ELSEVIER

International Journal of Pharmaceutics 193 (2000) 167–173

international journal of pharmaceutics

www.elsevier.com/locate/ijpharm

Effect of some physical parameters on the sustained drug-release properties of substituted amylose matrices

C. Chebli, L. Cartilier *

Faculté de Pharmacie, Université de Montréal, C.P. 6128, Succ. Centre-Ville, Montréal, Québec, Canada H3C 3J7

Received 30 April 1999; received in revised form 1 September 1999; accepted 24 September 1999

Abstract

Substituted amylose (SA) matrix drug tablets prepared by direct compression show sustained drug-release properties. The influence of compression force (CF) and tablet weight (TW) on release properties was studied. CF ranging from 0.5 to 5.0 tons/cm^2 has no significant effect on the release properties of SA,G (glycidol) polymers, with a degree of substitution (DS) greater than 1.5. For a low DS, an augmentation of CF increases the release time of acetaminophen, used as a model drug, until a certain limit is reached. On the other hand, TW has a major effect on the release time of acetaminophen. Release time is directly proportional to TW. The effect of the nature of the active material, its solubility and its concentration in the formulation on the release properties of SA,G polymers was also evaluated, demonstrating the versatility of the system.

Keywords: Substituted amylose; Direct compression; Tablet weight; Drug solubility; Drug loading

1. Introduction

The use of polymers for biomedical applications, especially in the pharmaceutical field, has increased dramatically in recent years. The biocompatibility and biodegradability of polysaccharides has favored them as oral drug-delivery systems.

Amylose is essentially a linear polymer of glucopyranose units with α-D-(1,4) linkages. Linkage between the groups is specified in the ordinary way: α-Glc-(1→4)-α-(Glc)n-(1→4)-Glc. The preferred conformation of amylose is a helix of variable dimensions, usually left-handed, with an open core. The consequence is that the hydroxyl group located on C-6 is pointed out of the open core. Since it is the most reactive, followed by hydroxyl groups on C-3, and finally C-2, a substituting agent can be used to chemically modify these OH groups by an etherification process, resulting in substituted amylose (SA) which was

* Corresponding author. Tel.: +1-514-3432470; fax: +1-514-3432102.

E-mail address: cartilil@pharm.umontreal.ca (L. Cartilier)

0378-5173/00/$ - see front matter
PII: S0378-5173(99)00332-4

recently proposed as a matrix for sustained drug release (Cartilier et al., 1999; Chebli and Cartilier, 1999). SA polymeric matrices allow constant drug release and are obtained by direct compression of a dry admixture of the drug and the SA polymer (Chebli and Cartilier, 1999). This semi-synthetic polymer has been introduced as a new excipient for sustained drug release in solid dosage forms. SA is obtained by the reaction of high-amylose cornstarch with a substituent such as glycidol in an alkaline medium. Different degrees of substitution can be obtained by varying the ratio of substituent to amylose in the reaction vessel. The SA polymers we developed will be referred to hereafter as SA,s-n where SA means substituted amylose, s is a code defining the substituent used and n represents the degree of substitution (DS) expressed as the ratio mole of substituent/kg of amylose. G stands for glycidol.

Acetaminophen transport in SA,G matrices has been analyzed using exponential expressions leading to the ratio of relaxational over Fickian contributions (k_2/k_1) (Sinclair and Peppas, 1984; Peppas, 1985; Peppas and Sahlin, 1989). For low DSs, SA,G matrices, having k_2/k_1 ratios lower than 1, reach the equilibrium state of relaxation so that Fickian diffusion of the drug is the dominant drug transport mechanism. At specific DSs ($2.0 < DS < 2.7$), SA,G chains draw more water into the tablet, which leads to a more gelatinous structure of the matrix. Relaxation and stresses of SA chains as a result of water uptake will then predominantly control drug transport out of the matrix. For higher DSs, SA,G matrices allow the penetration of a larger amount of water so that molecular rearrangement is hindered and erosion occurs, accelerating release of the drug with a decrease in the k_2/k_1 ratio (Chebli and Cartilier, 1999).

Since all SA tablets are prepared by direct compression, this manuscript describes the influence of compression force (CF) and tablet weight (TW) on the k_2/k_1 ratio and, consequently, on the release properties of SA polymers. In addition, the influence of the nature and loading of the active material was also studied. Analyzing these properties gave a better understanding and better application of SA as polymeric systems for controlled drug release.

2. Materials and methods

2.1. Materials

Hylon VII (high amylose corn starch that contains 70% of amylose chains and 30% of amylopectin) was obtained from the National Starch and Chemical Company (Bridgewater, NJ, USA), acetaminophen from Mallinckrodt Chemicals (Toronto, ON, Canada), theophylline and glycidol from Sigma Chemical Company (St Louis, MO, USA); Chlorpheniramine maleate (CPM) was obtained from Napp Technologies (Lido, NJ, USA). All chemicals were of reagent grade.

2.2. SA synthesis

First, 300 g of Hylon VII were added to 1.8 l of 1 N NaOH at 50°C; then, the system was homogenized for 15 min in a Hobart planetary mixer, at its slowest speed. To obtain SA,G-2.7, 50 ml of glycidol were added gradually and mixing continued for another 15 min at the same speed. The well-mixed mass was then neutralized as follows. First, 1.5 l of distilled water (heated to 50°C) was added, followed by the addition of 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 filtered through a Büchner funnel, and washed with water and acetone. The powder product was air-dried overnight at ambient temperature (Peterson and Sober, 1956; Encyclopedia of Polymer Science and Engineering, 1985).

Other degrees of substitution were obtained by simply varying the substituent/amylose ratio (mole of substituent/kg of amylose).

2.3. Preparation of tablets

Different tablets were prepared on a hydraulic press (C-30 Research and Industrial Instruments Company, London, UK) with a dwell time of 20 s. The drug and SA were mixed manually in a mortar. To study the influence of CF on the dissolution rate, tablets containing 10% of acetaminophen as a model drug and 90% of SA,G-2.7 polymer were prepared. They weighed 400 mg

each and were compressed at various CFs ranging from 0.5 to 5.0 tons/cm^2. Those employed to investigate the influence of the TW on the dissolution rate contained 10% of acetaminophen as a model drug and 90% of SA,G-2.7 polymer, weighed 150, 300, 400, 500, or 800 mg, and were all compressed at 2.0 tons/cm^2. All tablets used to demonstrate the versatility of SA as a delivery system contained 10% of the active material (acetaminophen, theophylline or CPM) and 90% of SA,G-2.7 polymer and were compressed at 2.0 tons/cm^2.

2.4. Dissolution study

Drug release from SA tablets was studied using an U.S.P. 23/NF18 No. 2 dissolution apparatus. The tablets were placed individually in 900 ml of a phosphate buffer solution, pH 7.34, at 37°C in a Distek 2100A Dissolution System (Distek, North Brunswick, NJ, USA) equipped with a rotating paddle (50 rpm). Acetaminophen, theophylline, and CPM release was followed spectrophotometrically at 242, 272, and 262 nm, respectively, and recorded continuously. Acetaminophen, theophylline, and CPM absorption showed no interference at 242, 272, and 262 nm, respectively. A Hewlett Packard 89092 pump (Hewlett Packard, Santa Clara, CA, USA) drew up a 1-ml sample every 30 min towards a Hewlett Packard 8452A Diode Array spectrophotometer. The drug-release results were expressed by the equation proposed by Peppas (1985):

$$M_t/M\infty = kt^n \quad (1)$$

where M_t is the amount of drug released at time t, $M\infty$ is the total amount of drug released, k is a kinetic constant and n is the diffusional exponent for drug release. Thus, each release profile is expressed as a plot of $M_t/M\infty$ as a function of time t. Each tablet formulation was tested in triplicate.

2.5. Drug-release mechanisms

Eq. (1) can be used to analyze the sustained release behavior of various pharmaceutical or other systems. It has been used to analyze the first 60% of a release curve, regardless of geometric shape. Two competing release mechanisms, Fickian diffusional release and Case-II relaxational release, are the limits of this phenomenon (Sinclair and Peppas, 1984). Fickian diffusional release occurs by molecular diffusion of the drug because of a chemical potential gradient. Case-II relaxational release is the drug transport mechanism associated with stresses and state-transition in hydrophilic glassy polymers, which swell in water or biological fluids. The two phenomena controlling release are considered additive. Therefore, one may write (Sinclair and Peppas, 1984; Peppas and Sahlin, 1989):

$$M_t/M\infty = k_1t^m + k_2t^{2m} \quad (2)$$

where the first term is the Fickian contribution and the second term is the Case-II relaxational contribution. Eq. (2) can be rewritten as:

$$M_t/M\infty = k_1t^m[1 + (k_2/k_1)t^m] \quad (3)$$

By comparing Eq. (1) and Eq. (3), it is concluded that $m = n$ when the relaxational mechanism is negligible. The percentage of drug release because of the Fickian mechanism, F, is clearly calculated as:

$$F = [1 + (k_2/k_1)t^m]^{-1} \quad (4)$$

which leads to the ratio of relaxational over Fickian contributions as:

$$R/F = (k_2/k_1)t^m \quad (5)$$

Consequently, Eq. (5) analyzes the release behavior of the drug from SA matrices by calculating the k_2/k_1 ratio.

3. Results and discussion

3.1. Effect of CF on acetaminophen release from SA,G-2.7 matrices

Fig. 1 shows the effect of CF on release time of the drug from tablets made of SA,G polymers of different DSs. At low DSs (DS < 1.5), CF had a significant effect on T95% release time of the drug until a certain limit was reached (CF = 3 and 2 tons/cm^2 for SA,G-1.1 and SA,G-1.5, respec-

tively). Above a certain pressure, the packing characteristics of the particles or high interparticulate friction between particles will prevent any further interparticulate movement (Parrott, 1989). The subsequent reduction of compact volume is, therefore, accompanied by elastic deformation of the initial particles. Consequently, CF ($2 < CF < 5$ tons/cm^2) had no significant effect on the release rate of the drug. Similarly, at high DSs ranging from 2.0 to 7.0, CF had no significant impact on the drug-release rate. Since an increase in the DS augments the number of chains attached to the amylose backbone, SA chains are more spaced and more suitable for elastic deformation when compressed.

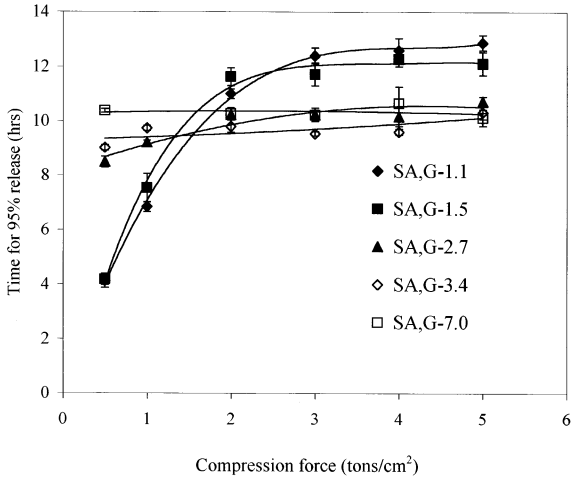

Fig. 1. Effect of compression force on acetaminophen release from glycidol (SA,G) matrices of different degrees of substitution.

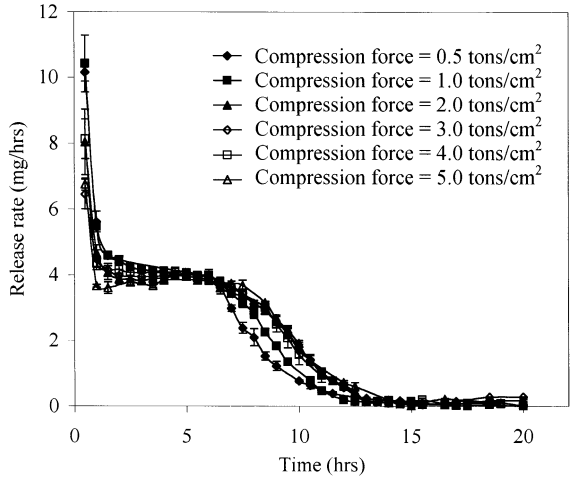

Fig. 2. Effect of compression force on the release rate of acetaminophen from glycidol (SA,G)-2.7 matrices.

Table 1
Ratio of relaxational over Fickian contributions (k_2/k_1) for acetaminophen release from SA,G-2.7 matrices

Tablet weight (mg)	Compression force (tons/cm^2)	k_2/k_1
400	0.5	1.6
400	1.0	1.0
400	2.0	0.8
400	3.0	5.1
400	5.0	7.9
150	2.0	7.9
300	2.0	0.9
400	2.0	0.8
500	2.0	0.3
800	2.0	0.3

According to the curves obtained in Fig. 2, it is obvious that compaction pressure had virtually no influence on the release rate (RR) of acetaminophen from SA,G-2.7 matrices. However, a faster release was observed during the first hour of the dissolution study, and this can probably be explained by free dissolution of the active material on the matrix surface. The RR varied between 4.5 and 3.5 mg/h after 1.5 h of dissolution for all CF ranges studied.

The overall release mechanism was calculated by fitting Eq. (5) to the data. This equation was originally derived for characterizing transport mechanisms in thin discs (Peppas, 1985; Peppas and Sahlin, 1989; Chebli and Cartilier, 1999). It has also been shown that the same expression can be adapted to characterize chain relaxation over diffusion drug-release mechanisms from other geometrical forms (Ritger and Peppas, 1987a,b). Table 1 presents the k_2/k_1 ratio reflecting the contribution of polymeric chain relaxation over diffusion as the mechanism of acetaminophen transport from SA,G-2.7 matrices. At usual CFs ($0.5 < CF < 2.0$), SA,G-2.7 chains were spaced

enough that the release of dissolved acetaminophen was controlled by relaxation of the chains but diffusion out of the matrix still played an important role. Since the apparent density of the tablet is exponentially related to the applied CF until the limiting density of the tablet is approached (Parrott, 1989), an increase of CF ($2.0 < CF < 5.0$) decreases the porosity of the matrix and, consequently, reduces the void space and spacing between two neighboring chains. Acetaminophen release was then more controlled by relaxation of the chains, which explains the increased k_2/k_1 ratio.

3.2. Effect of TW on acetaminophen release from SA,G-2.7 matrices

SA,G-2.7 matrices compressed at 2 tons/cm^2 showed the effect of TW on acetaminophen release (Fig. 3). Increasing TW slowed down the RR of acetaminophen used as a model drug. Since release of the active material from SA,G-2.7 matrix is mainly a result of the relaxation of the SA,G chains (Chebli and Cartilier, 1999), and because their rearrangement and RR are virtually independent of CF (Fig. 1), TW, or more precisely, tablet size is the only parameter, if any, that will influence, the RR.

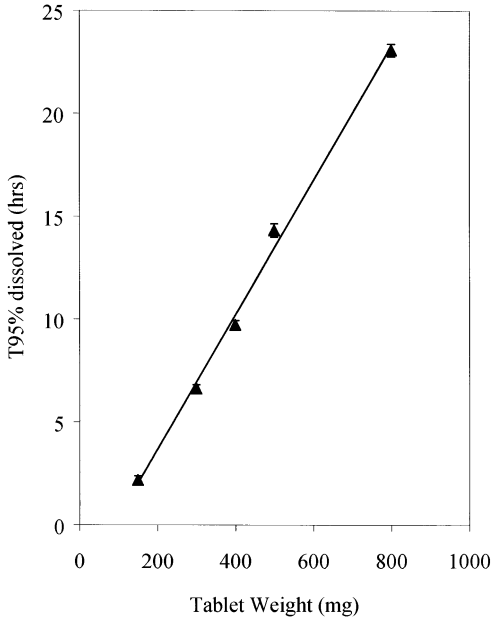

Fig. 3. Effect of tablet weight on acetaminophen release from glycidol (SA,G)-2.7 tablets.

A major effect of tablet size on the drug RR can be observed in the case of SA,G-2.7 matrix tablets containing a soluble drug, i.e. acetaminophen. It is hypothesized that water penetrates at the same rate to a certain depth of the tablet regardless of its size. After hydration, molecular rearrangement occurs, allowing the formation of a gel, which will hinder water penetration in deeper layers of the tablet and limit the diffusion and subsequent release of the dissolved drug. Thus, the gel layer will have the same thickness for different tablet sizes, but the dry and partially gelified core will not be equivalent, which explains the differences in the RR. Confirming what is mentioned above, the k_2/k_1 ratio values in Table 1 show that at low TWs, the tablets were thin, releasing 100% of the drug by simple relaxation of the chains. With an increase of TWs, a gel layer is formed around a dry core hindering water penetration into it, consequently, the release of the drug is controlled by its diffusion through the gel layer.

3.3. Effect of drug loading on the release properties of SA,G-2.7 matrices

To study the effect of tablet drug loading on the in vitro tablet release profile, theophylline was selected as a model for release profile investigation. Batches of tablets were prepared with the SA polymer SA,G-2.7 and theophylline, with a drug percentage ranging from 3 to 50%. All tablets prepared weighed 500 mg and were compressed at 2.5 tons/cm^2.

The results are presented in Fig. 4. A characteristic pattern was observed, demonstrating maximum release time for a 10% concentration of the drug. However, there was a clear control of drug release for concentrations ranging from 3 to 50% of theophylline. For low drug concentrations, release was controlled by a physical association between linear chains of SA and by the viscosity of the gel; these two phenomena occur in the

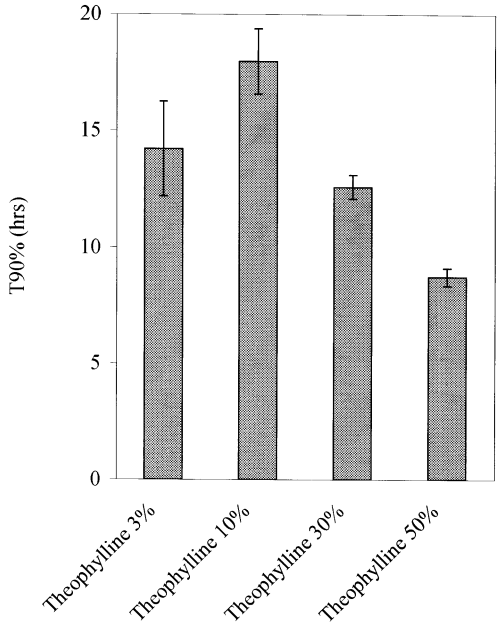

Fig. 4. Effect of theophylline loading on the sustained-release properties of glycidol (SA,G)-2.7 tablets.

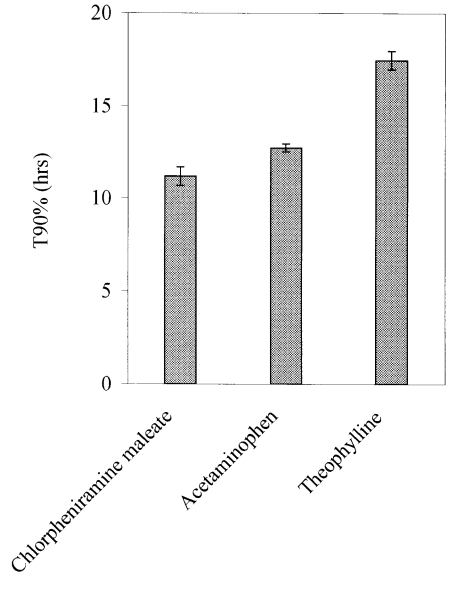

Fig. 5. Versatility of substituted amylose (SA) as a drug-delivery system.

presence of water and delay drug release by hindering drug diffusion inside the matrix. When the drug concentration increases, some erosion appears which competes with the above-mentioned mechanisms by accelerating the release process.

3.4. Versatility of SA as a drug-delivery system

Fig. 5 shows the 90% release time of different active materials. CPM was used as a freely-soluble model drug. Ninety percent of it was released in 11 h from the SA,G-2.7 matrix (TW = 500 mg and CF = 2.5 tons/cm^2). The T90% of acetaminophen, as a soluble model drug, was 13 h (TW = 500 mg and CF = 2.0 tons/cm^2). Theophylline, a slightly soluble model drug, was released in 18 h (TW = 600 mg and CF = 2.0 tons/cm^2). Fig. 5 confirms the excellent potential of this drug-delivery system.

4. Conclusion

This study reveals that CF has no significant effect on the release properties of SA,G polymers with a DS > 2.7. For DS < 2.7, T90% release time increases with an elevation of CF until a certain limit, beyond which CF has no further influence.

On the other hand, TW of SA,G-2.7 is directly proportional to the T90% of the drug used. If the T90% of the model drug is to be augmented as in the case of a very soluble drug, SA,G-2.7 matrix weight should be increased, independently of CF. In addition to these properties, the SA,G-2.7 matrix can be employed for a wide range of model drugs, independently of their nature, solubility, and concentration.

References

Cartilier, L., Moussa, I., Chebli, C., Buczkowski, S., 1999. Substituted amylose as a matrix for sustained drug release. US Patent No. 5, 879, 707.

Chebli, C., Cartilier, C., 1999. Substituted amylose as a matrix for sustained drug release, Pharm. Res. 16, 1436–1440.

Encyclopedia of Polymer Science and Engineering, 1985, vol. 4, second ed., Wiley, New York, pp. 386–388.

Parrott, E.L., 1989. Pharmaceutical Dosage Forms: Tablets, vol. 2, second ed., In: Lieberman, A., Lachman, L., Schwartz, J.B. (Eds.). Dekker, New York, pp. 201–220.

Peppas, N.A., 1985. Analysis of Fickian and non-Fickian drug release from polymers. Pharm. Acta Helv. 60 (4), 110–111.

Peppas, N.A., Sahlin, J.J., 1989. A simple equation for the description of solute release: III: coupling of diffusion and relaxation. Int. J. Pharm. 57, 169–172.

Peterson, E.A., Sober, H.A., 1956. Chromatography of proteins: I: cellulose ion-exchange adsorbents. J. Am. Chem. Soc. 78, 751–755.

Ritger, P.L., Peppas, N.A., 1987a. A simple equation for the description of solute release: I: Fickian and non-Fickian release from non-swellable devices in the form of slabs, spheres, cylinders or discs. J. Contr. Rel. 5, 23–36.

Ritger, P.L., Peppas, N.A., 1987b. A simple equation for the description of solute release: II: Fickian and anomalous release from swellable devices. J. Contr. Rel. 5, 37–42.

Sinclair, G.W., Peppas, N.A., 1984. Analysis of non-Fickian transport in polymers using a simplified exponential expression. J. Membrane Sci. 17, 329–331.