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In vitro release of theophylline from starch-based matrices prepared *via* high hydrostatic pressure treatment and autoclaving

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ABSTRACT

Recent works have demonstrated that release behavior of bioactive compounds varies with the nature of the matrix regarding its chemical composition, morphology and surface properties. Starch matrices varying in amylose content (maize, sorghum, Hylon VII) or pure amylopectin ones (waxy maize, amaranth starch), containing theophylline (10 mg, 50 mg/0.5 g of starch), were obtained *via* high hydrostatic pressure treatment (650 MPa/9 min) and autoclaving (120 °C/20 min). Both the treatment used and drug dose affected the theophylline release profiles from the matrices studied. The profiles of amylopectin starch matrices satisfactorily fitted with selected mathematical models, indicating a controlled theophylline release. The principal component analysis confirmed substantial differences in drug release between the amylose and amylopectin matrices. The differences in matrix morphology, internal surface area and porosity (mesopore diameter, cumulative pore volume) between the matrices studied were found to be key factors affecting the theophylline dissolution.

1. Introduction

As a biodegradable polymer with simple and well-defined chemical properties, starch is widely used in the food and non-food industry. To meet steadily increasing demands for improved specific starch properties, its granules are subjected to chemical or physical treatment (Pei-Ling, Qing, Qun, Xiao-Song, & Ji-Hong, 2012). Starch and its derivatives were successfully adopted to develop carriers for bioactive compounds or as a matrices/hydrogels for controlled drug delivery (Lopez-Cordoba, Deladino, & Martino, 2014; Xiao, 2013; Nair & Jyothi, 2013; Ismail, Irani, & Ahmad, 2013). Among different modifications and derivatization methods applied to produce new starch material from native granules, high hydrostatic pressure (HP) has attracted much attention as a non-thermal processing technology (Pei-Ling et al., 2012).

Although, HP has been defined as a "mild technology", it yields effective changes in the structure and in the physicochemical properties of starch granules (Pei-Ling et al., 2012). Starches composed of mainly amylopectin when subjected to HP treatment in excess of water was capable of forming an amorphous, three-dimensional network structure (Błaszczak, Wasserman, Fornal, & Yuryev, 2007). On the contrary, starches with medium and high concentration of amylose maintained their granular shape under HHP and demonstrated limited swelling and amylose release (Vallons & Arendt, 2009). The susceptibility (rate and degree) of HP-treated starches to retrogradation, their resistance to enzymatic activity or swelling power may differ significantly from those properties displayed by heat-gelatinized granules (Pei-Ling et al., 2012).

Hydrophilic matrices, including starch hydrogels produced *via* HP (Szepes et al., 2008) or these obtained by hydrothermal treatment and subsequent retrogradation (Yoon, Lee & Lim, 2009) have been recognized as interesting material for application in drug release formulation. They may be used for controlled release of both water-soluble and water-insoluble active compounds (Bialleck & Rein, 2011; Nair & Jyothi, 2013).

Theophylline as a model drug has been widely analyzed in various release systems (tablet, capsule, solution) since it demonstrated almost constant solubility (1 g/120 mL) in a wide range of pH values (Yoon et al., 2009). Since theophylline manifested narrow therapeutic range, it is crucial to investigate the differences in release rate of this drug between formulations (Wolny, Gruchlik, Chodurek, Szara, & Dzierżewicz, 2012). Recent works have demonstrated that the release behavior of theophylline varies with the nature of the matrix, and can be controlled among others through its chemical composition, method of formulation used and/or its physical properties (Nair & Jyothi, 2013).

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Ultrahigh hydrostatic pressure as an attractive physical process was also applied to formulate the main starch carrier for theophylline (Szepes et al., 2008). The potato (PS) and maize (MS) starches containing theophylline were treated with 700 MPa for 5 min in order to evaluate (*in vitro)* their effectiveness in drug delivery behavior. The release mechanism of theophylline from the starch-based matrices was characterized with different empirical models. The mechanism that regulates the release behavior of an active substance from the polysaccharide matrices involves such complex processes as: swelling, wettability, diffusion, biodegradation (erosion) processes, and their interactions (Nair & Jyothi, 2013). According to Szepes and co-authors, the release of theophylline from PS best fitted to the Hixon–Crowel model indicating that the drug release occurred only in vertical direction relative to matrix surface. However, the release of theophylline from MS matrices was best explained by the Krosmeyer–Peppas kinetics signifying that the theophylline release was governed by non-Fickian diffusion. This phenomenon was ascribed by the authors to the simultaneous water uptake during drug diffusion, which in turn affected matrix relaxation.

Little information is available in literature regarding applicability of HP and use of other types of starch *i.e.* with unique physicochemical properties (amaranth and sorghum starches) (Błaszczak, Misharina, Fessas, Signorelli, & Gorecki, 2013), or starches with complex polymorph structure (Hylon VII) to obtain novel material with suitable properties for drug release.

In this study the following starches: waxy maize and amaranth starch (composed of almost 100% amylopectin), maize and sorghum (~20% of amylose) as well as Hylon VII (68% of amylose), were evaluated as the main and potential carriers of theophylline. Theophylline as a model drug (at low and high drug content) was used to characterize drug delivery behavior from starch matrices prepared *via* hydrothermal (autoclaving, 121 °C, 0.1 MPa, 20 min) and non-thermal (HHP, 650 MPa, 9 min, 30 ± 2 °C) treatment. An *in vitro* study was conducted in order to determine kinetic parameters by fitting experimental data to selected mathematical models.

2. Materials and methods

2.1. Materials

Seeds of plant species *Amaranthus cruentus L.* were donated by the Metro Industrial Centre "Szarłat" s.c. (Łomża, Poland), and grains of *Sorghum bicolor* (v. Rona 1) were purchased from the Kutno-Centre for Sugar Beet Breeding in Straszkow, Poland.

The starch from amaranth seeds was isolated and purified according to the method developed by Walkowski, Fornal, Lewandowicz, and Sadowska (1997). Because amaranth starch granules (pure amylopectin starch) naturally form agglomerates that vary in diameter, the isolated starch granules were sieved through a screen with a mesh of 350—in order to unify their diameters.

The isolation procedure described by Olayinka, Adebowale, and Olu-Owolabi (2008) was used to obtain starch from sorghum grains (19.2% of amylose).

The other experimental materials were Hylon VII starch (68% of amylose), refined from high amylose maize (The National Starch & Chemical Co.), waxy maize starch (trace amounts of amylose) (Sigma, S-9679), and commercial maize starch (20.5% of amylose) which was donated by the Department of Food Concentrates in Poznan, the Institute of Agricultural and Food Biotechnology, Poland.

Since in our previous work these starches were fully characterized regarding their chemical composition (Błaszczak et al., 2013), the results were not presented herein.

Anhydrous theophylline (min. 99%, T-1633) was purchased from Sigma.

2.2. Sample preparation

Starch–water suspensions (3 g dm/10 mL) containing solubilized theophylline at the concentration of 10 mg and 50 mg (per 0.5 g dm of starch) were thoroughly mixed and homogenized with a Polytron Ultraturrax homogenizer IKA-T18 (IKA works, Wilmington, USA) for 1 min at 12,000 rpm.

2.2.1. Pressure treatment

The sample prepared was closed in a teflon tube (50 mL), thoroughly mixed, deaerated, closely sealed and subjected to HHP treatment using a high pressure device type Unipress U-303 (Warsaw, Poland). The teflon tube was put into a high pressure chamber (with the capacity of approximately 100 mL) filled with a pressure-transmitting medium which also minimized adiabatic heating. The samples were pressure-treated at 650 MPa for 9 min. The time needed to reach the working pressure was 2 min. The temperature inside the pressure chamber averaged 30 ± 2 °C. The pressure treatment was performed in two repetitions for each combination.

2.2.2. Autoclaving

For autoclaving the sample was closed into Pyrex® bottle (with cap and pouring ring), and pre-treated according to the method given by Yoon et al. (2009). In order to prevent the phase separation during autoclaving, the sample was heated in a water bath (70 °C/80 s), and then autoclaved (121 °C/20 min, 0.1 MPa) using a vertical steam sterilizer (type ASV, SMS Warsaw, Poland).

After the pressure treatment and autoclaving the starch matrices containing theophylline were frozen in liquid nitrogen, freeze-dried, grinded in a laboratory grinder (Sadkiewicz Instruments®, Poland) and sieved through a screen with a mesh of 170—in order to unify their diameters. The starch matrices were sealed in tubes and stored in a dark, cold and dry place until the analysis.

For better clarity, the following code of preparations has been proposed:

- *for starches*: maize starch (MS), sorghum starch (SS), Hylon VII (Hylon), waxy maize starch (WMS), and amaranth starch (AS);
- *for processing*: high pressure treatment (HP) and autoclaving (STR);
- *for theophylline* (T_f) concentration: 10 mg/0.5 g starch (T_{f10}), 50 mg/0.5 g starch (T_{f50}).

2.3. In vitro release studies

Each of starch preparations containing T_f was weighed on laboratory microbalance (Sartorius ME36S-OCE, Sartorius AG Germany) into eight gelatin capsules (B&E, Poland) in an amount of 100 mg.

The amount of T_f released from each capsule was evaluated over a 4-h period using an Erweka DT800 dissolution tester (Erweka GmbH, Germany). The test was accomplished by transferring 900 mL of purified water (Millipore, USA) to 6 dissolution vessels and the temperature was maintained at 37 ± 0.5 °C. One capsule was placed in each rotating basket within each vessel to begin the dissolution test at 50 rpm. In all the experiments, 6 mL of dissolution samples were collected from the vessels at: 5, 10, 15, 30, 45, 60, 90, 120, 150, 180, 210, 240 min and replaced with an equal volume to keep them submerged. A correction factor was included in the calculations to account for the drug lost in the sample. All determinations of T_f concentration and calibration curve were carried out using a UV-2501 PC spectrophotometer (SHIMADZU Corporation, Japan) at `λ = 273 nm. The calibration curve was plotted from