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Dissolution Studies of Papaverine Hydrochloride from Tablets in Three Pharmacopoeia Apparatuses

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A – research concept and design; **B** – collection and/or assembly of data; **C** – data analysis and interpretation; **D** – writing the article; **E** – critical revision of the article; **F** – final approval of the article

Abstract

Background. In tablet production, the most important aspects are the physical properties of the tablets and their dissolution studies, which can be performed in four pharmacopoeial apparatuses. There are differences between them in construction and action, so differences in the results obtained are possible.
Objectives. The aim of the study was to compare the release of a model drug substance (papaverine hydrochloride) from tablets in three pharmacopoeial dissolution apparatus: a basket, a paddle (closed system) and flow-through cell (open system).
Material and Methods. The one series of tablets were produced by direct compression in a tablet press. The physical properties of the tablets (weight and size uniformity test, friability and hardness tests, disintegration time test), drug content and the release study of papaverine hydrochloride from tablets were studied in three dissolution apparatuses. The content of the active substance was studied spectrophotometrically.
Results. All tablets met the pharmacopoeic requirements. Over 80% of the model substance released from the tablets after 14 min in flow through the cell apparatus, while in the basket and paddle apparatuses after about 7 min 30 sec. After 20 min, the amount of the substance released in all apparatuses was over 90%.
Conclusions. The release profiles of the drug substance in paddle and basket apparatuses were similar, while in the flow-through cell apparatus it was slightly slower. When the study conditions and composition of the tablets are the same, the release profile of the drug can be affected by the type of dissolution apparatus **(Polim. Med. 2015, 45, 1, 21–24)**.

Key words: tablets, release study, papaverine hydrochloride, pharmacopoeia dissolution apparatus.

The key roles in tablet production are played by both excipients and the parameters of the tabletting process [1]. Excipients have a huge impact on the physical properties of tablets and dissolution studies, but no less important is the preparation method factors such as suitable compression force, etc. [2, 3]. The release study was designed to assess the amount of the drug released from the pharmaceutical form and dissolved in the surrounding fluid in a specific period of time. Dissolution is a primary parameter defining the quality evaluation of the tablet's in vitro release rate of the drug from the dosage form [4, 5]. Polish Pharmacopoeia IX recommends examining the dissolution of solid dosage forms, such us tablets, using four dissolution apparatuses (basket, paddle, reciprocating cylinder and flow through cell apparatuses) [6]. In all dissolution apparatuses, the temperature of analysis should be constant (37 ± 0.5°C). Apparatus 1 (basket apparatus) consists of a transparent beaker, covers, engine drive shaft and cylindrical baskets which serve as stirrer. Apparatus 2 (paddle apparatus) is built like Apparatus 1, except the mixing element in this case is a paddle-type stirrer. The analysis in these two apparatuses is performed in closed system (no flow of a solution). The flow through cell apparatus is constructed from a fluid reservoir to release the flow chamber, a pump and a water bath. The pump can pump fluid at various rates, while the analysis can be performed in either a closed system or an open one (the solution flows at the set rate) [6].

Differences in release profiles of active substances in various pharmacopoeial dissolutions were noticed. During the first hour of study, there were differences in release profile reaching 42–73% [7]. Similar results (release in the flow through cell apparatus was slower than in the paddle/basket apparatuses) were observed by Sznitowska et al. [8]. On the other hand, Weennergren et al. [9] discovered that the release of prednisone from tablets in paddle and flow through cell apparatuses were similar, when a slow flow of the fluid was applied to the second apparatus. Also Chevalier et al. [10] did not notice significant differences in the release profile of the active substance (ibuprofen) in flow through cell and paddle apparatuses. These inconsistencies prompted us to investigate the release of the active substance from three apparatuses, using slow flow in a flow through cell apparatus.

The simple dosing, economic issue modifications easy to incorporate, and possibility of dissolution in different parts of the gastrointestinal tract, have resulted in tablets becoming the most widely used drug form [11]. The model substance used in this experiment is papaverine hydrochloride (PAP, Fig. 1), which is a powder, sparingly soluble in water and ethanol [6]. It inhibits phosphodiesterase, which has the effect of a smooth muscle relaxant, and therefore is most often used as an antispasmodic in gastrointestinal disorders, bile, intestinal and renal spikes [12, 13]. Nowadays, papaverine hydrochloride is commercially available as a solution for injection and combined preparations in the form of suppositories for rectal administration, but it is no longer available in the form of tablets [14]. It was selected as the model drug because it is well soluble in an acidic medium, while its solubility increases with the decrease of the medium's pH [15, 16].

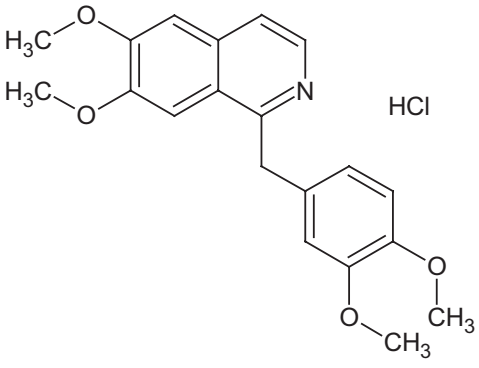

Fig. 1. Structure of papaverine hydrochloride

The purpose of this study was to compare the release profile of a model drug substance (PAP) in three pharmacopoeial dissolution apparatuses: a basket, a paddle and flow-through cell from non modified release tablets.

Material and Methods

Material

List of substances and reagents:

1) papaverine hydrochloride (PAP) (FARM-IMPEX SP. J., Poland);
2) gelatinized starch – CPharmGel (CPG) (Cargill Benelux BV, The Netherlands);
3) roscarmellose sodium (Ac-di-sol) (FMC BioPolymer, Belgium);
4) β-lactose (lactose) (SIGMA – ALDRICH CHEMMIE Gmbh, Germany);
5) polyvinylpyrrolidone K 10 000 (PVP) (SIGMA – ALDRICH CHEMMIE Gmbh, Germany);
6) magnesium stearate (StMg) (PPH POCH SA, Poland).

All other reagents and solvents were of analytical grade and distilled water was freshly distilled (Distiller IDPE-10, Poland).

Methods

Tablets were prepared with the ingredients given in Table 1 by direct compression in a tablet press machine (Erweka type EKO, Germany) with a 9 mm punch at a force of around 3kN. All components were sieved through a 0.710 mm mesh screen. Each tablet contains 80 mg of PAP and 320 mg of excipients (total weight = 400 mg ± 5%).

Weight uniformity test: twenty randomly selected tablets were first weighted together and then each one separately. Mean value and standard deviation (SD) were calculated for each tablet

Table 1. Composition of tablet formulation

Component	Quantity per tablet (%)
Papaverine hydrochloride	20
Polivinylopyrrolidone K 10 000	10
β-Lactose	41
Croscarmellose sodium	3
Gelatinized starch	25
Magnesium stearate	1

Tablet size: the thickness of twenty randomly selected tablets were measured and means with SD were calculated

Friability test: sixteen randomly selected tablets (weight equal or close to 6.5 g) were weighed and placed into a friabilator (Erweka TAR 120, Germany), which was set to 25 rpm for 4 min. After the test they were reweighed and calculated according to Equation 1 [5].

$$\text{Friability (\%)} = \frac{\text{loss in weight}}{\text{initial weight}} \times 100. \quad (1)$$

Hardness test: six randomly selected tablets were analyzed in a hardness tester (AEG Type AP 56 N2, Germany) and then calculated according to Equation 2 [5].

$$T = \frac{P_{max}}{2rh}. \quad (2)$$

where T = hardness ratio (kG/mm^2), P_{max} = force needed to crush the tablet (kg), h = thickness of the tablet (mm) and r = radius of the tablet (mm).

Tablet disintegration time assay: six randomly selected tablets were put into a USP Apparatus (Erweka Type ZT 222, Germany), more precisely into a basket-rack in a vessel with water at 37°C which then was covered with a disk and the disintegration time of the tablets was observed.

Drug content: ten randomly selected tablets were crushed together and accurately weighed of 400 mg and transferred into a 100 mL volumetric flask to which 50 mL 0.1M HCl was added. The flask was shaken for five min and diluted with 0.1M HCl to volume 100 mL. Next, the mixture was filtered with a Whatman filter and 2 mL of the obtained solution was transferred into a 100 mL volumetric flask and diluted with 0.1M HCl to volume 100 mL. The absorbance of this solution was determined by UV spectrophotometry at 251 nm (Omega UV – VIS, Thermo Scientific, England). PAP concentration was calculated from equations obtained from the standard curve of PAP ($y = 0.146 x + 0.106$ ($r^2 = 0.999$)) PAP (n = 5). This method obeys Beer's Law in the employed concentration ranges of 2.5–20 μg/mL for PAP.

In vitro release study: was carried out in paddle (Erweka DT 600, Germany), basket (Erweka DT 600, Germany) and flow through cell (Sotax Dissotest CE 1, Switzerland) apparatuses. As a dissolution medium, 900 mL of 0.1M HCl at 37 ± 0.5°C was used. The study in the first two apparatuses was as follows: Each tablet was placed in each of the six vessels of the paddle (or basket) apparatus and rotated at 75 rpm. After appropriate intervals of time, 2 mL samples were collected and an equivalent amount of a dissolution medium (2 mL) was added into a volume of 100 mL. All samples were analyzed spectrophotometrically at 251 nm. The amount of the released substance was calculated by reference to a Beer's plot based on the calibration curve. Performance in the flow through cell apparatus was quite different. The flow of the dissolution medium was calibrated at 4 mL/min. Each tablet was placed in the cell (22.6 mm diameter) and immersed in a water bath at 37 ± 0.5°C. All samples (containing 10 mL, 2 min and 30 sec flow) were collected to test tubes and then analyzed spectrophotometrically as described above.

Results and Discussion

All results of the physical properties are presented in Table 2.

All tested tablets complied with the pharmacopoeia requirements regarding weight, size, adequate hardness, friability, drug content, disintegration time and release profile. All tablets disintegrated within the 15 min required by the pharmacopoeia (2 min 30 sec). The release profiles of PAP (Fig. 2) in the basket and paddle apparatuses were similar, but the release profile in the flow-through cell apparatus showed a slower release of PAP. The biggest difference was seen after 5 min – in the paddle and basket apparatuses about 64% PAP was released, while in the flow through cell apparatus only 32%. After 10 min of the release study, 60% of PAP was released in the flow through cell apparatus, while in the other two apparatuses, the amount of released substance exceeded the value of 90%, which was reached in the flow through cell apparatus after 20 min. The release required by the pharmacopoeia of 80% of the substance was released in the flow through cell apparatus after 14 min, while in the paddle and basket apparatuses after only 7 min 30 sec.

Similar results were observed by other authors. Fotaki et al. [7] observed a much faster release of the active substance in the paddle apparatus than in the flow through cell apparatus within the first hour of the experiment. Also, a study performed by Sznitowska et al. [8] showed the differences between the release profiles of the active substance (lithium carbonate) depending on the apparatus used. Basket and paddle apparatuses are nowadays most commonly used to study solid dosage forms, but they did not have any flow of the dissolution medium, which would be closer to natural conditions. On the other hand, in the flow-through cell apparatus, a closed or open system may be used for the constant flow of fresh

Table 2. Characteristics of tablets

Test	Amount of tablets	Result	Standard
Mass (mg) SD (%)	20	410.0 ± 3.41	± 5%
Size (mm) SD (%)	20	3.3 ± 2.41	± 7.5%
Disintegration time (min:sec)	6	2:30	< 15 min
Breaking force (kg/mm^2) SD (%)	6	0.11 ± 6.82	> 0.1 kg/mm^2
Friability (%)	16	0.44	< 1%
Drug content SD (%)	10	99.36 ± 0.80	± 10%

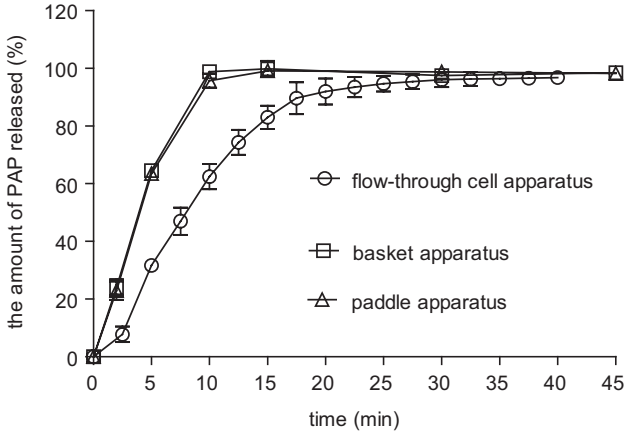

Fig. 2. Dissolution profile of PAP in three apparatuses (mean values ± SD, n = 6)

liquid for the release, thus mimicking the conditions in the gastrointestinal tract [17]. Our study confirmed that the drug release from tablets is affected by the type of dissolution apparatus, when agitation speed with volume, composition, temperature are constant [18].

The release profiles of the drug substance in the paddle and basket apparatuses were similar, while in the flow through cell apparatus it was slower. Over 80% of the model substance released from the tablets after 14 min in the flow through cell apparatus, while in the basket and paddle apparatuses after 7 min 30 sec. After 20 min, the amount of the substance released in all apparatuses was over 90%. When the study conditions and composition of the tablets are the same, the release profile of the drug can be affected by the type of dissolution apparatus used.

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