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.

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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.

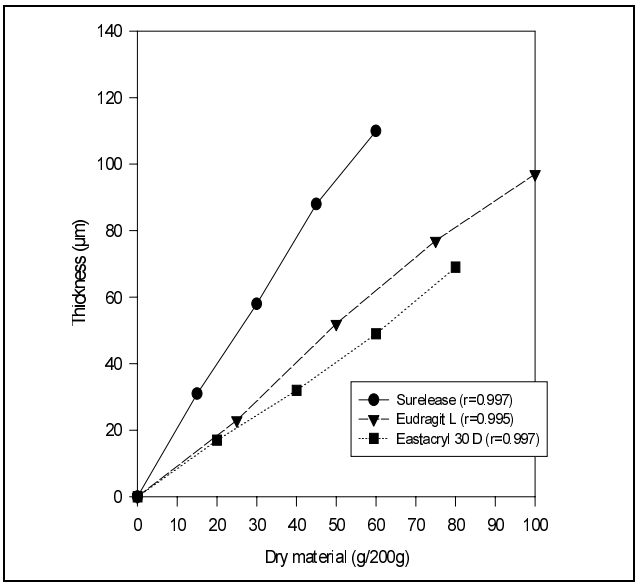

Fig. 1: Relationship between film thickness and dry material content of coating dispersion

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.

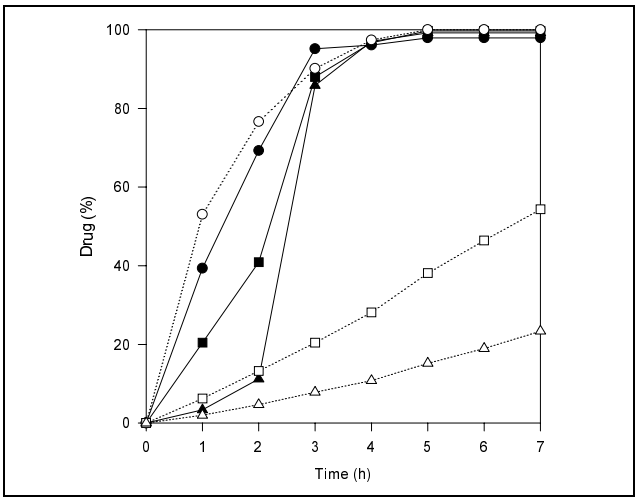

Fig. 2: Dissolution of theopylline from coated pellets
—●— Eudragit L 23 μm ($\beta = 1.026$; $t_{63.2} = 79$ min),
—■— Eudragit L 52 μm ($\beta = 1.429$; $t_{63.2} = 118$ min),
—▲— Eudragit L 77 μm ($\beta = 2.892$; $t_{63.2} = 161$ min),
····○··· Surelease 29.5 μm ($\beta = 1.335$; $t_{63.2} = 70$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

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