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Substituted amylose as a matrix for sustained-drug release: a biodegradation study

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Abstract

Substituted amylose polymers are prepared by reacting amylose chains with a suitable substituent such as 1,2-epoxypropanol (glycidol). Substituted amylose polymers are introduced as novel excipients for controlled release of bioactive materials. Since substituted amylose polymers are amylose-based polymers, they are subject to biodegradation by α-amylase enzymes present in the gastro-intestinal tract; thus, gamma spectroscopy is used to follow the release of the natural abundant rhenium (VII) oxide used as a drug model, and to test their resistance to α-amylase enzymatic degradation. Two substituted amylose solid dosage forms were prepared: (i) matrix system and (ii) dry-coated tablets. Matrix systems and dry-coated tablets maintained their structure, and controlled the release of [^{186}Re] showing no significant degradation of tablets by α-amylase. © 2001 Elsevier Science B.V. All rights reserved.

Keywords: Substituted amylose; Gamma spectroscopy; Rhenium VII oxide; Biodegradation; Controlled release

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1. Introduction

Amylose is an essentially linear polymer of glucopyranose units linked through α-D-(1,4) linkages (Fig. 1). The preferred conformation of amylose is a helix of variable dimensions, usually left-handed, with an open-core. The consequence of this conformation is that the hydroxyl group located on C-6 is pointed out of the open core (Short and Verbanac, 1960). Thus, it is possible to use a substituting agent like glycidol (1,2-epoxypropanol) and chemically modify these OH groups by an etherification process, leading to substituted amylose, SA,G-*n*, where SA stands for substituted amylose, G for glycidol and *n* the degree of substitution (DS) expressed as mole of substituent per kg of amylose. SA,G-*n* matrix systems have previously been used as a matrix for sustained drug release (Cartilier et al., 1999).

The release study of acetaminophen as a model drug from SA,G-*n* matrix systems depends on the DS and the nature of the substituent attached and clearly shows the controlled-drug release properties of SA,G-*n* matrix systems in a phosphate buffer solution (PBS pH 7.35) containing no enzymes. The release time of 90% (T90%) of acet

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aminophen as a drug model from SA,G-*n* matrix systems ranged between 5 and 20 h (Chebli and Cartilier, 1999a,c).

In previous work, it was shown, when the degree of substitution (DS) is low, that SA,G-*n* matrix systems reach the equilibrium state of relaxation extremely fast, with Fickian diffusion of the drug being the dominant drug transport mechanism. Higher DSs ensure SA,G-*n* chains withdraw more water into the tablet (Fig. 2), which lead to a more gelatinous structure of the matrix. Relaxation and stresses of SA chains due to water uptake will then be the predominant regulators of drug transport out of the matrix (Chebli and Cartilier, 1999b).

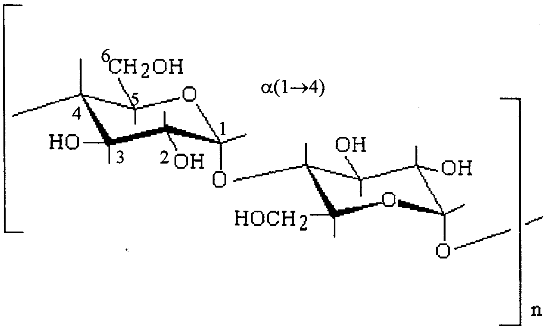

Fig. 1. Amylose structure.

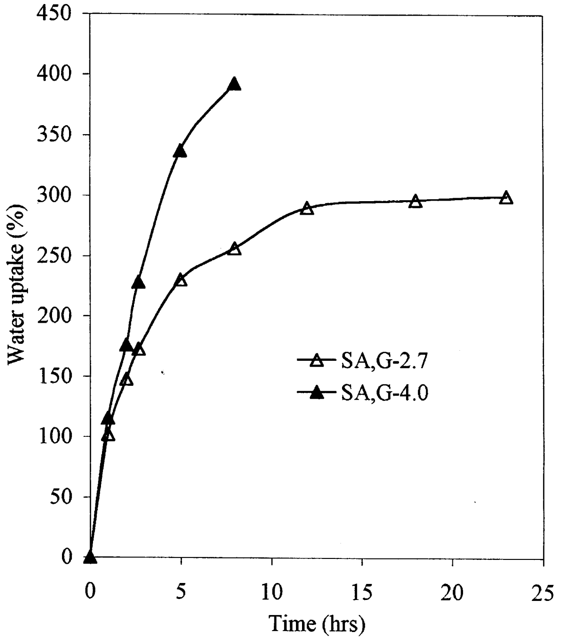

Fig. 2. Water uptake of SA,G-2.7 and SA,G-4.0 matrix systems.

Since these matrix systems are amylose-based polymers, they are subject to biodegradation by α-amylase enzymes present in the gastro-intestinal tract. In a classic tablet dissolution study, turbidity of the medium and the interference of enzymes present complicate standard analytical operations, such as spectrophotometry, giving non-valuable results. Seeking an accurate analytical method, in the present study gamma spectroscopy has been used, as a non-invasive method after the incorporation of the rhenium 186 radioisotope into SA,G delivery system. The idea is also to develop a simple procedure to test our different SA,G-*n* polymers' resistance to enzymatic biodegradation. For this reason, tablets containing natural abundant rhenium (VII) oxide as a model drug have been prepared. According to USP dissolution methods, all dissolution media are phosphate buffers with controlled pH. On the other hand, the certificate of analysis of COTAZYM® ECS-8 (Capsules commercialized by ORAGON CANADA LTD and containing a mix of enzymes including 30000 USP units of α-amylase per capsule) clearly indicates that the maximum activity of COTAZYM ECS-8 is at pH 6.8. The PBS pH 6.80 dissolution medium has contained 100000 units of α-amylase per liter medium. Rhenium (VII) oxide has been chosen for its attractive properties, which include a high neutron absorption cross-section, and solubility in water. In addition, there are two useful radioisotopes of rhenium, where the gamma energies vary between 100 keV and 200 keV for both [^{186}Re] and [^{188}Re] isotopes, with short half-lives of 3.77 days and 16.44 h respectively.

The SA dosage forms containing non-radioactive rhenium oxide (VII) are neutron-activated in a Slowpoke™ reactor, which is a safe, reliable, low-cost pool type nuclear reactor designed to operate automatically for extended periods of time without the use of skilled operators. The reactor provides a thermal neutron flux of 10^{12}

neutrons cm^{-2} sec^{-1}, which is higher than that available from small accelerators or radioactive sources. These advantages avoid the complexity and high costs normally associated with existing nuclear reactors making this activation approach particularly suitable for universities, hospitals and research establishments. Safety of operation is assured by limiting the maximum excess reactivity, thus permitting use of the inherent negative temperature coefficient as the safety mechanism.

In this manuscript, we discuss the controlled drug-release properties of such activated rhenium (VII) dosage forms and the resistance to enzymatic biodegradation of different SA,G-*n* matrix systems.

2. Materials and methods

2.1. Materials

Hylon VII (high amylose corn starch that contains 70% of amylose chains and 30% of amylopectine) was obtained from the National Starch and Chemical Company (Bridgewater, NJ), acetaminophen and Emcompress® from Mallinckrodt Chemicals (Toronto, Ontario, Canada), and glycidol from the Sigma Chemical Company (St Louis, MD); rhenium (VII) oxide was procured from the Aldrich Chemical Company (St Louis, MD) and Cotazym® ECS-8 from Organon Canada Ltd. (Scarborough, Ontario, Canada). All chemicals were of reagent grade.

2.2. Substituted amylose synthesis

First, 300 g of Hylon VII were added to 1.8 l of 1N NaOH at 50°C, and the system was homogenized for 15 min, at the slowest speed, in a Hobart planetary mixer. To obtain SA,G-2.7, 50 ml of glycidol was added gradually and homogenization continued for another 15 min at the same speed. The well-mixed mass was then neutralized. First, 1.5 l of distilled water (heated to 50°C) was added, followed by the necessary volume of acetic anhydride to obtain a pH of 7.0, and homogenization was continued for another 5 min at the same speed. The resultant gel was then filtered through a Büchner funnel, and washed with water and acetone. The powder product was exposed overnight to air (Encyclopedia of Polymer Science and Engineering, 1985; Peterson and Sober, 1956; Chebli and Cartilier, 1999c). Different degrees of substitution can also be obtained by simply varying the substituent/amylose ratio expressed as mole of substituent/kg of amylose.

2.3. Preparation of tablets

Different lots of tablets were prepared on a hydraulic press (C-30 Research & Industrial Instruments Company, London, UK) with a dwell time of 20 s. To prepare matrix tablets, weighing 400 mg, SA and rhenium (VII) oxide were mixed manually in a mortar and were compressed at 2.5 tons/cm^2 pressure. Their composition included 90% of a SA polymer, and 10% of rhenium (VII) oxide as model drug. Once compressed, the rhenium tablets were exposed to neutrons to render them radioactive. Dry-coated tablets consisted of a core and SA,G polymeric shell. The core weighed 80 mg and consisted of 50% of rhenium (VII) oxide and Emcompress®. The rhenium (VII) oxide and Emcompress® powder were mixed manually in a mortar and were compressed at 2.5 tons/cm^2 pressure. Once the core was compressed, it was neutron-activated, and then dry-coated with the shell that weighed 700 mg, and consisted either of 100% SA,G-2.7 or SA,G-4.0 polymer. All tablets prepared were 12.95 mm in diameter.

2.4. Dissolution study

The dissolution of SA tablets was studied in an U.S.P. XX No. 2 dissolution apparatus. The tablets were placed in Distek Dissolution System 2100A (Distek Inc., North Brunswick, NJ) equipped with a rotating paddle (50 rpm). The tablets were placed individually in 900 ml of a phosphate buffer solution, pH 6.8 at 37°C in the absence or the presence of α-amylase enzymes. The concentration of α-amylase enzymes was 100000 units of α-amylase per liter medium. Volumes from each dissolution vessel were collected at various time intervals. Each tablet formulation was tested in duplicate.

2.5. Gamma spectroscopy

Tablets containing natural abundant rhenium (VII) oxide as a model drug were neutron-activated in a Slowpoke™ reactor using the (n,γ) reaction in a flux of 1.0×10^{12} neutrons cm^{-2} sec^{-1} for 2 h. Since natural abundant rhenium is used, sufficient time is allowed for decay of the [^{188}Re] before commencing with the dissolution study. Volumes of 1 ml were taken from each tablet's dissolution vessel at various time intervals, and subsequently counted in a Ge(Li) detector automated well counter, and all spectrograms were corrected for decay using the [^{186}Re] energy peaks.

3. Results and discussion

3.1. Release of [^{186}Re] from SA polymeric matrix systems

Fig. 2 revealed that increased substitution of the glucosidic units allows penetration of a larger amount of water by augmenting the number of OH groups grafted on the amylose chains and consequently rendering the SA matrix more hydrophilic (Cartilier et al., 1999; Chebli and Cartilier, 1999a,b,c). It is hypothesized that increasing the DS hinders the α-amylase enzymes reaching their sites of degradation, which are α-D-(1,4) linkages between two glucopyranose units of amylose chains. This could be due to the steric effect generated from the increased number of substituent chains grafted on the amylose backbone and the hydrogen-bonding network formed between the OH groups. It is noteworthy to mention that no disintegration of SA,G-n matrix systems was observed with the DSs studied (Chebli and Cartilier, 1999c).

Therefore, the [^{186}Re] release from SA,G direct compressed matrix systems (Figs. 3 and 4) was studied in PBS pH 6.8 medium in the presence or the absence of α-amylase enzymes revealing a slightly faster controlled release of the drug from SA,G-2.7 matrix systems in the presence of the α-amylase enzyme in the dissolution medium by 0.52 h and no significant influence on the release properties when DS was increased to 4.0, confirming our hypothesis. In other terms, increasing the DS makes the matrix less accessible to the enzymes.

Other investigations have also reported that the T90% release time of acetaminophen from SA,G-2.7 and SA,G-4.0 matrix systems in PBS pH 7.34 is 10 and 9 h compared to 5 and 6 h in PBS pH 6.80 respectively, as shown in Figs. 3 and 4 (Cartilier et al., 1999). Therefore, an effect of neutron radiation, and/or an influence of activation time on SA chains conformation and their ability of gelling and controlling the release of the drug was suspected, regardless the solubility of the model drug and the dissolution medium (Harmon, 1957; Blouin and Arthur, 1958). It was therefore decided to study the release properties of different direct compressed tablets (tablet weight = 400 mg, compression force = 2.5 tons/cm^2) consisting of 90% of SA,G-2.7 and 10% of acetaminophen activated for different intervals of time.

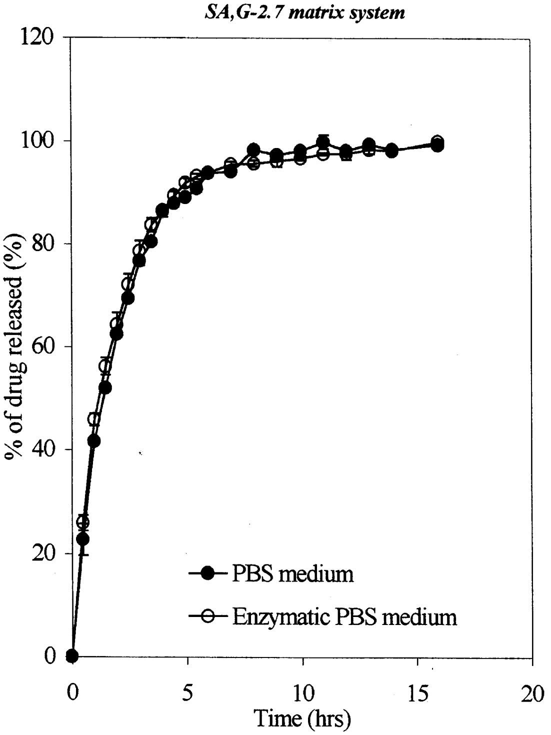

Fig. 3. Release profile of [^{186}Re] from SA,G-2.7 matrix tablets in the presence or the absence of α-amylase enzymes.

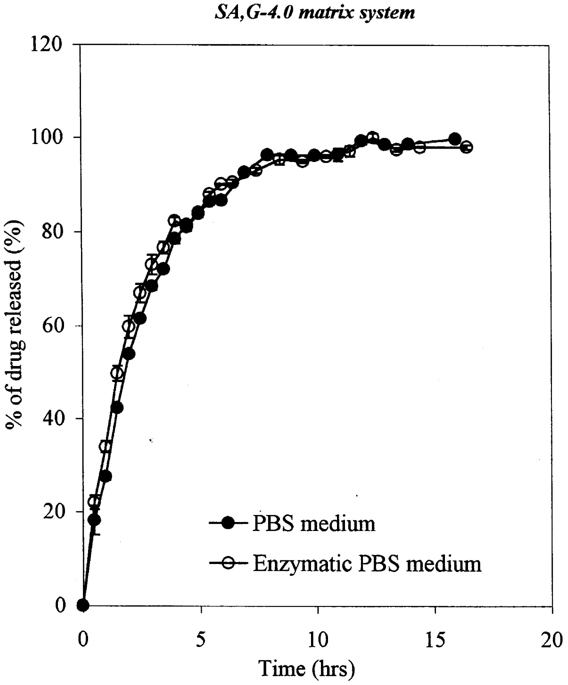

Fig. 4. Release profile of [^{186}Re] from SA,G-4.0 matrix tablets in the presence or the absence of α-amylase enzymes.

Fig. 5 shows a clear influence of activation time on T90% release time, where an increase of activation time slows down the release rate of the model drug. This could be explained by some physical or chemical changes in the SA network when energy (thermal or radiation) is supplied while activating the rhenium (VII) oxide. From a standpoint of product formation, several investigators studied the action of high-energy radiation on cellulose in order to understand the radiation effects on any other carbohydrates in the solid state. Cellulose in various forms has been irradiated with X-rays, β-rays, cathode rays, γ-rays and neutrons, under various atmospheric conditions (Blouin and Arthur, 1958; Glegg and Kertesz, 1957; Harmon, 1957). The overall results were similar and demonstrated that the physical and the chemical properties of cellulose are not affected significantly until a certain limit is reached where the most prominent chemical effect observed was the formation of reducing group. This decrease of free OH groups could be the reason of the observed decrease of swelling properties of SA,G matrix systems after neutron-activation.

3.2. Release of [^{186}Re] from SA dry-coated tablets

To be able to study the biodegradation of SA,G-*n* matrix systems and to bypass any influence of the activation on the release properties of SA polymers, a core consisting mainly of the model drug was compressed and then activated. The activated core is then dry-coated with unactivated SA polymer. The outer SA,G shell is a gel-forming matrix layer, and the core is the drug reservoir containing the rhenium (VII) oxide. The release of [^{186}Re] occurs by its dissolution at the shell-core interface and its diffusion through the polymeric gelified membrane. The time required for the model drug to diffuse through the shell is expressed as a lag time. Therefore any cracks in the shell, resulting from a possible erosion process in the presence of α-amylase enzymes, will be noticed by a dramatic shortening of the lag time.

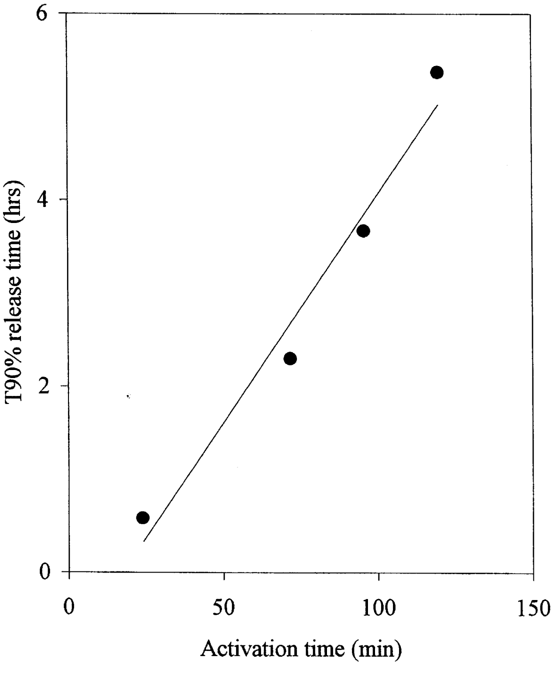

Fig. 5. Influence of activation time on the release properties of SA,G-2.7 matrix systems.

As Figs. 6 and 7 reveal, with a shell of either SA,G-2.7 or SA,G-4.0 (weighing 700 mg), the lag time was almost 7 h, followed by a linear release of [^{186}Re]. During the lag time, the dissolution profiles of [^{186}Re] from either SA,G-2.7 or SA,G-4.0 in the presence or the absence of α-amylase enzymes were superimposed, proving that these SA,G polymers are resistant to biodegradation, thus the release properties of SA,G tablets are not influenced by the presence or the absence of α-amylase enzymes.

4. Conclusion

Substituted amylose polymers are interesting excipients for controlled release of drug in solid dosage forms. In addition to the easy manufacturing of tablets by direct compression, results show that SA polymers can resist α-amylase biodegradation. Consequently, SA polymer matrix systems can be designed to facilitate colonic drug delivery.

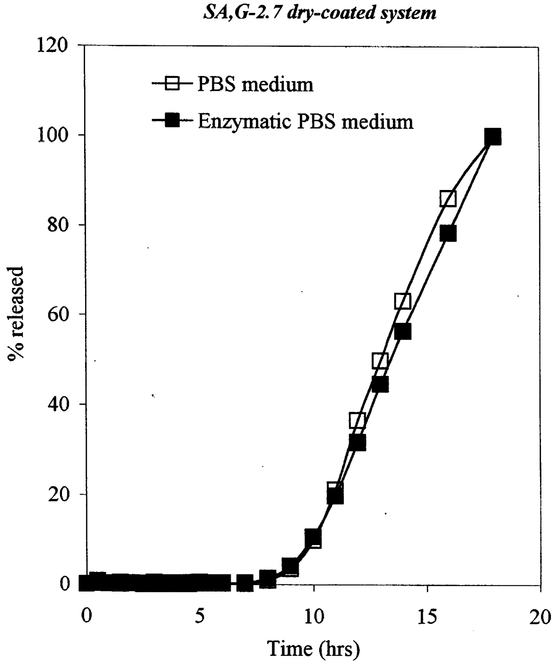

Fig. 6. Release profile of [^{186}Re] from SA,G-2.7 dry-coated tablets in the presence or the absence of α-amylase enzymes.

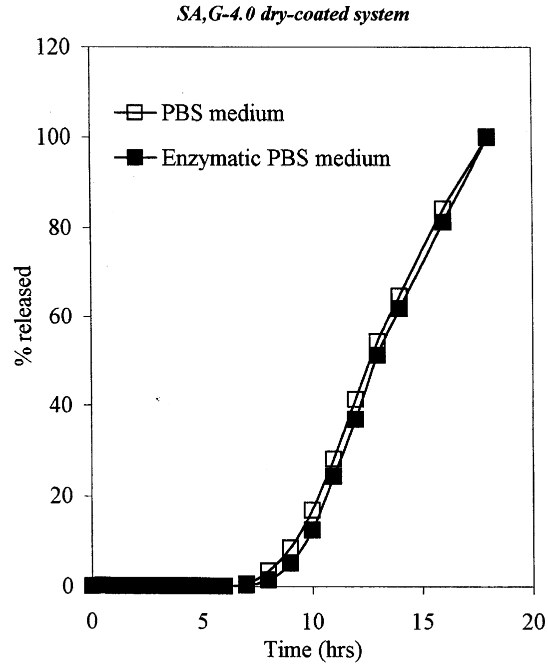

Fig. 7. Release profile of [^{186}Re] from SA,G-4.0 dry-coated tablets in the presence or the absence of α-amylase enzymes.

On the other hand, gamma spectroscopic analysis is a simple quantitative 'non-invasive' analytical method that can be used when the medium turbidity and/or the interference of enzymes present complicate standard analytical operations, such as spectrophotometry or chromatography when taking in consideration the possible influence of the energy supplied to the tablets during activation.

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