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ORIGINAL ARTICLE

Comparison of physicochemical properties of suppositories containing starch hydrolysates

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KEYWORDS

Starch hydrolysate;
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Abstract The purpose of this work was to determine the effect of starch hydrolysates (SH) on the physicochemical properties of suppositories. The study was conducted with suppositories with acetaminophen (AAP) a typical antipyretic analgesic, as model drug on lipophilic (cocoa butter) and hydrophilic base (polyethylene glycol 1500 + 400). The suppositories with and without the addition of SH were examined for physicochemical tests according to European Pharmacopoeia 8th edition (Ph. Eur.): the uniformity of mass of single-dose preparation test, the softening time determination of lipophilic suppositories test, the disintegration of suppositories test, and dissolution test with flow-through apparatus. The results confirm the possibility of using starch hydrolysates as a cheap and safe addition to modify physicochemical properties of suppositories.

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1. Introduction

The rectal route for drug administration is useful because it can avoid hepatic first-pass effect, decrease gastrointestinal side effects and avoid undesirable effects of meals on drug absorption (de Boer et al., 1979, 1982). Drugs with systemic effect such as, antipyretic, anti-rheumatic, muscle relaxants, hypnotics are used in the rectal suppositories (Lou et al., 2012; Setoguchi et al., 2013). Drugs with local effect are mainly used: anti-inflammatories, and local anesthetics astringent nor-

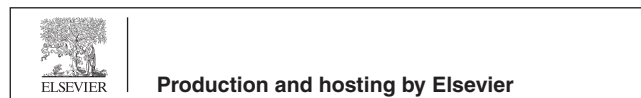
mally used in the treatment of hemorrhoids, and substances with laxative activity (Carbone et al., 2013; Ramadan, 2013). Suppositories are currently a small part of the available dosage forms. However, the administration by the rectal route is important for patients with peptic ulcers, children and geriatric's treatment. Sustained release suppositories are preferable to conventional suppositories because they reduce the frequency of drug administration. Several approaches have been performed to prepare the controlled release suppositories by using various additives such as lecithin (Nishihata et al., 1985), sucrose fatty ester (Nakajima et al., 1990), carboxyvinyl polymer (Azechi et al., 2000; Yahagi et al., 2000) and various hydrogel formulations (Morimoto et al., 1989; Miyazaki et al., 1998).

Unfortunately, the amount of data on formulations containing starch hydrolysates is limited. Therefore, the purpose of this study was to demonstrate the effect of starch hydrolysis products on physicochemical properties of suppositories.

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2. Materials and method

2.1. Materials

The following materials were used: potato starch (Nowamyl S. A., Lobeż, Poland), acetaminophen (AAP) (Sigma-Aldrich, St. Louis, MO, USA), citric acid (CA), glacial acetic acid (GAA), ethanol (760 g/L) - (ET), and phosphate buffer (pH 7.2) - (PB), (Avantor Performance Materials S.A., Gliwice, Poland).

2.2. Methods

2.2.1. Hydrolysis of starch

Potato starch was treated with solutions of CA, GAA and water at 95 °C for 2 or 4 h to obtain starch hydrolysate SH2 or SH4 respectively. Received sediments were cleaned by ET and evaporated to eliminate the solvent (Czarnecki and Belniak, 2007). Molecular mass of obtained hydrolysates was estimated in cryoscope (Trident 800 CL, Poland) on the ground of freezing point determination. Molecular mass of SH2 amounts 2.356 kDa and 1.105 kDa for SH4. Both hydrolysates are readily soluble in water and in PB. Hydrolysates dissolved in water form solutions of pH 3.74 and pH 3.54 while PB solutions reach pH 7.11 and pH 7.07, respectively for the SH2 and SH4.

2.2.2. Preparation of suppositories

Rectal suppositories were prepared by fusion method at 36 °C on lipophilic base - cocoa butter and 60 °C on a hydrophilic base - PEG 1500 + PEG 400 (95:5, m/m). Each one contains 125 mg of AAP. The molten bases were mixed with SH2, SH4 (Table 1), and poured into polyethylene molds of capacity 1 g. After solidification, formed suppositories were stored at 4 °C until use.

2.2.3. Physical tests of suppositories

The uniformity of mass of single-dose preparation test was carried out as follows: twenty suppositories were individually weighted (Mettler AT201 FACT Switzerland) from each formula. Average mass and standard deviation (SD) were calculated.

The softening time determination of lipophilic suppositories test was conducted using apparatus for measuring the softening time of suppositories ($n = 3$).

The disintegration of suppositories test was performed in water maintained at 37 °C \pm 0.5 °C using ST30 apparatus (Erweka, Germany) ($n = 3$).

The resistance to rupture of suppositories test was carried out on 10 suppositories using SBT apparatus (Erweka, Germany) at room temperature (22 °C \pm 0.5 °C). Results of above tests are shown in Table 2.

2.2.4. Assay of acetaminophen by spectrophotometry

Spectrophotometric measurements were carried out on spectrometer Helios Omega UV-VIS (Thermo Scientific, USA). Absorbance of AAP in PB was taken at 242 nm and was plotted against its respective concentrations to obtain standard curve. The amount of AAP was calculated from the linear regression equation $A = 0.0625 C + 0.0188$ ($r = 0.9997$).

2.2.5. Chemical test of suppositories

The uniformity of content of single-dose preparation test. The content of AAP in suppositories was tested on five suppositories randomly selected from each formula. The suppository was individually placed in 1000 ml standard flask containing 100 ml of PB and heated. The flask was shaken until complete dissolution of AAP from suppository. Then 10 ml of solution was taken, filtrated through PVDF membrane filter (Sartorius 0.2 μ m) and assayed spectrophotometrically against the blank prepared using respective suppository without AAP. The mean contents of drug \pm SD were calculated and are given in Table 2.

The dissolution test for solid dosage forms. The dissolution test of suppositories was carried out according to the flow-through method. Each suppository was located in dual chamber cell (Sotax, Switzerland) through which PB was pumped (4 mL/min) at a temperature of 37 \pm 0.5 °C. The eluate was filtered (Whatman GF/D 3 μ m) upon leaving the cell and then was collected in fractions with fraction collector (Buchi, Switzerland). Samples were suitably diluted and assayed spectrophotometrically at 242 nm against PB. Results were expressed as the mean of five determinations.

2.2.6. Statistical analysis

Presented data, as mean \pm SD ($n = 3$) were analyzed by the one-way analysis of variance ANOVA with post-hoc Dun-

Table 1 Code and constituents of suppositories.

Codes	Substances (g)					
	AAP	SH2	SH4	Cocoa butter	PEG 1500	PEG 400
C0	0.125	–	–	0.875	–	–
C1	0.125	0.1	–	0.775	–	–
C2	0.125	0.2	–	0.675	–	–
C3	0.125	0.3	–	0.575	–	–
C4	0.125	–	0.1	0.775	–	–
C5	0.125	–	0.2	0.675	–	–
C6	0.125	–	0.3	0.575	–	–
P0	0.125	–	–	–	0.831	0.044
P1	0.125	0.1	–	–	0.736	0.039
P2	0.125	0.2	–	–	0.641	0.034
P3	0.125	0.3	–	–	0.546	0.029
P4	0.125	–	0.1	–	0.736	0.039
P5	0.125	–	0.2	–	0.641	0.034
P6	0.125	–	0.3	–	0.546	0.029

Table 2 Physicochemical tests.

Codes	Average weight (g) ± SD n = 20	Softening time (min) ± SD n = 3	Disintegration time (min) ± SD n = 3	Resistance to rupture (kg) ± SD n = 10	Drug content (%) ± SD n = 5
C0	1.081 (0.32)	3.06 (0.86)	2.68 (1.46)	1.7 (0.15)	98 (2.06)
C1	1.127 (0.29)	4.43 (0.56)	3.97 (1.06)	2.7 (0.45)	98.2 (2)
C2	1.144 (0.41)	4.43 (0.48)	4.15 (0.57)	2.9 (0.35)	100.8 (1.9)
C3	1.190 (0.05)	5.38 (0.77)	4.25 (0.73)	2.5 (0.77)	101.8 (0.76)
C4	1.095 (0.46)	4.06 (1.29)	3.7 (0.81)	2.5 (0.82)	99.9 (2.17)
C5	1.159 (0.08)	4.28 (0.54)	4.5 (0.41)	2.0 (0.46)	100.1 (1.35)
C6	1.178 (0.11)	5.55 (0.47)	10.98 (0.67)	2.5 (0.56)	102.1 (1.7)
P0	1.324 (0.12)	15.51 (0.96)	15.75 (1.02)	1.0 (0.29)	107.9 (1.75)
P1	1.348 (0.21)	19.3 (0.68)	16.93 (0.76)	0.8 (0.64)	105.4 (1.99)
P2	1.358 (0.36)	17.5 (1.22)	25.36 (1.21)	1.0 (1.23)	107.8 (2.13)
P3	1.361 (0.25)	19.23 (0.76)	32.53 (0.95)	0.9 (0.84)	106.5 (1.63)
P4	1.348 (0.36)	17.46 (0.49)	16.0 (0.52)	0.9 (0.61)	104.5 (1.83)
P5	1.344 (0.09)	14.5 (0.88)	20.08 (0.62)	0.9 (0.39)	105.3 (1.43)
P6	1.364 (0.15)	15.23 (0.66)	25.05 (0.43)	1.0 (0.17)	103.2 (1.38)

nett's test. Differences of $p < 0.05$ were considered statistically significant.

3. Results and discussion

3.1. The evaluation of physicochemical properties of suppositories

The preparation of starch hydrolysates (SH2 and SH4) was obtained according to our patent. Next, 14 series of rectal suppository were prepared by Fusion method (Table 1). Physical and chemical studies were carried out on all prepared series. The obtained average results of physicochemical tests are summarized in Table 2 and the results of dissolution of AAP were presented in Figs. 1–4.

It was found that the uniformity of mass of single-dose preparation test of all series of suppositories was within $\pm 5\%$, and thus met the requirements of Ph. Eur.

The softening time of all series of suppositories was found to be within acceptable values of Ph. Eur. All lipophilic suppositories were deformed in 15 min, and hydrophilic suppositories were dissolved during the 60 min. Furthermore, in the case of a lipophilic suppositories, it was noted that the higher the percentage of SH addition, the longer the time of softening: suppositories without SH – 3.06 min. Series of suppositories with 30% of SH2 increased the time by 2.32 min and 30% of SH4 – 2.49 min compared to suppository without SH. There was no correlation between the increasing time of deformation and an increasing percentage of SH addition, for PEG suppositories.

Examining the disintegration time, it was found that suppositories without SH were disintegrated quickly (cocoa oil – 2.68 min, PEG – 15.75 min), while suppositories with SH were disintegrated proportionally longer, respectively by 1.57 min for 30% of SH2, 8.3 min for 30% of SH4 - cocoa oil, and 16.78 min for 30% of SH2, 9.3 min for 30% of SH4 - PEG based. All series met the requirements of Ph. Eur.

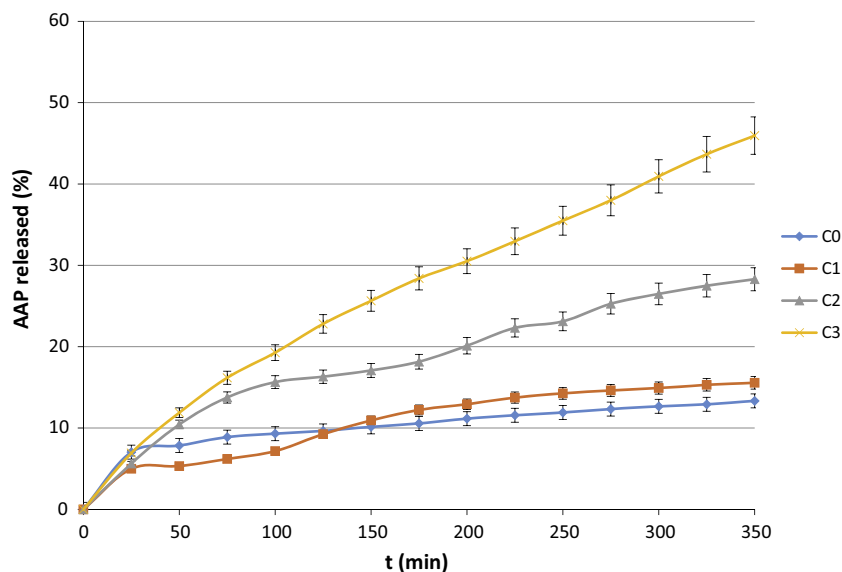


Figure 1 The effect of SH2 on the release of AAP from cocoa butter suppositories.

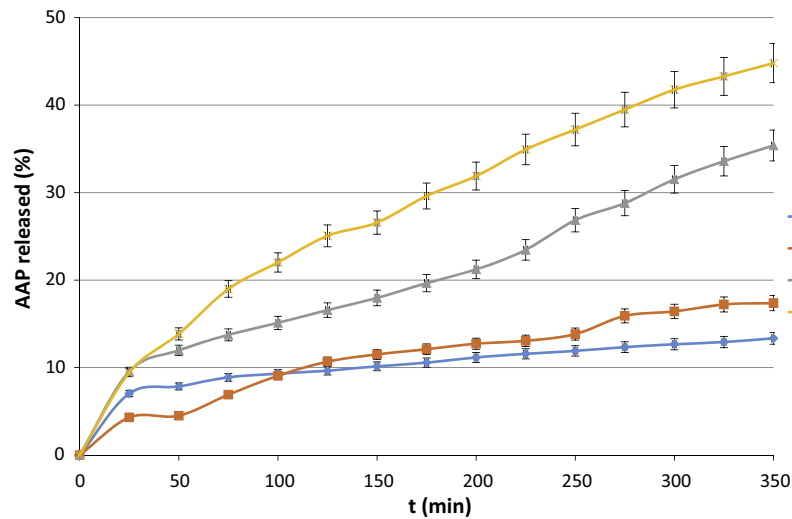


Figure 2 The effect of SH4 on the release of AAP from cocoa butter suppositories.

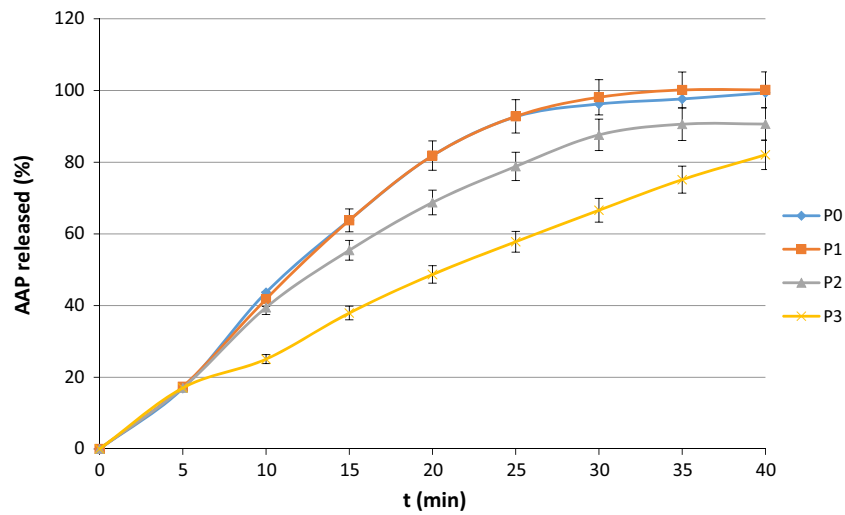


Figure 3 The effect of SH2 on the release of AAP from PEG suppositories.

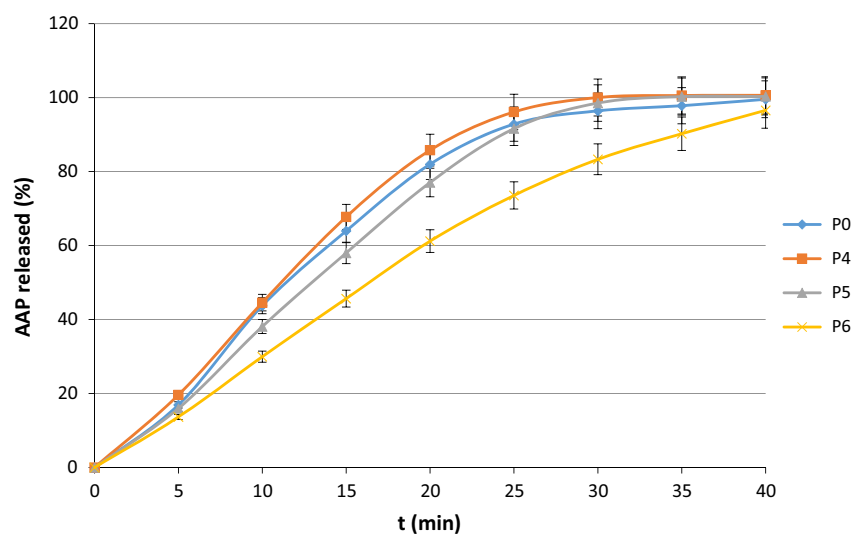


Figure 4 The effect of SH4 on the release of AAP from PEG suppositories.

The resistance to rupture of suppositories test showed that cocoa oil suppositories without SH, characterized the lowest hardness (1.7 kg). While suppositories containing 20% of SH2 were the hardest (2.9 kg), PEG suppositories with 10% of SH2 had the lowest hardness (0.8 kg), and the similar hardness (0.9–1.0 kg) was obtained at the same time for suppositories: without hydrolysates, 20% and 30% of SH2 and SH4. No correlation was found between the percentage of starch hydrolysates and resistance to crushing.

The research of the uniformity of content of single-dose in each series of suppositories, confirmed, that all series met the requirements of *Ph. Eur.* in the range of $\pm 10\%$.

3.2. The dissolution of AAP from suppositories in vitro

The study of dissolution of AAP from lipophilic suppositories was performed during 6 h, and hydrophilic suppositories required much shorter time - 40 min according to the literature (Janicki et al., 2001; Saleem et al., 2008).

The lipophilic suppositories without SH released only 15.88 mg AAP in 350 min, which was approximately 13% of the total drug content. The addition of both SH2 and SH4 significant increased the amount of released AAP – series with SH2 - C2 ($p < 0.01$) and C3 ($p < 0.001$) compared to C0 (the one-way ANOVA: $F(3,35) = 18.77$). Series with SH4 – C5, C6 ($p < 0.01$) (the one-way ANOVA: $F(3,52) = 21.45$). It is noted that the addition of 10% of both SH2 and SH4 had no significant effect on the amount of release AAP ($p > 0.05$).

The release of AAP from the PEG suppositories was carried out in 40 min. It was observed that this time was sufficient to release the whole amount of the drug from the suppository. Suppositories without SH released 133.38 mg AAP, and increasing the amount of SH2 resulted in a prolongation of the release time and consequent approximately 20% decrease in the amount of the drug released for a series of 30% of SH2, whose release profile was similar to the zero-order reaction. In the case of suppositories with SH4 addition of 10% or 20% did not cause significant differences between suppositories without SH ($p > 0.05$). Only addition of 30% of SH4 showed a different release profile and a small decrease in the quantity of the released substance (approx. 5%).

The highest release rate of the drug from the PEG suppositories was observed during the first 20 min of the study.

4. Conclusion

The addition of starch hydrolysates increased time of softening and disintegration of suppositories. The suppositories containing 30% SH have the longest softening and disintegration time. No correlation was found between the percentage of starch hydrolysates and resistance to crushing. Higher percentage of the starch hydrolysate in PEG suppositories caused longer active substance release but for cocoa oil suppository, it caused reduction in dissolution time. This can be explained

that the readily soluble starch hydrolysates facilitate the penetration of water into lipophilic suppository, and therefore AAP has better conditions for release.

The use of starch hydrolysates as a suppository modifying excipient of physicochemical properties, seems promising.

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