (Pharmacoat 603) (ShinEtsu Chemical Co., Ltd, Japan). Methylhydroxy ethylcellulose (Tylose MH 1000P) (Hoechst AG, Germany). Cross-linked povidone (Kollidon CL) (BASF Aktiensgesellschaft, Germany). Magnesium stearate (Ph. Eur. 3rd).

2. Methods

2.1. Homogenization

Powder mixing was performed with a Turbula mixer (Willy

A. Bachofen Maschinenfabrik, Basel, Switzerland) (50 r/min for 10 min).

2.2. Granulation

Granulation was performed using a fluid bed apparatus (Strea-1, Niro-Aeromatic AG, Switzerland). 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 r/min,;
- duration of process: 30-40 min.

2.3. Tabletting

Tabletting was carried out using a Korsch EK0 eccentric tablet machine (E. Korsch Maschinenfabrik, Germany) mounted with strain gauges, and a displacement transducer applied:
- 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,
- quantity compressed: 500 tablets,
- temperature of the machine table: 25.0-27.6°C at the start of compression, and 26.1-28.5°C at the end of compression,
- temperature of tablets: 30-32°C.

The compositions of tablets are presented in *table I.*

Table I - Composition of tablets (mg).

Components	Sample 1	Sample 2	Sample 3	Sample 4
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 1000P	-	-	-	3.34
Magn. stearate	2.65	1.8	1.76	1.66
Average mass	300.00	308.00	298.00	298.00

3. Test methods

3.1. Morphological study

A Hitachi S2400 (Hitachi Scientific Ltd, Japan) scanning electron microscope (SEM) was used. A polaron sputter coating apparatus (Polaron Equipment Ltd, UK) was applied to induce electric conductivity on the surface of samples. The air pressure was 1.3-13.0 mPa.

3.2. Particle size distribution

A Laborlux S light microscope and a Quantimet 500 (Q500MC) image processing and analysis system (Leica Cambridge Ltd, UK) were used. Before tests, the samples were dispersed in glycerine, because of their tendency to aggregate.

3.3. Mass by volume

This was tested using an ASTM apparatus (ASTM D 392-38) according to Ph. Hg. VII.

3.4. Flow properties

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

3.5. 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 [17].

3.6. Tablet testing

3.6.1. Uniformity of mass

The tablets were weighed on an analytical balance with an accuracy of 0.1 mg, and the variation in mass was then calculated.

3.6.2. Breaking hardness

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

3.6.3. Friability

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

3.6.4. Disintegration time

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

3.6.5. Dissolution rate

The rate of dissolution of metronidazole was studied using a rotary basket method:
- apparatus: Pharma Test PTWII (equipped with a rotary basket) (Pharma Test GmbH, Germany),
- dissolution medium: 900 ml artificial gastric juice (pH 1.2 ± 0.1),
- temperature: 37 ± 0.5°C,
- rotation speed: 50 r/min,
- sampling time: 5, 10, 20, 30, 60 min,
- number of tablets: 6,
- measurement: at 277 nm with a UV spectrophotometer (Spectromom 195D, MOM, Budapest, Hungary).

II. RESULTS AND DISCUSSION

1. Metronidazole crystals

The results of morphological studies can be seen in *figure 1.* It can be stated that metronidazole consisted of heterodisperse, stubby columnar crystals. Most crystals had a length in the range 10-30 μm, and a breadth in the range 5-20 μm (*figure 2*). In accordance with the roundness value (*table II*), this crystal shape results in unsuitable flow properties. Roundness is a shape factor that provides information on the circularity of particles. It is calculated by software according to the following formula [18]:

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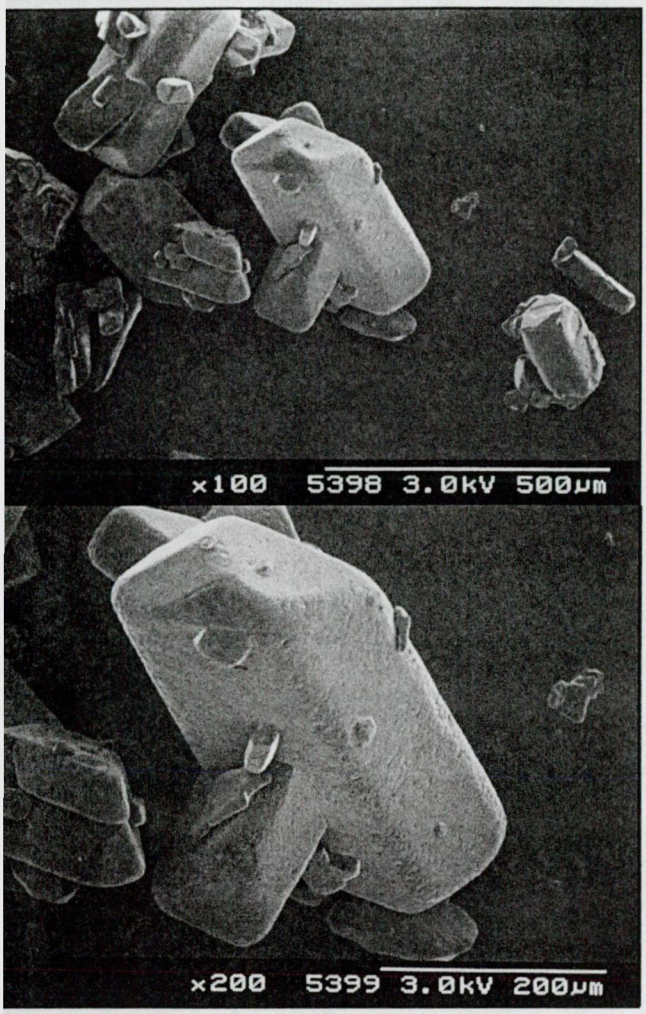

gure 1 - Metronidazole crystals (SEM) x 100 (top) and x 200 (bottom).

ble II - Particle size of metronidazole crystals.

	Length (µm)	Breadth (µm)	Roundness
Average	31.279	18.416	1.427
Std.	30.624	19.211	0.333
Minimum	4.154	17.780	1.049
Maximum	280.0	168.235	3.688

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

The perimeter is calculated from the horizontal and vertical ojections, with an allowance for the number of corners. An justment factor of 1.064 corrects the perimeter for the effect the corners produced by digitization of the image.

Roundness influences the flowability of the materials, and therefore an important parameter. When its value is close to ıe, the particles are close to spherical. The shape can be ›served from SEM pictures, but the degree of sphericity can only obtained from this parameter.

Granules

The rheological parameters of granules were influenced by e binder used (*table III*). With the exception of the angle of

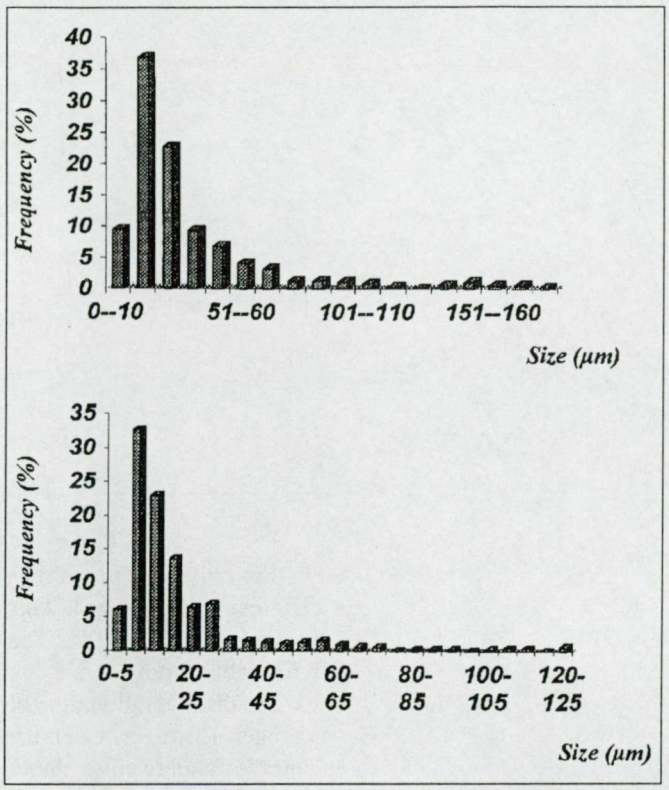

Figure 2 - Particle size distribution of metronidazole crystals by length (top) and breadth (bottom).

Table III - Rheological parameters of granules.

Samples	Flowing time (s)	Angle of repose (°)	Mass by volume (g/100 ml)	Hausner factor	Carr's index (%)
M	23	37.3	65.0	1.15	13.33
S 1	11	40.6	36.0	1.05	4.99
S 2	11	41.6	28.3	1.05	5.02
S 3	14	39.1	38.0	1.10	8.69
S 4	11	38.6	41.3	1.04	4.00

M: metronidazole. S: sample.

repose, it was seen that all parameters were improved relative to metronidazole alone. The mass by volume and flow time were decreased. Data on the angle of repose were unchanged or even increased a little, but this can be corrected by the application of a glidant before tableting.

The Hausner factor and Carr's index revealed excellent compactibility and compressibility after granulation. These data were calculated from the loose and tapped volumes, in accordance with the literature.

3. Tablets

The data are presented in *table IV*. In all cases, uniformity of mass was within the limited range according to Ph. Hg. VII [19]. It can be seen that this value was best for Sample 2, which was prepared using hydroxypropyl cellulose (Klucel LF).

The hardness of tablets prepared using hydroxypropyl cellulose (Klucel LF) was the most satisfactory. The hardness of other tablets was too low. A small increase in hardness was

Table IV - Physical parameters of tablets.

Samples	Average mass (mg)	Uniformity of mass (mg)	Friability (%)	Breaking hardness (N)	Disintegr. 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

S: sample.

observed at higher pressure levels, but only with the tablets prepared using hydroxypropyl cellulose (Klucel LF). This conclusion was in accordance with friability results. The disintegration time was longest for tablets prepared using hydroxyethyl cellulose (Cellosize). The disintegration time of tablets compressed at 10 kN was longer. However, when the pressure was increased, 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 tablets. Dissolution of the drug was very rapid (100% within 10-20 min), except with tablets prepared using hydroxyethyl cellulose (Cellosize) (*figure 3*). Dissolution from this tablet was slow and uniform. Furthermore, an increase in the pressure had practically no influence on the dissolution rate of the drug.

Overall, it can be concluded that the best physical parameters and most rapid dissolution were achieved with the tablets prepared using hydroxypropyl cellulose (Klucel LF) at 10 kN.

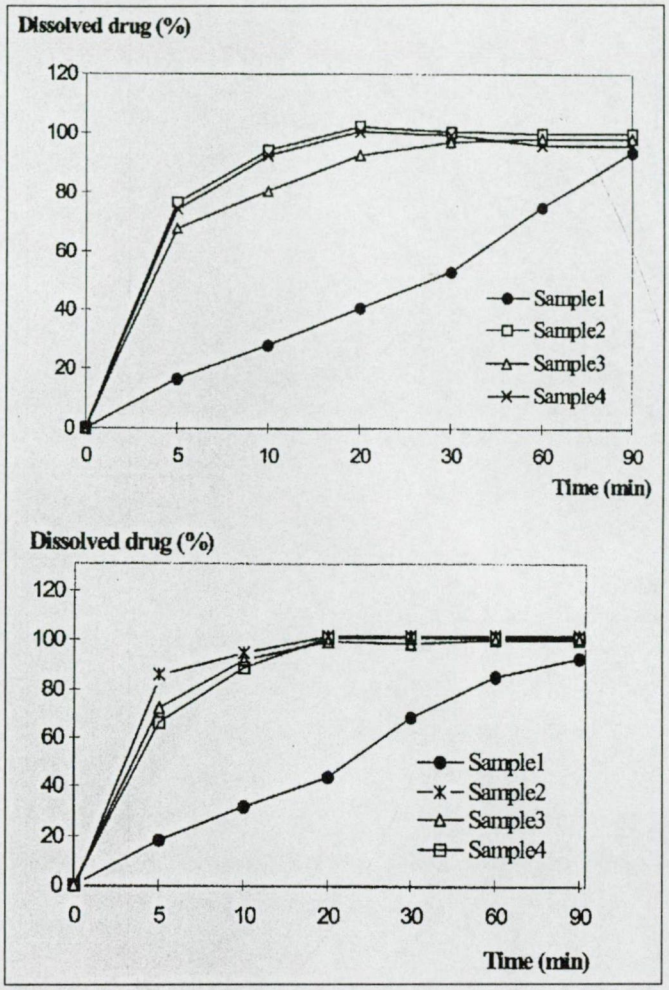

Figure 3 - Dissolution rate of metronidazole from tablets. Pressure: 10 kN (top) and 15 kN (bottom).

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ACKNOWLEDGMENTS

This work was supported by OTKA T026351 grant.

MANUSCRIPT

Received 6 July 1999, accepted for publication 9 September 1999.

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Received August 31, 1999
Accepted November 15, 1999

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Mathematical evaluation of the dissolution of metronidazole from tablets

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Metronidazole 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 [1]. The single oral dose is generally 250 mg, and the tablets have a high active agent content. Its use has been discussed in various papers [2–4].
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 amounts of excipients must be applied.
The flow properties of metronidazole crystals are unsuitable, and wet granulation was therefore, selected as tablet manufacturing method. Different cellulose derivatives were chosen as binders. They exhibit surface activity and can promote the dissolution of the drug from the tablet [5]. The compositions of the tablets are listed in Table 1. Granulation was performed with a fluid bed apparatus, and tableting with an excentric tablet machine. The metronidazole dissolution rate was studied with a rotary basket method.

Table 1: Composition of the tablets

Components	Preparation 1 (mg)	Preparation 2 (mg)	Preparation 3 (mg)	Preparation 4 (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 1000P	–	–	–	3.34
Magnesium stearate	2.65	1.8	1.76	1.66
Average mass	300.00	308.00	298.00	298.00

The aim of this work was to study the rate of dissolution of the drug from the tablets and to evaluate the results mathematically. Mathematical evaluation of the dissolution process is known from the literature [6, 7].
The results for metronidazole were evaluated according to 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 [8]:

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

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 sigmoid curve can be seen. This means that a slow release is followed by faster dissolution.
Linearized regression from parameters β and a without T gives:

$$\ln \ln \frac{M_0}{M_0 - M} = \beta \cdot \ln t - \ln a, \qquad (2)$$

where β is slope; ln a is intercept.
After transformation according to Langenbucher:

$$\ln a = \beta \ln t_{63.2\%};\ t_{63.2\%} = 10^{-a/\beta} \qquad (3)$$

where $t_{63.2\%}$ is the characteristic dissolution time.
Regression analysis was carried out with the Statgraphics package (Copyright STSC, Inc. and Statistical Graphics Co., USA); the confidence limit was 95%.
The results are presented in Table 2. It can be seen that the characteristic dissolution time was very short for preparations 2, 3 and 4. For these tablets, 63.2% of the metronidazole were released from the tablets within 5 min. The correlation coefficients were close to 1. On the basis of the shape parameter (β), it can be supposed that for preparations 1 and 3 drug release followed first-order kinetics with $\beta = 1$, but in the other cases the dissolution processes were of exponential type.

Table 2: Characteristical dissolution time

Preparations	$t_{63.2\%}$ (min)	Slope (β)	Intercept (lna)	Correlation coefficient (r) $p < 0.05$
Preparation 1				
10 kN	26.27	0.9908	−3.2388	0.9941
15 kN	29.31	0.9438	−3.1883	0.9951
Preparation 2				
10 kN	4.03	1.3332	−1.8570	0.9879
15 kN	3.06	1.1238	−1.2561	0.9715
Preparation 3				
10 kN	3.63	1.0435	−1.3458	0.9832
15 kN	4.08	1.0562	−1.4850	0.9988
Preparation 4				
10 kN	4.70	1.3721	−2.1246	0.9196
15 kN	5.13	1.5396	−2.5185	0.9795

It may be concluded that a fast release of metronidazole can be achieved with tablets prepared with hydroxypropyl cellulose (Klucel LF). The tablets prepared with other cellulose derivatives had longer characteristic dissolution times, i.e. a slow dissolution of the drug.

Experimental

1. Materials

Metronidazole (Ph. Eur. 3rd), corn starch (Ph. Eur. 3rd), microcrystalline cellulose (Avicel PH 101) (FMC Corp., USA), 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), methylhydroxy ethylcellulose (Tylose MH 1000P) (Hoechst AG., Germany), cross-linked povidone (Kollidon CL) (BASF Aktiengesellschaft, Germany), magnesium stearate (Ph. Eur. 3rd) were used.

2. Methods

Powder mixing was performed with a Turbula mixer (Willy A. Bachofen Maschinenfabrik, Switzerland) (50 rpm for 10 min).
Granulation was performed with a fluid bed apparatus (Strea-1, Niro-Aeromatic AG., Switzerland). The powder mass was 293 g.
Parameters: Atomizing pressure: 2.0 bar, blow-out pressure: 4.5–5.0 bar, drying temperature: 60 °C, outlet temperature: 40 °C, peripump speed: 10–12 ml/min, duration of process: 30–40 min.
The tableting was carried out with a Korsch EK0 eccentric tablet machine (E. Korsch Maschinenfabrik, Germany) mounted with strain gauges, and a displacement transducer was applied. 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 machine table: 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.
The rate of dissolution of metronidazole was studied with a Pharma Test PTWII apparatus (Pharma Test GmbH, Germany) equipped with a rotary basket.
Test conditions: Dissolution medium: 900 ml artificial gastric juice (pH = 1.2 ± 0.1), temperature: 37 ± 0.5 °C, rotation speed: 50 rpm, sampling time: 5, 10, 20, 30, 60 min, number of tablets: 6, measurement: at 277 nm with an UV spectrophotometer (Spektromom 195D, MOM, Hungary). The regression analysis was carried out with the 6 parallel values. Standard deviations were 2–10% at 10 kN compressed tablets, and 1–7% at 15 kN compressed tablets.

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Received July 22, 1999
Accepted November 15, 1999

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HUNGARIAN JOURNAL
OF INDUSTRIAL CHEMISTRY
VESZPRÉM
Vol. 28. pp. 117 - 120 (2000)

INFLUENCE OF THE GRANULATING PROCESS ON THE PARAMETERS OF TABLETS

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Received: August 31, 1999

The aim of this work was to study the influence of the granulating method on the parameters of tablets. Metronidazole tablets were prepared with Povidone K-30 as binder. The morphological and powder rheological parameters of metronidazole were tested. It was concluded that the flow property of the crystals was unsuitable, and wet granulation was therefore preferred as manufacturing method. Granulation was performed with a fluid bed apparatus and a high-speed mixer; tabletting was carried out with an eccentric tablet machine. The physical parameters of tablets and the rate of dissolution of the drug were tested. It was concluded that better physical parameters and better dissolution features were attained with tablets prepared with the fluid bed apparatus.

Keywords: metronidazole; fluid bed granulation; compactibility; compressibility; dissolution

Introduction

A number of methods are available in tablet making. One possibility is direct compression. 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 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. The preparation of tablets with a high active agent content is particularly difficult. The aim is not to increase the weight of tablets during tablet making. The only way to achieve this is to use the smallest amount of excipients.

One possibility for wet granulation is the kneading process. After homogenisation 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 [1-4].

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 be come solid bridges during drying [5,6].

Experimental

Materials

Metronidazole (Ph. Eur. 3rd) 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 [7]. The simple oral dose is generally 250 mg, and tablets have a high active agent content. It has been discussed in various papers [8-10].

Microcrystalline cellulose (Avicel® PH 101) (FMC Corp., Philadelphia, USA) is a white, odourless, tasteless powder. It is virtually water-insoluble, it has a high binding capability and in enhances the compression of other excipients [11]. It exhibits a low Young modulus and would be classified as ductile rather than brittle [12].

Povidone® K-30 (ISP, Belgium) is a fine, white to creamy-white, odourless, hygroscopic powder. It is used in a variety of pharmaceutical formulations, primarily in solid dosage forms. In tableting, povidone solutions are used as binders in wet granulation processes. Povidone is also added to powder blends in the dry form and granulated *in situ* by the addition of water, alcohol or hydroalcoholic solutions. Povidone solutions may also be used as coating agents. As a tablet binder, tablet diluent or coating agent, it is used in concentration of

0.5-5.0%. It is very hygroscopic, significant amounts of moisture being absorbed at low relative humidity. In water, the concentration of its solution is limited only by the viscosity of the resulting solution, which is a function of the K value. The dynamic viscosity of aqueous povidone solutions depends on both the concentration and the molecular weight of the polymer employed. (The dynamic viscosity of 10% w/v aqueous Povidone K-28/32 solutions at 20 °C is 5.5-8.5 mPa s) [13].

Cross-linked povidone (Kollidon® CL) (BASF) is a white, odourless, tasteless, fine granulous powder with good flow characteristics. It is a super-disintegrant, used in 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 [14]. The resulting swelling pressure breaks up tablets [15].

Magnesium stearate (Ph. Eur. 3rd) 0.5 w/w % was applied as lubricant. This material was chosen because it is probably the most widely-used lubricant [16] and is known to have excellent lubricating and good antiadherent properties. However, it exhibits little glidant action [17].

Methods

Homogenisation

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

Granulation

The same quantities of components were used in both granulating processes.

Sample 1 was prepared with a fluid bed apparatus (Strea-1, Niro-Aeromatic AG., Switzerland).

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
Duration of process:	30-40 min

For Sample 2, the ingredients of the granules were blended in a high-speed mixer (Keripar, Tatabánya, Hungary) for 2 min. After the addition of Povidone K-30 solution, the 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% [18].

Tabletting

Tabletting was carried out with a Korsch EK0 eccentric tablet machine (E. Korsch Maschinenfabrik, Germany) mounted with strain gauges, and a displacement transducer was applied.

Table 1 Composition of Tablets

Materials	Samples, (mg)
Metronidazole	250.00
Avicel PH 101	33.00
PVPP	5.00
PVP K-30	23.20
PVPP	2.00
Mg-stearate	1.80
Average mass	315.00

Pressure force: 15±1.5 kN

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^{-1}
Compressed quantity: 500 tablets

Temperature of Table of Tabletting machine:
at the start of compression: 25.0-27.6 °C
at the end of compression: 26.1-28.5 °C

Temperature of Tablet: 30-32 °C

The compositions of tablets are presented in *Table 1*.

Test Methods

Morphological Study

A Hitachi S2400 (Hitachi Scientific Ltd, Japan) scanning electron microscope (SEM) was used. A polaron sputter coating apparatus (Polaron Equipment Ltd, UK) was applied to induce electric conductivity on the surface of samples. The air pressure was 1.3-13.0 mPa.

Powder Rheology

Mass by Volume: This was tested with an ASTM apparatus (ASTM D 392-28) according to Ph. Hg. VII.

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

Compactibility and Compressibility Tests: Calculations were based on the loose and tapped densities. A tap density volumeter (Stampfvolumeter 2003, J. Engelsmann AG Apparatebau, Germany) was used for the determinations according to the literature [19].

Test of Tablets

Uniformity of Mass: Tablets were used weighed on an analytical balance, with an accuracy of 0.1 mg, and the variation in mass was then calculated.

Breaking Hardness: The breaking hardness of tablets was measured on a Heberlein apparatus (Heberlein & Co. AG., Switzerland).

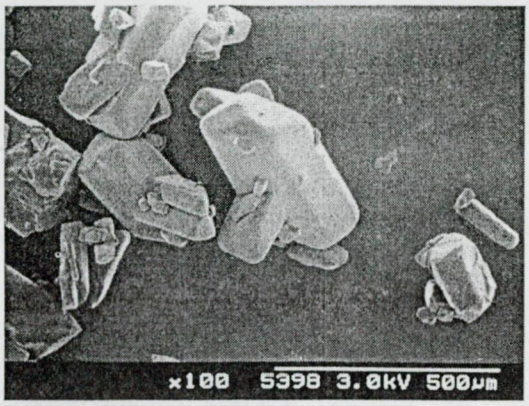

Fig.1 Metronidazole crystals (SEM)

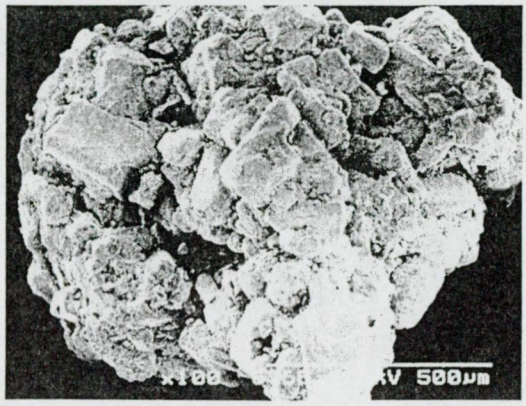

Fig.2 Sample 1 granule (SEM)

Table 2 Rheological parameters of the granules

Samples	Flowing time, s	Mass by volume, g cm^{-3}	Angle of repose, deg.	Carr's index, %	Hausner-factor
Metronidazole	23	0.65	37.3	13.33	1.15
Sample 1	10	0.37	39.6	4.66	1.04
Sample 2	10	0.47	33.7	6.67	1.07

Height: The height of tablets was measured with a screw micrometer (Mitutoyo Corp., Japan).

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

Disintegration Time: This was determined for 20 individual tablets, using an Erweka VZ4 disintegration tester (Erweka Apparatebau GmbH, 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 cm^3 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)

Results and Discussion

The SEM study revealed that metronidazole consisted of heterodisperse, stubby columnar crystals (*Fig.1*). This crystal shape results in unsuitable flow properties (*Table* 2), but the shape of the granules (*Figs.2* and *3*) leads to better powder rheological parameters (*Table* 2). The conventional granule consists of larger particles (*Fig.2*) and the fluid granule of smaller particles (*Fig.3*). Adhering crystals can be observed in each granule particle.

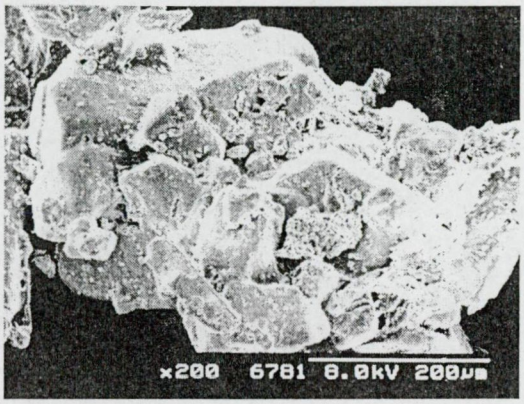

Fig.3 Sample 2 granule (SEM)

The rheological parameters demonstrated that, with the exeption of the angle of repose, all the parameters were improved relative to those of metronidazole alone. The mass volume and the flow time were decreased. The angle of repose was increased a little in the case of Sample 1 and decreased in the case of Sample 2. The reason for this lies in the particle size and shape. The Sample 2 granule consists of larger particles, but the sphericity is better, and the flowability is therefore also better. This value can be corrected by the use of some glidant. The value for Sample 2 is suitable, and thus the use of some glidant is not necessary.

The data in tablets are presented in *Table* 3. The uniformity of mass is in every case in the limiting range according to Ph. Hg. VII [20]. It can be seen that this value was better for Sample 1, which was prepared with the Strea-1 fluid bed apparatus. The hardness of tablets was better for Sample 2, which was prepared by the conventional method, than for Sample 1. This was in accordance with the friability results. The disintegration time of tablets was too long: more than 15 minutes. It can be observed in *Fig.4* 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 Sample 1 tablet.

Table 3 Physical parameters of tablets

Samples	Uniformity of mass, g	Breaking hardness, N	Disintegration time, min	Friability, %
Sample 1	0.3131 $s = 0.0020$	54	<15	1.16
Sample 2	0.3024 $s = 0.0061$	80	<15	1.04

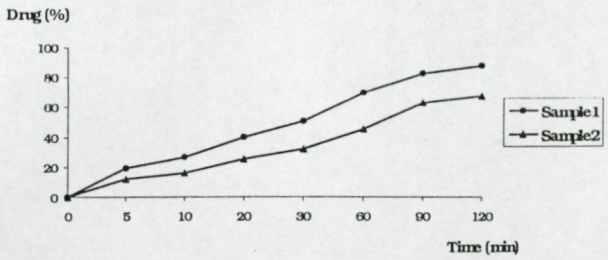

Fig.4 Dissolution of metronidazole from tablets

The results on the rate of dissolution of metronidazole were evaluated via Rosin-Rammler-Sperling-Bennett-Weibull (RRSBW) distribution, and the characteristic dissolution time ($t_{63.2\%}$) was determined after linearized regression and formation according to Langenbucher [21, 22].

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 4*. It can be seen from the data that the characteristic dissolution time is shorter for the Sample 1 tablet. The reason lies in the lower hardness of this tablet. The solid bridges can break more easily and the drug can be released faster. On the basis of the shape parameter (β), it can be concluded that an exponential process is involved. This means that a fast drug release is followed by a slow saturated process.

Table 4 Mathematical evaluation of dissolution

Samples	$t_{63.2\%}$, min	Shape parameter, Slope β	Intercept, ln *a*	Correlation coefficient, $r, p < 0.05$
Sample 1	45.63	0.7441	-2.8429	0.9977
Sample 2	106.95	0.7080	-3.3084	0.9949

Conclusions

It was concluded that the flow properties of the crystals were unsuitable, and wet granulation was therefore preferred as tablet manufacturing method. As indicated by the powder rheological parameters, the flow time of the granules was shorter, and the compactibility and compressibility were excellent.

It can be stated that the granulation process influenced the parameters of tablets. Tablets prepared by the kneading process had a higher hardness and displayed a lower drug release. This means that the fluidization method, where the mechanism of particle formation is different, needs a greater quantity of binder for the same physical parameters of tablets to be attained.

Acknowledgement

This work was supported by OTKA T-026351 grants.

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were obtained from Merck (Darmstadt, Germany), ammonium acetate was obtained from Balex (Pardubice, Czech Republic), acetic acid from Lachema (Neratovice, Czech Republic), water was purified by Osmium™ and Elix™ system (Millipore Corporation, MA, USA). All reagents used were of analytical-reagent grade.

2. *Chromatography conditions*

The HPLC consisted of an isocratic pump HPP 5001 (Laboratory Instruments, Prague, Czech Republic), a detector Waters™ 486 and data module Waters 746 (Waters Corporation, Milford, MA, USA), a LCI 30 injection valve (ECOM, Prague, Czech Republic) with a 10 µl loop. Analyses were performed on a column 5 µm SGX C18 (150 × 3mm I.D., Tessek, Prague, Czech Republic). The optimal mobile phase was a mixture of acetonitril/20 mM ammonium acetate, pH = 5.5 (20 : 80). The flow rate was set at 0.5 ml/min. The UV absorbance was monitored at 273 nm.

3. *Preparation of standard solutions*

Stock standard solution of caffeine and paracetamol (IS) were prepared in methanol by dilution of 0.2 mg/ml and 28 mg/ml, respectively. Calibration standards were prepared by volumes of stock standards solution of caffeine and IS (concentration range 20–120 µg/ml for caffeine).

4. *Sample preparation*

One ml of the pharmaceutical preparation was pipeted into a 50 ml volumetric flask, 1ml of solution of IS was added and diluted to the mark with methanol. The sample was placed in an ultrasonic bath for 5 min and after sonication was filtered with SPARTAN 30/B 0.45 µm.

This work has been supported by Internal Grant Agency of Charles University No. CEZ : J13/98 : 11600001, No. CEZ : J13/98 : 11600003 and No. 29/1998/B CH/FaF.

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Received October 11, 1999
Accepted December 15, 1999

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Measurement of film thickness on the surface of coated pellets and its influence on drug dissolution rate

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Film-coated solid dosage forms, e.g. pellets and tablets, are currently of increasing importance. An appropriate coating fluid applied to a pellet surface produces a macromolecular film coat, the properties of which will influence the pellet parameters and the liberation of drug from the pellets and from the tablets manufactured from them [1–5].

The thickness of this film influences the kinetics of dissolution of the drug. For this reason, characterization of such a film is of great importance. Such measurements are very easy in the case of tablets. It is possible to measure the geometrical parameters of the tablets with a screw micrometer before and after the coating process. Application of this method is not possible in the case of pellets because of the smallness of the particles [6]. Therefore, the aim of the present work was to investigate another method for thickness measurement and the influence on the drug dissolution rate.

An image analysis method was used to determine the thickness of the coating films. Before the determination, a sieved range of pellets (0.63–0.75 mm) was selected. This separated fraction was coated. The diameters of the pellets were measured before and after coating. Three series of coated pellets were prepared. Each series consisted of three batches and the same mass of pellet core (200 g) was used in each batch. In the first group of batches, 100 g of different coating dispersion was sprayed onto the pellet core. In the second group of batches, 200 g of coating dispersion was used. In the third group of batches, 300 g of coating dispersion was sprayed onto the pellet core. Finally, 400 g of coating dispersion was used. The dry material content of the dispersions was different. The results of the film thickness measurements are presented in Fig. 1.

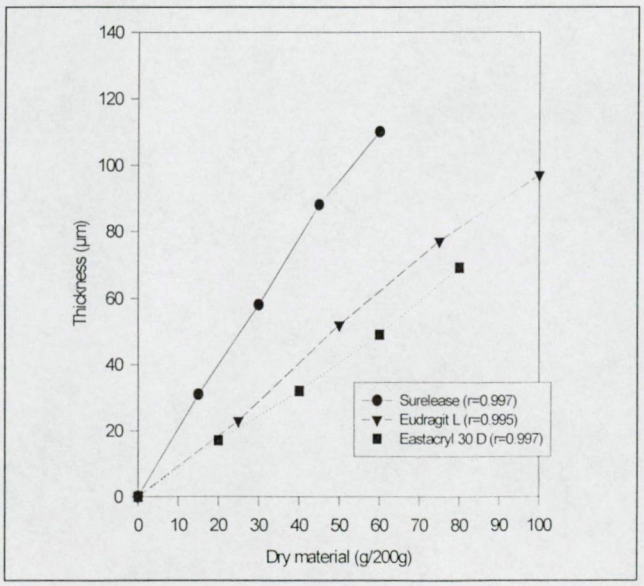

Fig. 1: Relationship between film thickness and dry material content of coating dispersion

There is a linear relationship between the thickness of the film formed and the dry material content of the coating dispersion. It can further be stated that the coating material influences the film thickness. As an example, at the same dry material content, the film formed in the case of Surelease was almost twice as thick as that formed in the case of Eastacryl.

The results of the dissolution tests demonstrated the influence of the nature and the quantity of the coating material on the release of the drug (Fig. 2). The polymethacrylate film (Eudragit) with the lowest dry material content proved to be protective film. Increase in dry material content of the coating dispersion led to a slower 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. The dissolution profile in the case of Eastacryl film was similar.

It can further be concluded that a lower Surelease quantity was sufficient to attain a slow-release coated pellet. The dissolution started in the gastric juice, because of the pH-independence, but an increase of the dry coating material content hindered total liberation of the drug during 7 h.

The results relating to the rate of dissolution of theophylline were evaluated via Rosin-Rammler-Sperling-Bennett-Weibull (RRSBW) distribution. The shape parameter (β), the time parameter (a) and the characteristic dissolution time ($t_{63.2\%}$) were determined after linearized regression and Langenbucher transformation [7, 8]. $\beta = 1$ 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 sigmoid curve can be seen. In this case a slow release is followed by faster dissolution. In all cases the correlation coefficients were close to 1.0, indicating that the data points fit well to a straight line.

The characteristical dissolution time increased with the increase of film thickness. An almost linear active agent release was found for pellets with a Eudragit L coating with a film thickness of 23 µm, but for pellets with a film thickness of 52 µm a tendency to a sigmoid curve can be seen. Drug release at an initially low but later increasing rate was only seen for the Eudragit coatings. This was due to the enteric property of the coating materials. The coating film is dissolved and the drug is released not at the pH of the gastric fluid, but only in an alkaline medium corresponding to the enteric fluid. The β values of Surelease coatings are of particular interest. The dissolution profile of the drug does not depend on the dry coating material content, because in this case the drug is liberated by diffusion through the coating.

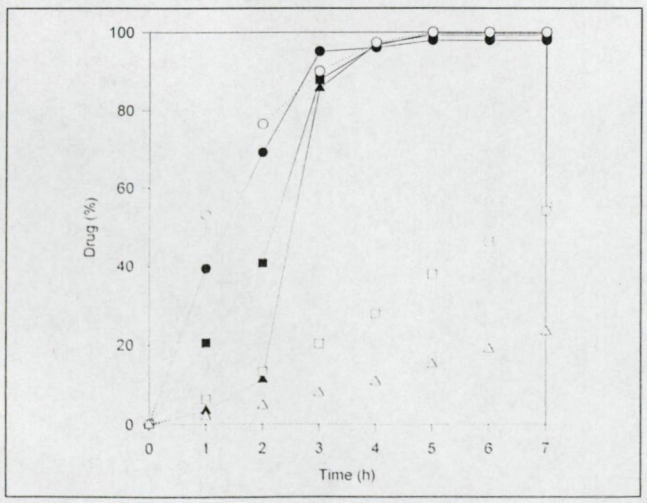

Fig. 2: Dissolution of theopylline from coated pellets
—●— Eudragit L 23 µm (β = 1.026; $t_{63.2}$ = 79 min),
—■— Eudragit L 52 µm (β = 1.429; $t_{63.2}$ = 118 min),
—▲— Eudragit L 77 µm (β = 2.892; $t_{63.2}$ = 161 min),
····○··· Surelease 29.5 µm (β = 1.335; $t_{63.2}$ = 70 min),
····□··· Surelease 60 µm (β = 1.052; $t_{63.2}$ = 453 min),
····△··· Surelease 90 µm (β = 1.018; $t_{63.2}$ = 986 min),

Experimental

1. Materials

Theophylline pellets as core, Eudragit® L 100–55 (Röhm GmbH Chemische Fabrik, Darmstadt, Germany), Eastacryl® 30 D (Eastman Chemical Company, Kingsport, USA), Surelease® (Colorcon Ltd., Orpington, UK) as coating polymer were used.

2. Methods

Coating was performed with a fluid bed apparatus (Strea–1 fluid bed apparatus with a Wurster container, Niro-Aeromatic, Bubendorf, Switzerland). Different masses of coating dispersion were applied.

Pellet core: 200 g of theophylline pellets (20% of theophylline, 30% of mannit, 50% of Vitacel A300® (Rettenmaier & Söhne Faserstoff-Werke, Ellwangen-Holzmühle, Germany)).

Coating dispersions: Eudragit L (LatexA: Eudragit L 100–55: 300 g, sodium hydroxyde 0.1 n 100 g, distilled water 750 g, silicone emulsion 20 drops; coating dispersion: Latex A 500 g, Macrogol 6000 25 g, distilled water 150 g, talc 33.75 g); Eastacryl (Eastacryl 30D 64.4 g, distilled water 28.8 g, triethyl citrate 1.9 g, talc 4.7 g, silicone emulsion 10 drops); Surelease (Surelease 180 g, talc 15 g, distilled water 120 g).

Coating parameters: Drying temperature: 40 °C, outlet temperature: 30 °C, atomizing pressure: 2 bar, blow-out pressure: 5 bar, peripump speed: 2 ml/min, nozzle: 1.0 mm in diameter, drying time: 5 min (at the end of the process).

Film thickness measurement: A Laborlux S light microscope and a Quantimet 500 MC (Q 500 MC) image processing and analysis system (Leica Cambridge Ltd, Cambridge UK) were used. Product fraction: DIN sieves 0.63 and 0.75 mm in hole diameter.

Dissolution of active agent: The rotating basket method with half change was used. The test was started with artificial gastric fluid, one half of which was changed to intestinal fluid every hour [9]. In this way, the pH changes were similar to those seen in the digestive tract (0–1 h: pH = 1.18; 1–2 h: pH = 1.91; 2–3 h: pH = 6.24; 3–4 h: pH = 6.92; 4–5 h: pH = 7.22; 5–6 h: pH = 7.39; 6–7 h: pH = 7.48).

Test conditions: Apparatus: Pharma Test PTW II (equipped with a rotary basket) (Pharma Test GmbH, Germany), basket speed: 50 rpm, temperature: 37 ± 1 °C, dissolution medium volume: 900 ml, samples taken at 1, 2, 3, 4, 5, 6 and 7 h, measurements: with an UV spectrophotometer (Spectromom 195D, MOM, Budapest, Hungary) at 268 nm for pH = 1.18 to 1.91, at 270 nm for pH = 6.24 to 6.92 and at 271 nm for pH = 7.22 to 7.51. Computerized data processing: SPSS for Windows 6.1.2.

This work was supported by OTKA T–023029 grants.

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Received September 27, 1999
Accepted January 15, 2000

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HUNGARIAN JOURNAL
OF INDUSTRIAL CHEMISTRY
VESZPRÉM
Vol. 28. pp. 111 - 115 (2000)

STUDY OF THE INFLUENCE OF POLYMER COATING FILMS ON DRUG RELEASE

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Received: July 15, 1999

The influence of polymer coating films were tested on drug liberation from pellets. The results relating to the rate of dissolution of drug were evaluated mathematically. 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 Wurster container. The surface of uncoated and coated pellets was investigated by scanning electron microscope (SEM). It was concluded that a suitable and uniform coating film is formed on the spherical pellet surface. Moreover, it was established that drug was most rapidly liberated from pellets coated with Eudragit film containing 25 g of dry material. Surelease films of the same thickness liberated the active agent much more slowly than did polymethacrylate film.

Keywords: theophylline; pellet; film coating; Wurster's principle; dissolution; RRSBW-distribution

Introduction

Film-coated solid dosage forms, e.g. pellets and tablets, are currently of increasing importance. Pelletization is a form of wet granulation where granulate particles are gradually built up from the pulverized raw material under the influence of a granulating fluid (a colloidal macromolecular solution). Pelletization may be necessary to improve the compressibility of materials not directly processible into tablets. Pellets, however, can also fill in capsules. An appropriate coating fluid applied onto the pellet surface produces a macromolecular film coat, the properties of which will influence the parameters and the drug liberation from the pellets and Tablets manufactured from them, so that preparations with controlled drug release can potentially be made.

Film coating can be performed by various types of technology and equipment [1]. In the procedure, the granules are kept in motion and the coating fluid is sprayed onto them.

The atomizer utilised can be:

- pneumatic, with the use of compressed air;
- rotational, with the use of a swiftly spinning atomizer rotor;
- a special spray head, atomizing the fluid fed in at high speed into small droplets.

The granules can be moved:

- mechanically, or
- by fluidization.

Film coaters working mechanically are the following:

- rotating drum,
- pelletization disk,
- centrifugal granulator,
- dragée pan.

In this, the coating fluid can be applied by an atomizer head placed over or submerged into the core bed.

In coating based on fluidization, the granules are moved by the compressed air fed in [2]. The coating fluid can be applied into the container by upper spraying or by Wurster's principle. In the latter, both fluidizing air streams and atomizing air are introduced from below. This principle is realised for example, in the Strea-1 fluidizer, which is suitable for upper spraying and, on change of the coating column, for Wurster coating. Wurster's principle is at present widely applied in pharmaceutical technology [3-6].

In this process, there may be two possibilities for the coating of dosage forms: gastric film coating or enteric film coating.

The aim of gastric solvent film formation may be the protection of an active agent (light, air humidity, etc.) or the masking of an unpleasant taste. Chemicals widely used in the production of gastric coatings include polyethylene glycol derivatives and different cellulose derivatives in dilute aqueous or alcoholic solution.

These substances, e.g. polyethylene glycol and macrogol, can also be combined. Further macromolecules, such as polyvinylpyrrolidone (PVP) or polyvinyl alcohol (PVA) are also used for this purpose [7].

Polymethacrylates are other up-to-date film coatings, sold under different registered names. For gastric coating, for instance, primarily Eudragit E is used, dissolved in organic solvents. It can be used for taste masking or for making a protective coat against atmospheric moisture [8]. In the literature, 2 mg cm^{-2} of Eudragit E quantity is suggested on the surface for protective coating, and 4-8 mg cm^{-2} for taste masking [9]. More recently, aqueous dispersions are preferred (e.g. Eudragit E 30D), with a solid content of 28.5-31.5% [10].

Enteric coatings are needed in the following cases:

- to protect the stomach against the irritating effect of a drug;
- to protect a drug against the gastric acid;
- to eliminate the discomforting effect of substances interfering with the gastric digestion;
- to achieve a retard action;
- to limit the action of the agent to the intestinal fluid (local action).

Of all these applications, the use of film coatings to achieve a retard action are of primary interest here. The majority of current research on coatings is directed to this topic.

In the manufacturing of an enteric coating, the following physiological factors are to be considered [11]:

- the dwell time of the given dosage form in the stomach and in the different intestinal sections;
- the pH of the gastric and intestinal fluids;
- the effects of the enzymes of the digestive tract on the coating.

As concerns the passage through the gastrointestinal system, solid dosage forms dwell in the empty stomach 30-45 min. After a meal, this time is prolonged to 90 to 180 min [12]. The dwell time in the small intestine is 4.5 to 6 h, and that in the large intestine is 8 to 12 s [13].

In earlier times, shellac was the material most commonly used for enteric coatings. Today, the most important are the cellulose derivatives - primarily cellacephate, a cellulose ester involving acetic and phthalic acids. The plasticity of the coating is often increased by the use of a plasticizer such as polyethylene glycol, 1,2-propylene glycol, dimethyl phthalate, dibutyl phthalate, triacetine, castor oil, etc. [14, 15].

Of the new kinds of coatings, certain *polymethacrylates* are often used. The best known of them here too are Eudragit products. The aqueous Eudragit dispersions developed in 1972 broadened the field of use of these coating materials to a considerable extent.

To make enteric coatings, Eudragit L or S can be used [16-18]. Both are anionic polymerates of methacrylic acid and methacrylic esters. The low viscosity of the aqueous dispersion of the acrylic resin permits a combination with pigments and other additives up to 40% solid content [19].

Films made from an aqueous dispersion of Eudragit L 100-55 start to dissolve above pH 5.5, while those made from a solvent solution of Eudragit L 100 do so above pH 6.0. In this way, pH-dependent drug release can be achieved and a retard dosage form produced [20]. Interestingly, films formed from aqueous dispersions are less permeable than those made from organic solvent solutions; this is due to the higher density of the former [21]. The film-forming temperature of Eudragit L 100 and S 100 dispersions is high, but can be lowered with plastifiers.

Eastacryl 30 D, a similar acrylic polymer, can likewise be used for the film coating of pellets and tablets. It can be used in either aqueous or solvent solution.

Among cellulose-based polymers, *ethyl cellulose* is one of the frequently used film coating materials [22]. As compared with polymethacrylate films, ethyl cellulose film is of low resistance and high fragility. Accordingly, its elongation value is < 5 %. The hardness of coating can be improved by means of a solvent-based coating fluid [23].

Release of the drug is influenced by the amount of plastifier used in the film and also by the pH of the test medium [24, 25]. In the case of films plastified by dibutyl sebacate, drug release is accelerated by a longer storage time and a higher temperature, while in the case of films with tributyl citrate it is slowed, as evidenced by stability tests [26].

Most of the coating procedures described in the literature were performed in a fluidized bed apparatus. For slow liberation of the active ingredient, the application of ethyl cellulose latex at higher temperature and a slow atomizing rate are suggested [27, 28].

Experimental

Materials

Core: Theophylline pellets prepared with centrifugal granulator (Freund CF-360, Japan). (The preparation will be reported in an other paper.)

Coating Materials:

Eudragit L 100-55® (Röhm-Pharma GmbH Chemische Fabrik, Darmstadt, Germany)

An anionic copolymer of methacrylic acid and acrylate with an average molecular mass of 250000. It is a fine white powder also containing sodium dodecylsulphate (0.7%) and polysorbate 80 (2.3%). The diameter of at least 95% of the particles is below 0.25 mm. Eudragit is soluble in organic solvents. In water, it does not dissolve, but is dispersed [29]. The film formed from a water dispersion of Eudragit L 100-55 starts to

dissolve at pH 5.5, which makes it suitable for enteric coatings.

Eastacryl 30 D® (Eastman Chemical Company, Kingsport, USA)

An acrylic polymer can be used in both aqueous and organic media. Its average molecular mass is 200000. Eastacryl 30D is sold as a ready-to-use solution of 0.145 Pa·s viscosity and 64.4% solid content. Under improper storage conditions, the solution may condense, which makes it unusable for coating. To make it usable for coat forming, the factory preparation needs to be supplemented with water (28.8%), plasticizers (1.9%), talc (4.7%) and an antifoam agent (0.2%) prior to use. Plasticizers compatible with Eastacryl 30 D are triacetin, polyethylene glycol, dibutyl phthalate and triethyl citrate [30].

Surelease® (Colorcon Ltd., Orpington, UK)

Surelease is an aqueous dispersion of ethyl cellulose, ammonium hydroxide, triglycerides and oleic acid with 25% solid content. Ethyl cellulose will not dissolve in water and in artificial gastric fluid; hence, its dispersion in water can be used to form a film coating for sustained release preparations [31]. As this dispersion also contains plasticizers, it can be used directly after dilution with water to 15% solid content.

Methods

Preparation of Coating Dispersions

The Eudragit dispersion was prepared in two steps:

1. (Latex)
   Eudragit L 100-55 300 g
   Sodium hydroxide 0.1N 100 g
   Distilled water 750 g
   Silicone emulsion 20 drops
2. Latex 500 g
   Macrogol 6000 25 g
   Distilled water 150 g
   Talc 33.75 g.

Eastacryl dispersion was prepared from

Eastacryl 30 D 64.4 g
Distilled water 28.8 g
Triethyl citrate 1.9 g
Talc 4.7 g
Silicone emulsion 10 drops.

Surelease dispersion was prepared from:

Surelease 180 g
Talc 15 g
Distilled water 120 g.

Coating Process

A Strea-1 fluid bed apparatus was used with a Wurster container (Niro-Aeromatic, Bubendorf, Switzerland). The pellet core was 200 g. Different masses of the coating dispersions were used, so different thicknesses of the coating film were formed on the surface of the pellets.

Table I Calibration concentration of theophylline for different pH values

Dissolution time (h)	Dissolution medium pH	Calibration concentration, μg cm^{-3}
0 - 1	1.18	1.75
1 - 2	1.91	1.73
2 - 3	6.24	1.67
3 - 4	6.92	1.66
4 - 5	7.22	1.76
5 - 6	7.39	1.72
6 - 7	7.48	1.72

Coating parameters were

Drying temperature: 40°C
Outlet temperature: 30°C
Atomizing pressure: 2 bar
Blow out pressure 5 bar
Peripump speed: 5 rpm
Nozzle: 1.0 mm in diameter.

For morphological study, a scanning electron microscope (SEM) (Hitachi 2400S, Japan) was used to study the surfaces of uncoated and coated pellets. A sputter coating apparatus (Polaron Equipment Ltd., UK) was applied to induce electric conductivity on the surface of the sample. The air pressure was 1.3-13 mPa.

For dissolution of the active agent, the rotating basket method with half change [32] was used. The test was started with artificial intestinal fluid, one half of which was changed to gastric fluid every hour. In this way, the pH changes were similar to those seen in the digestive tract (*Table I*).

Test Conditions:

The apparatus involved a Pharma Test PTW 2 with 6 measuring places and microprocessor control (Pharma Test GmbH, Germany). Operating conditions were:

Rotation speed: 50 rpm,
Temperature: 37 ± 1 °C,
Dissolution medium volume: 900 cm^3,
Sampling time: 1, 2, 3, 4, 5, 6 and 7 h.

Measurement was done with a UV spectrophotometer (Spektromom 195D, MOM, Hungary) at 268 nm for pH = 1.18 to 1.91, at 270 nm for pH = 6.24 to 6.92, and at 271 nm for pH = 7.22 to 7.51.

The software SPSS for Windows 6.1.2. Copyright (C) SPSS Inc.,USA was used in computerized data processing.

Results and Discussion

Based on the SEM study it can be stated that a suitable and uniform coating film is formed on the approximately spherical pellet surface (*Figs.1* and *2*).

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.3a*, *3b* and *3c*). It can be seen that the polymethacrylate films (Eudragit and Eastacryl) with the smallest dry material

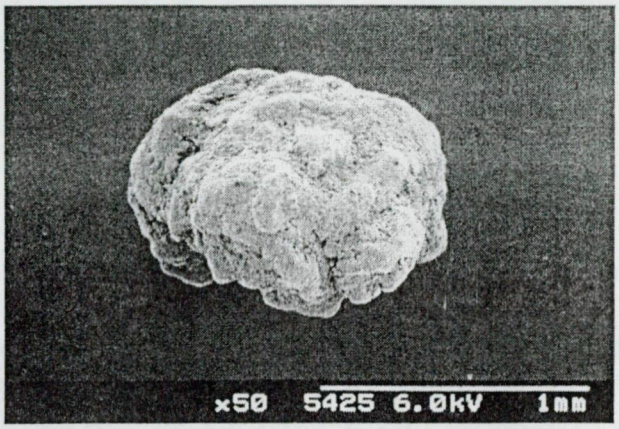

Fig.1 Surface of uncoated pellet (SEM)

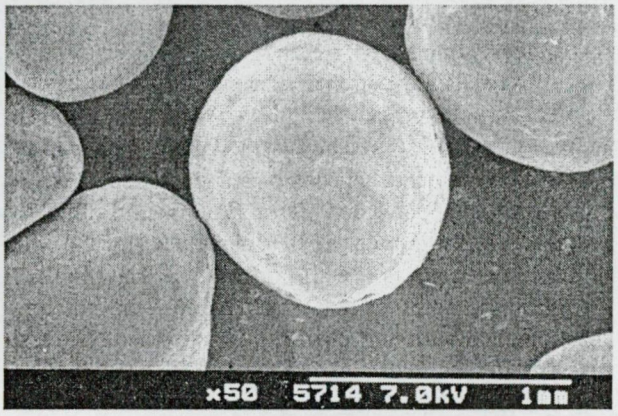

Fig.2 Surface of coated pellet (SEM)

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.

It can be concluded furthermore that a slower Surelease quantity was sufficient to attain a slow release coated pellet. The dissolution started in the gastric juice, because of the pH-independence, but increase of the dry coating material content hindered the total liberation of the drug during 7 h.

The results relating to the rate of dissolution of theophylline were evaluated via Rosin-Rammler-Sperling-Bennett-Weibull (RRSBW) distribution, and the characteristic dissolution time ($t_{63.2\%}$) was determined after linearized regression and Langenbucher transformation according to *Eq.(1)* [33]:

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

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 of curve and a is a time parameter. If $\beta > 1$, a sigmoid curve can be seen. This means that a slow release is followed by faster dissolution.

Table 2 Mathematical evaluation of the dissolution of the active agent

Coated pellet	$t_{63.2\%}$, min	Slope*, β	Intercept, ln a	Corr. coeff. r, $p < 0.05$
Eudragit L (25 g)	49.64	1.026	-1.41	0.983
Eudragit L (55 g)	99.04	1.429	-6.56	0.993
Eudragit L (82 g)	171.74	2.892	-14.88	0.961
Eastacryl (36 g)	78.10	1.326	-5.77	0.995
Eastacryl (52 g)	93.42	1.346	-6.10	0.998
Eastacryl (78 g)	196.93	2.510	-13.26	0.984
Surelease (15 g)	96.46	1.533	-7.00	0.993
Surelease (30 g)	535.28	1.335	-8.38	0.999
Surelease (45 g)	1105.30	1.272	-8.91	0.999

* shape parameter

Linearized regression from parameters β and a without T gives

$$\ln\ln\frac{M_0}{M_0 - M} = \beta \cdot \ln t - \ln a \qquad (2)$$

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

After Langenbucher transformation:

$$\ln a = \beta \ln t_{63.2\%} \qquad (3)$$

$$t_{63.2\%} = 10^{-a/\beta} \qquad (4)$$

where $t_{63.2\%}$ is the characteristic dissolution.

Regression analysis was carried out with the Statgraphics package (Copyright STSC, Inc. and Statistical Graphics Co., USA); the confidence limit was 95%.

Through use of the results of the "half change" dissolution tests, the characteristic dissolution time ($t_{63.2\%}$) can be determined via the above formula (plotting ln ln $M/(M\text{-}M_o)$ vs. ln t). *Table 2* presents the data obtained with pellets coated by upper spraying together with the correlation coefficients (r) proving the goodness of fit. Moreover, it can be seen how long the characteristic dissolution time is and how this time increases with increase of the dry coating material.

The correlation coefficients were in all cases near 1.0, indicating that the data points fit well on a straight line. A nearly linear active agent release was found for pellets with an Eudragit coating containing 25 or 55 g of dry material, an Eastacryl coating containing 36 or 52 g of dry material, or a Surelease coating containing 15, 30 or 45 g of dry material. Drug release at an initially low but later increasing rate was seen for the Eudragit and Eastacryl coatings only. This was due to the enteric property of the coating materials. The coating film is dissolved and the drug is released not at the pH of the gastric fluid, but only in an alkaline medium corresponding to the enteric fluid. The β values of Surelease coatings are of special interest. This material can not solve in the dissolution medium. In this case, the drug is released by diffusion through the coating.

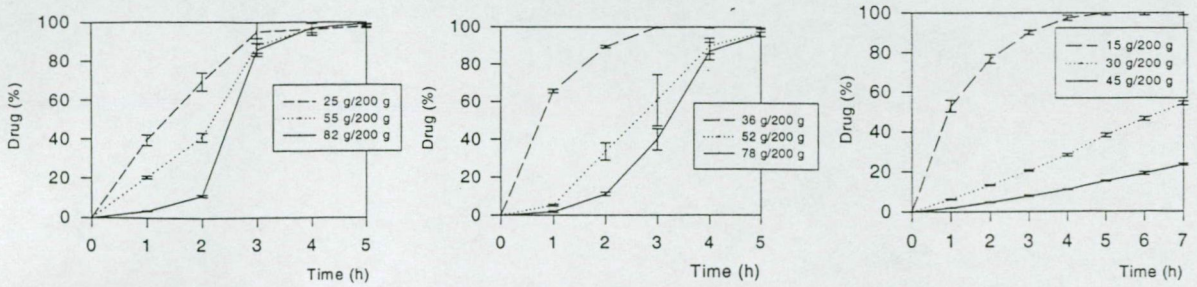

Fig.3 Drug dissolution from coated pellets: a) Coating material Eudragit 100-55; b) Coating material Eastacryl 30D; c) Coating material Surelease

Conclusions

As indicated by the characteristic dissolution time, the agent was most rapidly liberated to 63.2% from pellets coated with Eudragit film containing 25 g of dry material. A comparison of Eudragit vs. Eastacryl coatings of identical thickness revealed a close similarity in the $t_{63.2\%}$. This is not really surprising because the two substances are both polymetacrylate 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 release of the active agent from Surelease-coated pellets is thus considerably slower, but also more even.

Acknowledgement

This work was supported by OTKA T-023029 grant.

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