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Influence of Polymer Type on the Physical Properties and Release Profile of Papaverine Hydrochloride From Hard Gelatin Capsules

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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. The capsule is one of the most important solid dosage forms in the pharmaceutical industry. It is easier and faster to produce than a tablet, because it requires fewer excipients. Generally, capsules are easy to swallow and mask any unpleasant taste of the substances used while their release profiles can be easily modified. Papaverine hydrochloride was used as a model substance to show different release profiles using different excipients.
Objectives. The main aim of the study was to analyze the impact of using different polymers on the release profile of papaverine hydrochloride from hard gelatin capsules.
Material and Methods. Six series of hard gelatin capsules containing papaverine hydrochloride as a model drug and different excipients were made. Then, the angle of repose, flow rate, mass flow rate and volume flow rate of the powders used for capsule production were analyzed. The uniform weight and disintegration time of the capsules were studied. The dissolution study was performed in a basket apparatus, while the amount of papaverine hydrochloride released was determined spectrophotometrically at 251 nm.
Results. Only one formula of powder had satisfactory flow properties, while all formulas had good Hausner ratios. The best properties were from powder containing polyvinylpyrrolidone 10k. The disintegration time of capsules varied from 1:30 min to 2:00 min. As required by Polish Pharmacopoeia X, 80% of the active substance in all cases was released within 15 minutes. The capsules with polyvinylpyrrolidone 10k were characterized by the longest release. On the other hand, capsules containing microcrystalline cellulose had the fastest release profile.
Conclusions. Using 10% of different polymers, without changing the other excipients, had a significant impact on the physical properties of the powders and papaverine hydrochloride release profile. The two most preferred capsule formulations contained either polyvinylpyrrolidone 10k or microcrystalline cellulose **(Polim. Med. 2015, 45, 2, 51–55).**

Key words: release study, papaverine hydrochloride, capsules.

Capsules are one of the most popular solid dosage forms of drugs in the pharmaceutical industry. They are easy to swallow, are tasteless and odorless and are available in a wide range of colors, which is important for older patients (as it reduces errors). They contain fewer excipients than tablets and thus are easier and faster to produce [1]. Gelatin capsules disintegrate rapidly in the stomach, often speeding up active substance dissolution [2].

The selection of excipients yields capsules of the desired active substance release profile and subsequent bioavailability of the drug [3]. Microcrystalline cellulose is a polysaccharide composed of D-glucose units linked together by a β-1,4-bond. It is commonly used as a disintegrant (10%) or filler (5–20%) [4]. Polyvinylpyrrolidone is synthetic linear polymer, soluble in water. Its molecular weight can range from 2500 to 1,000,000. It is mainly used in a wet granulation as a binder, since it significantly in-

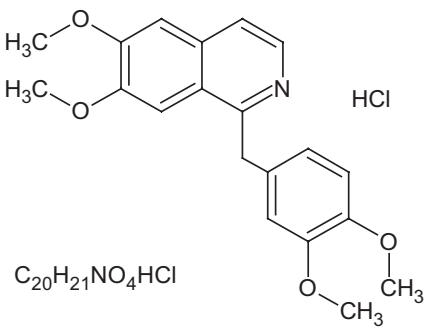

Fig. 1. Structure of papaverine hydrochloride (1-D and 2-D)

creases the hardness and strength of a solid dosage form [6, 7]. Starches are commonly used in drug technology as binders, fillers and disintegrants. Gelatinized starch is prepared by modifying the chemical structure of starch in order to improve the flow rate, can be used as a binding agent in a wet granulation and has high hygroscopicity [7]. Hypromellose (hydroxypropyl methylcellulose) is widely used in oral dosage forms, as a binder, part of a tablet coat or release delaying agent [8]. Lactose is a disaccharide containing galactose and glucose, commonly used as a filler in solid dosage forms [9].

The release profile of the active substance from the capsule, according to the European Pharmacopoeia, can be represented as the total amount of the active substance released over time [10]. Papaverine hydrochloride (PAP, Fig. 1) was used as a model drug substance, since it is well soluble in an acidic medium, because with the decrease of average pH, its solubility increases and its concentration in the release medium can be easily determined in a spectrophotometer [11, 12]. It is a spasmolytic drug, which inhibits phosphodiesterase resulting in a smooth muscle relaxant. Therefore it most often used in gastrointestinal disorders, bile, intestinal and renal spikes [13, 14].

There have been a few reports about the influence of polymer PAP release from tablets [15, 16], but there are none which concern powders or capsules containing PAP. The purpose of the present study was to examine the effects of different polymers with all other components unchanged, on the physical properties of powders and capsules together with the release profile of the model substance.

Materials and Methods

The following materials were used: hard gelatin capsules size 00 (Capsugel-Bornem, Belgium), papaverine hydrochloride (Farm-Impex Sp. J., Poland), polyvinylpyrrolidone k10, polyvinylpyrrolidone k30, (hydroxypropyl)methyl cellulose (Sigma-Aldrich Chemmie GmbH, USA), potato starch, lactose monohydrate, D-mannitol, magnesium stearate (POCH S.A., Poland), gelatinized starch (CPharmGel, Cargill Benelux BV, Netherlands), and microcrystalline cellulose (Vivapur 102, JRS Pharma Gmbh & CO KG, Germany). All other reagents and solvents used were of analytical grade, while distilled water was freshly distilled. The ingredients were weighed and mixed in an all-purpose motor with a cube mixer (Erweka KB 155, Germany). Six series (C1–C6) of hard gelatin capsules containing PAP and various excipients (Table 1) were prepared in a manual capsule filling machine (Capsunorm® 00/100, Eprus, Poland).

The angle of repose, flow rate, mass flow rate and volume flow rate of the powders were studied in the granulate and powder flow tester (Erweka Type GTB, Germany). A sieve analysis was carried out in vibratory sieve shaker AS 200 basic (Retsch, Germany), compressibility was analyzed in a tapped density tester (Erweka, type SVM 222, Germany). All these studies were performed in accordance with the requirements of the European Pharmacopoeia [10]. The disintegration times of six randomly-selected capsules from each batch were determined using the disintegration tester (Erweka Type ZT 222, Germany). The capsules were then put into a basket-rack in a vessel with water at 37°C ± 0.5°C. The disintegration time of the capsules was recorded.

Table. 1 Composition of capsule formulations

Component	Quantity in percent per capsule					
	C1	C2	C3	C4	C5	C6
PAP	10	10	10	10	10	10
PVP 10k	10	–	–	–	–	–
PVP 30k	–	10	–	–	–	–
Potato starch	–	–	10	–	–	–
CPharmGel	–	–	–	10	–	–
Hypromellose	–	–	–	–	10	–
Microcrystalline cellulose	–	–	–	–	–	10
Mannitol	10	10	10	10	10	10
Magnesium stearate	1.5	1.5	1.5	1.5	1.5	1.5
Lactose	68.5	68.5	68.5	68.5	68.5	68.5

The PAP content was determined in ten randomly-selected capsules from each batch. The 200 mg powder was weighed into a 100 ml volumetric flask, dissolved in 50 ml 0.1 M HCl, diluted to 100 ml, shaken and filtered in a Whatman filter (0.45 μm pore size). 2 ml of the solution was diluted to 100 with 0.1 M HCl. The absorbance was determined by UV spectrophotometry at 251 nm (Spectrophotometer Helios Omega, Thermo Scientific, USA). The amount of the released substance was calculated by reference to a Beer's plot based on a calibration curve ($y = 0.1467x + 0.1068$, $R^2 = 0.9992$).

The dissolution test was carried out in a basket apparatus (Erweka, Germany) according to European Pharmacopoeia [10]. Each capsule was placed into vessels containing 900 ml of 0.1 M HCl (37 ± 0.5°C) and mixed (100 rpm) [10]. After appropriate periods of time (2, 5, 10, 15, 30 and 45 minutes), 2 ml samples were collected, while 2 ml of 0.1 M HCl was added to the dissolution medium. All samples were diluted by adding 3 ml of dissolution medium and analyzed spectrophotometrically. Basket apparatuses were chosen according to the pharmacopoeia requirements, because as shown by previous studies on PAP release from tablets, results can differ slightly in various apparatuses [17].

The results are expressed as the mean of six experiments (± SEM). For statistical evaluation, the data of the release profiles of papaverine hydrochloride were assessed by the one way ANOVA analysis with post-hoc Tukey test, where $p < 0.05$ was considered as statistically significant (GraphPad Prism 5.01, GraphPad Software, USA).

Results and Discussion

The powder properties are summarized in Table 2. Angle of repose values > 25° means excellent flow of a powder. Generally, a lower value of the angle of repose indicates better flowability [18]. In our study, the lowest value of angle of repose was from a powder containing PVP 10k (35.0° – good flow), slightly higher values were found in powders with CPharmGel (40.0° – sufficient) and microcrystalline cellulose (42.6° – sufficient). Three other formulas had much higher values of angle of repose (44.1–48.1° – poor). The tested powders, except for formulation C1, did not possess satisfactory flow properties. On the other hand, the Hausner ratio was good (1.15 for C1), fairly good (1.22 for C6) and sufficient for other powders. A sieve analysis showed that 50% of the particles in the analyzed powders had less than 0.090 μm in four powders and less than 0.125 μm in two powders (C1 and C5). The values of the flow rate (3.3–7.9 s/100 g) and volume flow rate (1.9–4.8 s/100 ml) were similar in all powders. On the other hand, mass flow rate differed a lot, with the lowest from powder from C6 and C2 capsules (respectively 8.1 and 8.3 g/s), while the highest values were from powder from C5 (36.2 g/s). Nevertheless, all of the tested powders had satisfactory properties, while C1 was the best.

The characteristic of the capsules are shown in Table 3. The average weight of the capsules varies from 0.5610 g (C4) to 0.5985 (C6). Deviations from the average weight met the pharmacopoeial requirements (± 7.5%), and C1 had the biggest deviations (± 4.5%). The

Table. 2. Characteristics of powder formulations

Formula	Angle of repose [°]	Flow rate [s/100 g]	Volume flow rate [s/100 ml]	Mass flow rate [g/s]	Hausner ratio	X_{50} (μm)
Powder formulation C1	35.0	6.0	4.1	14.2	1.15	0.125
Powder formulation C2	45.2	7.8	2.2	8.3	1.34	0.090
Powder formulation C3	48.1	4.2	1.0	23.1	1.37	0.090
Powder formulation C4	40.0	5.9	4.0	14.0	1.27	0.125
Powder formulation C5	44.1	3.3	4.8	36.2	1.28	0.090
Powder formulation C6	42.6	5.2	1.9	8.1	1.22	0.090

Table. 3. Characteristics of capsules

Formula	Average weight[a] (without shell)(g)	Deviations from the average weight (%)	Disintegration time[b] (min:s)	Drug content[b] (%)
C1	0.5749	± 4.5	1:30	91.72 ± 2.51
C2	0.5972	± 2.1	2:00	98.97 ± 4.73
C3	0.5836	± 3.4	2:00	102.31 ± 2.92
C4	0.5610	± 2.2	2:00	99.43 ± 5.07
C5	0.5641	± 3.6	1:45	93.44 ± 4.96
C6	0.5985	± 2.8	1:30	100.34 ± 3.19

[a]mean from twenty capsules without shells [b]mean from six capsules.

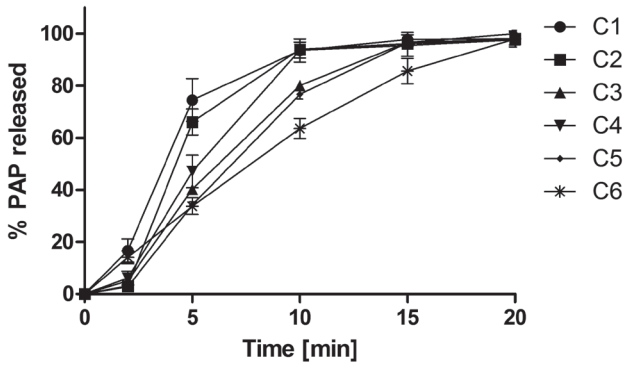

Fig. 2. Mean dissolution profiles of PAP from capsules C1–C6 (mean values n = 6, ± SD)

disintegration time of the capsules was almost the same (1 min. 30 s for C1 and C6, 2 min. for C2, C3 and C4). Drug content varied from 91.72% (C1) to 102.31% (C3).

Figure 2 shows the PAP release profile for six capsule formulas. 80% of the active substance was released within 15 minutes in all of the tested formulations. Moreover, in all capsules except for C6, 100% of the PAP released within 15 minutes. Generally, the capsules containing polyvinylpyrrolidone 10k had the longest release, while capsules containing microcrystalline cellulose the fastest (except for first 2 minutes). On the other hand replacement of polyvinylpyrrolidone 10k with polyvinylpyrrolidone 30k only slightly delayed release. A delaying of the release of PAP (especially within the first five minutes) came from a conversion of polyvinylpyrrolidone to CPharmGel, potato starch or hypromellose 10k. Similar results were observed for tablets containing CPharmGel [15]. Also, granulates with PAP containing polyvinylpyrrolidone had the best flow rates and slightly longer disintegration time, while tablets produced from them slightly delayed release [16]. Formulations C1–C6 did not show any statistically significant differences, in regard to papaverine chloride release after 20 minutes ($p > 0.05$). On the other hand, formulation C4 released a lower amount of papaverine after 10 minutes, as compared to C2–C3 and C5–C6 ($p < 0.05$). The results are shown in table 4.

Table. 4. Statistical analysis of papaverine hydrochloride release profile

Compared formulas	The amount of papaverine released after	
	10 minutes	20 minutes
C1 vs. C2	ns	ns
C1 vs. C3	ns	ns
C1 vs. C4	ns	ns
C1 vs. C5	ns	ns
C1 vs. C6	ns	ns
C2 vs. C3	ns	ns
C2 vs. C4	**	ns
C2 vs. C5	ns	ns
C2 vs. C6	ns	ns
C3 vs. C4	**	ns
C3 vs. C5	ns	ns
C3 vs. C6	ns	ns
C4 vs. C5	**	ns
C4 vs. C6	*	ns
C5 vs. C6	ns	ns

* – $p < 0.05$, statistically significant result; ** – $p < 0.01$ statistically very significant result; ns – $p > 0.05$ statistically insignificant result.

Powders containing polyvinylpyrrolidone 10k had the best properties. The use of different polymers in the amount of 10%, without changing the other components, substantially changed the physical properties of the powders and the release profile of PAP. The rate of release profiles of PAP were the highest for formulations containing polyvinylpyrrolidone 10k followed by: polyvinylpyrrolidone 30k, CPharmGel, potato starch, hypromellose 10k and microcrystalline cellulose. The most promising capsule formulation was one containing polyvinylpyrrolidone 10k (good powder properties and faster release) or one with microcrystalline cellulose (good powder properties and slower release).

References

[1] **Pietkiewicz P., Janicki S., Szmitowska M.:** Kapsułki jako nowoczesna postać leku. Ter. Leki 2001, 29, 26–30.
[2] **Adesunloye T.A., Stach P.E.:** Effect of glycine/citric acid on the dissolution stability of hard gelatin capsules. Drug Dev. Ind. Pharm. 1998, 24, 493–500.
[3] **Bertocchi P., Antoniella E., Valvo L., Alimonti S., Memoli A.:** Diclofenac sodium multisource prolonged release tablets – a comparative study on the dissolution profiles. J. Pharm. Biomed. Anal. 2005, 37, 679–685.
[4] **Kiska T.:** Mikrokrystaliczna celuloza i jej zastosowanie. Najczęściej spotykane problemy technologiczne. Pharmaceutica 2003, 24, 53–58.
[5] **Ahmad A.L., Sarif M., Ismail S.:** Development of an integrally skinned ultrafiltration membrane for wastewater treatment: effect of different formulations of PSf/NMP/PVP on flux and rejection. Desalination 2005, 179, 257–263.
[6] **Zhang P.Y., Wang Y.L., Xu Z.L., Yang H.:** Preparation of poly (vinyl butyral) hollow fiber ultrafiltration membrane via wet-spinning method using PVP as additive. Desalination 2011, 278, 186–193.
[7] **Mimura K., Kanada K., Uchida S., Yamada M., Namiki N.:** Formulation study for orally disintegrating tablet using partly pregelatinized starch binder. Chem. Pharm. Bull. 2011, 59, 959–964.

[8] **Nokhodchi A., Raja S., Patel P., Asare-Ado K.:** The role of oral controlled release matrix tablets in drug delivery systems. Bioimpacts 2012, 2, 175–187.
[9] **Gohel M.C.:** A review of co-processed directly compressible excipients. J. Pharm. Sci. 2005, 8, 76–93.
[10] European Pharmacopoeia 7th ed., Vol. 1, Council of Europe, Strasbourg 2010.
[11] **Miyajima M., Koshika A., Okada J., Kusai A., Ikeda M.:** Factors influencing the diffusion-controlled release of papaverine from poly (L-lactic acid) matrix. J. Control. Release. 1998, 56, 85–94.
[12] **Serajuddin A.T., Rosoff M.:** pH-solubility profile of papaverine hydrochloride and its relationship to the dissolution rate of sustained-release pellets. J. Pharm. Sci. 1984, 73, 1203–1208.
[13] Martindale: The Complete Drug Reference. [online] London: Pharmaceutical Press http://www.medicinescomplete.com (Accessed 01.06.2015).
[14] **Kaneda T., Hayasaka R., Nagai Y., Tajima T., Urakawa N., Nakajyo S., Shimizu K.:** Effect of papaverine on twitches in mouse diaphragm. Pharmacology. 2010, 86, 273–280.
[15] **Kasperek R., Polski A., Zimmer Ł., Poleszak E.:** Release kinetics of papaverine hydrochloride from tablets with different excipients. Sci. Pharm. 2014, 82, 683–696.
[16] **Kasperek R., Polski A., Sobótka-Polska K., Poleszak E.:** Wpływ rodzaju polimeru na właściwości fizyczne i proces uwalniania chlorowodorku papaweryny z tabletek. Polim. Med. 2014, 44, 5–12.
[17] **Polski A., Kasperek R., Rogowska M., Iwaniak K., Sobótka-Polska K., Poleszak E.:** Dissolution studies of papaverine hydrochloride from tablets in three pharmacopeia apparatuses. Polim. Med. 2015, 45, 21–24.
[18] **Wells J.:** Pharmaceutical preformulation: The physicochemical properties of drug substances. Halsted Press, New York, 1988.

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