Substituted Amylose as a Matrix for Sustained Drug Release

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Purpose. Amylose derivatives form an important group of polymers, and many of them can be used as drug sustained-release systems.
Methods. Substituted amylose can be prepared in a 1-step reaction with substituent(s) in a basic medium. The substituents can be represented as (A—R), where (A) serves an epoxy, halide or suitable organic or inorganic function reacting with hydroxyl groups located on the amylose chain, and (R) is an organic radical.
Results. The present work shows the synthesis of different polymers and the effect of different (A) and/or (R) and their different degrees of substitution (n) on the sustained drug release from matrix tablets prepared by direct compression.
Conclusions. SA polymers are interesting excipients for the preparation of controlled drug release tablets.

KEY WORDS: substituted amylose; polymer; sustained drug release; direct compression.

INTRODUCTION

Among the many oral dosage forms designed for controlled release of drugs, tablets are of major interest to the pharmaceutical industry because of their highly efficient manufacturing technology. Many systems have been proposed to control drug release; they are based on release controlled by drug diffusion, solvent activation, polymer swelling, chemical reaction or osmosis. Most of the time, 2 or more mechanisms that obey Fick's law are combined (1).

Biodegradable polysaccharide matrices are interesting because the degradation of a natural product like starch occurs naturally in the human body (2). Starch is composed of 2 distinct fractions: amylose is the non-ramified fraction containing about 4,000 glucose units, and amylopectin is the branched fraction containing about 100,000 glucose units (3). Starch and modified starch are widely and safely used with approval by the Food and Drug Administration in the food (thickeners, enhancers of organoleptic properties, texture modifiers) and pharmaceutical industries (fillers, binders, disintegrants) (3). Short and Verbanac (4) disclosed a binder/disintegrant constituted of starches physically modified by compaction. Trubiano (5) described modified starches which demonstrated low swelling in cold water and which are suitable for use as disintegrants in compressed tablets. Chemical modification of starch has produced cold water-soluble intact granular starches, such as starch phosphate, starch sulfate and especially carboxymethylstarch (6). However, these starches are only employed in tablets as disintegrants. Physically modified starch (pregelatinized starch) has been used as an excipient for sustained release (7,8). Only thermally modified starches have been proposed and evaluated as hydrophilic matrices for controlled oral delivery (9,10). On the other hand, cross-linked amylose has proven to be a very efficient tool for controlled drug release (11). Cross-linked amylose is produced by the reaction of amylose with epichlorohydrin in an alkaline medium. Depending on the amount of epichlorohydrin, different degrees of cross-linking can be obtained. However, increasing the degree of cross-linking of amylose leads to an accelerated drug release rate from cross-linked amylose tablets. At high degrees of cross-linking, amylose is used as a tablet binder and/or disintegrant (12).

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 (4). 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, it is possible to use a substituting agent and chemically modify these OH groups by an etherification process, resulting in substituted amylose (SA) which is proposed hereafter as a matrix for sustained drug release (13).

The 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 will be used for glycidol, E4 for 1,2- epoxybutane, E12 for 1,2-epoxydodecane and C4 for 1-chlorobutane.

MATERIALS AND METHODS

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, U.S.A.), acetaminophen from Mallinckrodt Chemicals (Toronto, Ontario, Canada), and glycidol from the Sigma Chemical Company (St. Louis, MD, U.S.A.); 1,2-epoxybutane, 1,2-epoxydodecane and 1-chlorobutane were procured from the Aldrich Chemical Company (St. Louis, MD, U.S.A.). All chemicals were of reagent grade.

SA Synthesis

First, 300 g of Hylon VII were added to 1.8 L of 1N 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 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) were 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 (14,15). Different degrees of substitution can also be obtained by simply varying the substituent/amylose ratio (mole of substituent/kg of amylose).

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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 seconds. The drug and the SA were mixed manually in a mortar. Tablets used for dissolution tests, weighing 400 mg each, were compressed at 2.5 tons/cm^2 pressure. They were 12.9 mm in diameter and 2.8 mm thick. Their composition included 90% of a SA polymer, and 10% of acetaminophen as the model drug. Tablets used for water uptake, weighing 400 mg each, contained 100% of the SA polymers studied.

Dissolution Study

The dissolution of SA tablets was studied in an U.S.P. XX No. 2 dissolution apparatus. The tablets were placed individually in 900 ml of a phosphate buffer solution, pH 7.34, at 37°C in Distek Dissolution System 2100A (Distek Inc., North Brunswick, NJ, U.S.A.) equipped with a rotating paddle (50 rpm). Drug release was followed spectrophotometrically at 242 nm, and recorded continuously. A Hewlett Packard 89092 pump (Hewlett Packard, Santa Clara, CA, U.S.A.) drew up a 1-ml sample every 30 min towards a Hewlett Packard 8452A Diode Array spectrophotometer. The drug release results were expressed using the equation proposed by Peppas (16):

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

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 was expressed as a plot of $M_t/M\infty$ in a function of time t. Each tablet formulation was tested in triplicate.

Water Uptake

The swelling behavior of a polymer can be characterized by measuring its water uptake ability. A gravimetric method was used to record water uptake in triplicate. At appropriate time intervals, each tablet was removed from the water with forceps, briefly patted with lint-free cleaning tissues to remove the solution wetting its surface, and weighed. The swelling study was done in a distilled water medium, pH 6.5, at 37°C. The results were expressed as % of water uptake (100 × weight of water/weight of tablet before hydration) in a function of time (hours). Water uptake equilibrium was also used to evaluate the influence of the DS and of the attached chain on the swelling behavior of these polymers.

Drug Release Mechanisms

Equation 1 can be used to analyze the sustained release behavior of various pharmaceutical or other systems. Equation 1 has also been used for the first 60% of a release curve, regardless of geometric shape, and 2 competing release mechanisms, Fickian diffusional release and Case-II relaxational release, are the limits of this phenomenon (17). Fickian diffusional release occurs by molecular diffusion of the drug due to 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 (18):

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

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

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

By comparing of equations 1 and 3, it is concluded that m = n when the relaxational mechanism is negligible. The percentage of drug release due to 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, equation 5 was used to analyze the release behavior of the drug from SA matrices by calculating the ratio k_2/k_1 (Table I).

RESULTS AND DISCUSSION

SA Synthesis

Interesting polymers can be obtained through different substituents where the maintain of the tablet structure and sustained release properties of the final product will depend on the length of the chain R, its hydrophobicity, the presence of hydroxyl groups and of an ionisable function.

Substituents can be represented as A-R, where A is the attacking head that reacts with the polymer and consequently attaches the tail R to it. Two different attacking groups were used: i) an epoxy function that generates a hydroxyl group attached to adjacent carbon after the ring opening, such as 1,2-epoxypropanol, 1,2-epoxybutane and 1,2-epoxydodecane, and ii) a halide such as 1-chlorobutane.

Table I. Ratio of Relaxational Over Fickian Contributions

Polymer	m[a]	Relaxational over Fickian contribution (k_2/k_1)
SA,G-0.8	0.453	0.4
SA,G-1.5	0.453	0.9
SA,G-2.0	0.451	12.7
SA,G-2.7	0.450	15.1
SA,G-3.4	0.448	4.6
SA,G-5.4	0.446	3.5
SA,G-7.0	0.445	2.6
SA,E4-2.0	0.454	2.6
SA,E4-5.0	0.450	4.5
SA,E4-7.0	0.449	1.1
SA,E4-10.0	0.448	1.3
SA,E12-4.0	0.445	0.9
SA,E12-5.0	0.453	0.4
SA,E12-6.0	0.449	0.6
SA,E12-7.0	0.448	0.9

[a] Diffusional exponent, m = d / h, where d is tablet diameter and h is tablet thickness.

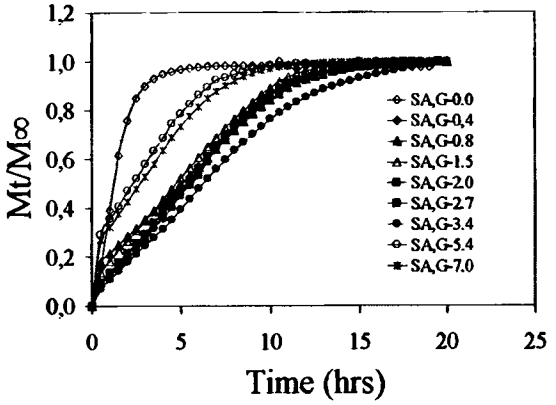

Fig. 1. Effect of DS on acetaminophen release from SA,G-n tablets.

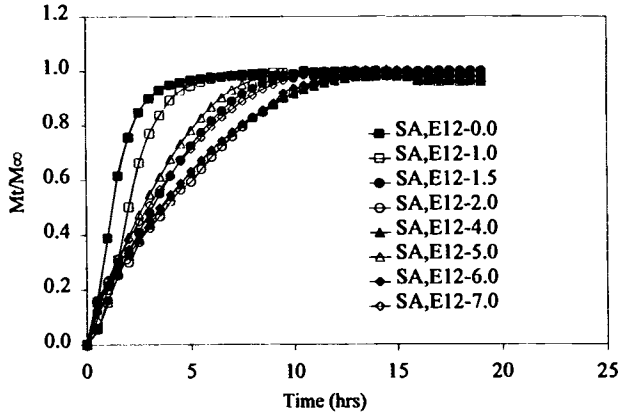

Fig. 3. Effect of DS on acetaminophen release from SA,E12-n tablets.

Dissolution Study

Effect of DS on the In Vitro SA,s-n *Tablet Release Profile*

Figure 1 illustrates the influence of DS on the release profile of 10% of acetaminophen as a model drug from SA,G-n tablets. Clearly, all the curves show a sustained release of the drug with a virtually linear profile. Release time of 95% of the drug ranges from 9 to 20 hours for all DSs studied. It is evident that low DSs ranging from 0.4 to 3.4 have no significant effect on the release profile. For high DSs ranging from 5.4 to 7.0, a slight decrease in total release time is observed. On the other hand, it is obvious that amylose treated under the same conditions but in the absence of a substituent does not present any sustained release properties.

The use of more hydrophobic substituents, such as 1,2-epoxybutane and 1,2-epoxydodecane, makes the resulting polymers, SA,E4-n and SA,E12-n respectively, more hydrophobic than SA,G-n polymers. As Figures 2 and 3 show, an increase of DS slows the rate of drug release till a certain limit is reached.

Knowing that the free end of 1,2-epoxybutane and 1,2-epoxydodecane chains is a methyl group, no possible side reaction may occur once attached to the amylose chains. It can be assumed that increasing the DS saturates the possible reactive sites of the amylose chains and accelerates T95% release time of the model drug, by rendering the matrix less hydrophilic, until a certain extent where no more substituents can be attached to the amylose chains. Consequently, increasing the DS has no effect on the release profile of the drug. Figures 2 and 3 confirm that the substitution threshold (St) for SA,E4 and SA,E12 polymers is $DS_{St} = 5$ and $DS_{St} = 2$ respectively.

On the other hand, the free end of glycidol, once attached to the amylose chain, is a hydroxyl group. Consequently, glycidol polymerization may occur, increasing the number of hydroxyl groups and the length of the chain attached to the amylose helix, since both the number of hydroxyl groups and the length of the chain are directly proportional to the degree of glycidol polymerization.

Effect of the Number of Hydroxyl Groups Attached on the Chain on the In Vitro Release Profile

Figure 4 shows acetaminophen release from 2 SA polymers, SA,C4-n and SA,G-n, with 2 different DSs (DS = 2.7 and 5.4). Knowing that a 4-carbon chain with no OH groups is grafted on the SA,C4-n polymer, the polymer is more hydrophobic, thus slowing down drug release by forming a drug diffusion barrier. Consequently, an increase of DS makes the matrix more hydrophobic, slowing down the release of the drug.

On the other hand, SA,G-2.7 polymer has a 3-carbon chain with 2 OH groups grafted on the amylose helix, which makes the matrix much more hydrophilic than SA,C4-2.7 matrix, accelerating water pumping into the matrix, but also favoring the molecular rearrangement (entanglement, hydrogen bond,

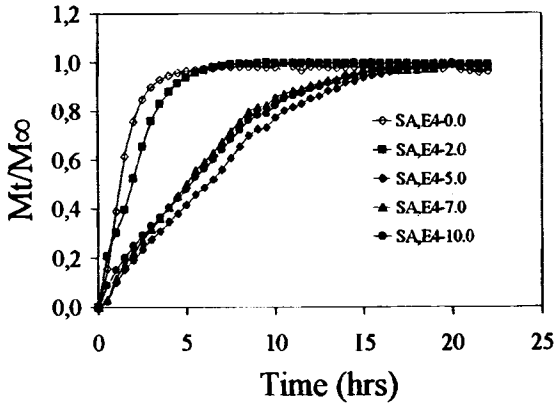

Fig. 2. Effect of DS on acetaminophen release from SA,E4-n tablets.

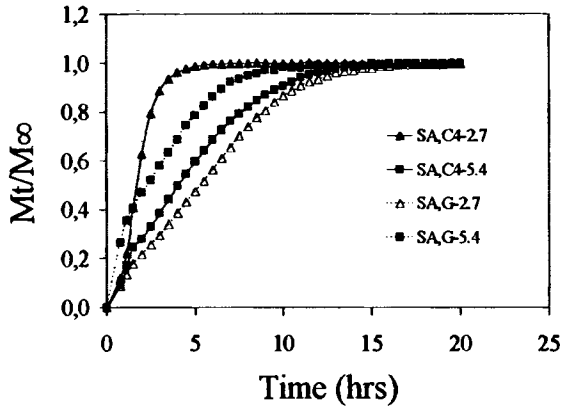

Fig. 4. Effect of OH groups attached on acetaminophen release profile.

recrystallisation of amylose chains, polymorphic transition) (19) that controls and slows down drug release.

At a DS of 5.4, the SA,G matrix swells so much that erosion of the surface takes place, increasing the release of the drug.

Effect of Attached Chain Length on the In Vitro Release Profile

Figures 2 and 3 show the release profiles of two SA polymers, SA,E4-2.0 and SA,E12-2.0 in particular, where SA,E12-2.0 has the longest sustained drug release time. This could be due to the higher steric effect of the 12-carbon chain, added to its higher hydrophobicity. Figures 2 and 3 confirm the higher steric effect of the 12-carbon chain, since St of SA,E12 polymers is DS_{St} = 2, compared to DS_{St} = 5 for SA,E4 polymers.

Water Uptake

Effect of DS on the In Vitro SA,G-n Tablet Water Uptake

The results of water absorption by SA,G-n tablets are presented in Figure 5. Analysis of water uptake as a function of time reveals a significant increase in the amount of water taken up when the DS of amylose is augmented. The absorbed quantity of water is high, especially for higher DS. No disintegration of the tablets was observed with the DSs studied. Surprisingly, DSs ranging from 0.4 to 3.4 had no effect on the drug release profile, but exerted a major action on its swelling properties. It can be assumed that increased substitution of the glucosidic units allows penetration of a larger amount of water. For higher DS (DS = 5.4–7.0), molecular rearrangement of the amylose chains is hindered and erosion occurs, accelerating the release rate of the drug; on the other hand, the increase in the number of OH groups enhances viscosity of the gel, decreasing the release rate. Consequently, a higher burst is observed in SA,G-n release profiles for higher DSs, then, the gel layer is formed and controls release of the drug.

Effect of Hydroxyl Groups on the Water Uptake Profile

Figure 6 shows the water uptake profiles of SA,C4-5.4, containing no free attached hydroxyl groups on the chain, and SA,G-5.4, containing 2 hydroxyl groups. The OH-rich chain

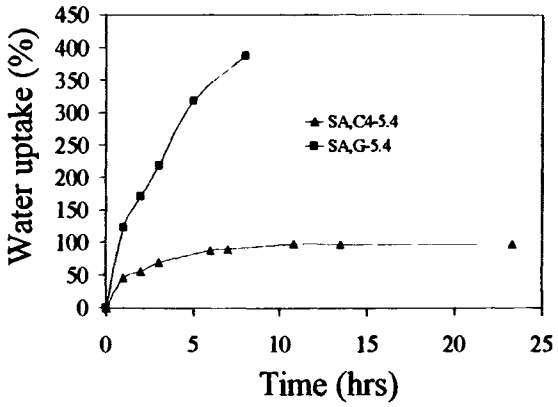

Fig. 6. Effect of OH groups on SA polymer water uptake profile.

grafted onto the SA,G polymer makes the SA,G-5.4 matrix draw almost 400% [water(g)/polymer(g)] in 7 hours, compared to a SA,C4-5.4 matrix drawing 100% [water(g)/polymer(g)] in 8 hours. Having no free hydroxyl group attached on the grafted chain, SA,C4-5.4 polymer is more hydrophobic than SA,G-5.4; therefore, it calls less water into the matrix and the release rate of the drug is consequently slower, as shown in Fig. 4. Slight erosion of SA,G-5.4 matrix might also contribute to its high drug release rate.

Effect of Attached Chain Length on the Water Uptake Profile

Figure 7 shows the water uptake profiles of SA,E4-2.0 and SA,E12-2.0 compared to SA,G-2.0. The hydrophobic aspect of the attached chains on SA,E4-n and SA,E12-n polymers makes the tablets not as absorbent as SA,G-n for the same degree of substitution. Knowing that both chains are free to move by free rotation of the C-C bond and are able to exert, to a certain extent, a repulsive force between 2 neighboring amylose helixes, they may end up in a sandwich position between 2 neighboring helixes.

SA,E4-2.0 matrix absorbs water slowly, allowing a slow molecular rearrangement before reaching the equilibrium state in 11 hours. SA,E12-2.0 matrix absorbs water faster than SA,E4-2.0, leading to a faster molecular rearrangement and reaching faster the equilibrium state in 6 hours. However,

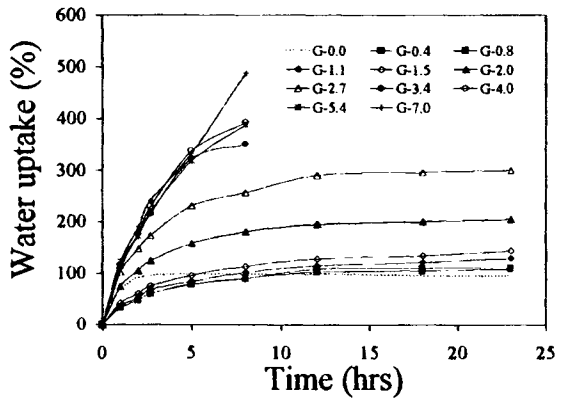

Fig. 5. Effect of DS on SA,G-n tablet water uptake profile.

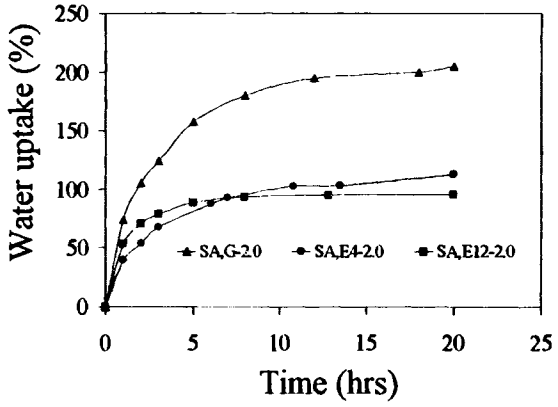

Fig. 7. Effect of the length of chain attached on SA polymer water uptake profile.

SA,E12 helixes are still able to form a gel network and, therefore, control drug release.

Analysis of Drug Transport in SA Polymers

Acetaminophen release data from SA polymers are very reproducible with a margin of error of approximately 1% (error bars are not plotted since they overcrowd the figures). Data on drug transport in SA polymers are analyzed using exponential expressions (Eqs. 1 and 2), leading to the ratio of relaxational over Fickian contributions (Eq. 5). Table I shows the k_2/k_1 ratio values.

For low DSs, SA,G matrices, having k_2/k_1 ratios lower than 1, reach the equilibrium state of relaxation so fast with Fickian diffusion of the drug being the dominant drug transport mechanism. At specific DSs ($2.0 < DS < 2.7$), SA,G chains call more water into the tablet (Fig. 5), which leads to a more gelatinous structure of the matrix. Relaxation and stresses of SA chains due to water uptake will then predominately control drug transport out of the matrix. For higher degrees, SA,G matrices allow penetration by a larger mount of water so that molecular rearrangement is hindered and erosion occurs, accelerating drug transport out of the matrix and allowing a decrease in k_2/k_1 ratio.

SA,E4-2.0 matrix absorbs water slowly, allowing a slow molecular rearrangement before reaching the equilibrium state in 11 hours (Fig. 7). Consequently, drug release is more controlled by this slow chains relaxation ($1.1 < k_2/k_1 < 4.5$), allowing the total release of the drug in almost 6 hours (Fig. 2). As for SA,E12-2.0 matrix, it absorbs water faster than SA,E4-2.0, leading to a faster molecular rearrangement and reaching a faster equilibrium state in 6 hours (Fig. 7). It can be concluded that drug release is more controlled by the diffusion through the matrix than by the relaxation of the chains, as k_2/k_1 ratios are smaller than 1. In addition to this fast rearrangement of chains, the hydrophobic 12-carbon chain attached to the amylose chains retard the diffusion phenomenon of the drug by steric effect, leading to a total release of the drug in almost 12 hours (Fig. 3).

CONCLUSIONS

SA polymers are interesting excipients for the preparation of controlled drug release tablets. Their advantages include very easy synthesis of the polymer, easy manufacturing of tablets by direct compression, and the safety of modified amylose.

In the case of SA,G-n polymers, DSs ranging from 0.4 to 3.4 have no significant effect on release of the model drug but exert a very remarkable influence on the water uptake of these polymers.

On the other hand, the versatility of the hydrophilic/hydrophobic aspect of SA matrices can reduce or inhibit α-amylase activity through the steric effect of a hydrophobic substituent grafted on the amylose helix, or the increased viscosity of the amylose matrix by the presence of a hydrophilic substituent. Grafting an ionisable function on the amylose chain could also indirectly reduce α-amylase enzyme activity by complexing Ca^{2+} ions.

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