References

1 Grech-Belanger, O.; Turgeon, J.; Gilbert, M.: Br. J. Clin. Pharmacol. **21**, 481 (1986)
2 McErlane, K. M.; Igwemezie, L.; Kerr, C. R.: Res. Commun. Pathol. Pharmacol. **56**, 141 (1987)
3 Igwemezie, L.; Beatch, G. N.; Walker, M. J.; McErlane. K. M.: Xenobiotica **21**, 1153 (1991)
4 Vandamme, N.; Broly, F.; Libersa, C.; Courseau, C.; Lhermitte, M.: J. Cardiovasc. Pharmacol. **21**, 77 (1993)
5 Kowk, D. K.; Igwemezie, I.; Kerr, C. R.; McErlane, K. M.: J. Chromatogr. B, Biomed. Appl. **661**, 271 (1994)
6 Lanchote, V. L.; Bonato, P. S.; Dreossi, S. A., Goncalves, P. V.; Cesarino, E. J.; Bertucci, C.: J. Chromatogr. B, Biomed. Appl. **685**, 281 (1996)
7 Franchini, C.; Celucci, C.; Corbo, F.; Lentini, G.; Scilimati, A.; Tortorella, V.; Stasi, F.: Chirality **6**, 590 (1994)

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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.

References

1 Mutschler, E.; Derendorf, H.: Drug Actions, Medpharm Scientific Publishers, Stuttgart, 1995
2 Index Nominum. International Drug Directory, Edited by Swiss Pharmaceutical Society, Medpharm Scientific Publishers, Stuttgart, 1992
3 Rote Liste, Bundesverband der Pharmazeutischen Industrial E. V., 1996
4 Reynolds, J. E. F. (ed).: Martindale, The Extra Pharmacopoeia, Thirty-first Edition, Royal Pharmaceutical Society, London 1996
5 Szabó-Révész, P.; Keresztes, A.; Selmeczi, B.: Pharmazie **33,** 287 (1978)
6 Gaizer, S. N. B.; Pintye-Hódi, K.; Selmeczi, B.: Pharmazie **42,** 463 (1987)
7 Konrad, R.; Zessin, G.: Pharmazie **51,** 12 (1996)
8 Langenbucher, F.; Pharm. Ind. **38**, 472 (1976)

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