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RESEARCH PAPERS

EFFECT OF pH ON THEOPHYLLINE RELEASE FROM PARTIALLY ESTERIFIED ALGINIC ACID MATRICES

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ABSTRACT

The effect of dissolution medium pH on theophylline release from co-compressed matrices composed of a 40% benzyl ester of alginic acid was investigated using both the USP rotating paddle method and a modification of the USP rotating basket method. Release rates for each pH were compared using a measure of the time for approximately 80% release ($t_{80\%}$). Results show release of theophylline from these matrices to be significantly slower at pH 1 than at pH 2 and above. Beyond pH 2, drug release is relatively insensitive to dissolution medium pH but is affected by dissolution method because of the tendency of the alginate to form an adhesive, gel-like layer at pH values higher than four. The drug release characteristics of this polymer, under various pH conditions, make it potentially suitable for use in delayed/controlled release oral delivery systems containing compounds that are acid labile or irritating to the gastric mucosa.

INTRODUCTION

One of the major efforts in modern pharmaceutical research is the development of controlled-release drug delivery systems to optimize drug therapy, decrease frequency of dosing, and minimize undesirable side effects. The majority

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of the systems now available use synthetic polymers in the production of matrix and reservoir devices, micro encapsulated systems, polymeric prodrugs, ion exchange resins and erodible polymer matrix systems.[1-3] However, greater emphasis is currently being placed on development of controlled-release systems composed of biodegradable materials such as polyesters, poly-lactide/glycolide co-polymers, hyaluronates and gelatin.[4-13]

The alginates, a group of natural, hydrophilic, biodegradable polysaccharides have traditionally served as binding agents in both the food and the pharmaceutical industries and have a long history of safe use.[14-17] Recently, extensive studies have been conducted to evaluate the alginates for use in novel drug delivery systems.[18-25] Alginic acid is made up of two repeating sugar residues, L-guluronic acid and D-mannuronic acid, each with a pKa between 3 and 4. By partial or complete esterification of the acid groups on these sugar residues, the polymer's physical properties, such as aqueous solubility, may be modified, thus producing a material that is potentially well suited for oral drug delivery. Preliminary studies conducted with nominal 20% to 100% benzyl esters of alginic acid suggested that nominal 40% to 50% esters show the most favorable controlled release behavior. The structures of alginic acid and its benzyl ester are shown in Figure 1.

Studies conducted by various research groups have shown that the drug release behavior of unesterified alginic acid and its salts is sensitive to dissolution medium pH.[18, 20, 26] Consideration of the effect of pH on drug release is of fundamental importance in the development of any orally administered dosage form, particularly those made up of ionizable polymers, because of the variation in pH environment found throughout the gastrointestinal tract. In the present study, the effect of dissolution medium pH on the in vitro release of a small, water soluble drug molecule, theophylline (pKa 8.8), from compressed matrices composed of 40% benzyl esterified alginic acid is investigated. In addition, because results were found to be affected by in vitro dissolution method, use of the USP rotating paddle versus a modified rotating basket method is also presented.

MATERIALS

The 40% benzyl ester of alginic acid, with the remaining 60% of the acid groups present as the sodium salt, was supplied by Fidia S.p.A. (Abano Terme, Italy). Theophylline was purchased from Sigma Chemical Company and was used

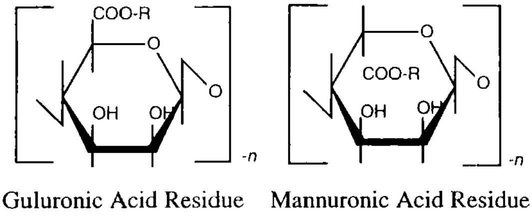

FIGURE 1

Structure of the repeating sugar residues of alginic acid, where R=H for alginic acid, R=Na for sodium alginate, and R=Benzyl for the benzyl ester of alginic acid.

without further purification. All buffer components were of reagent grade and were obtained from commercial sources.

METHODS

Matrices, weighing 250 mg and consisting of 30% theophylline and 70% polymer, were prepared by direct compression at 8000 lbs for 1 minute using a Carver tablet press. Matrices were then placed in 625 ml dissolution media of various pH values: 0.1 M HCl (pH 1.0); 0.01 M HCl (pH 2.0); 0.04 M acetate buffer (pH 4.0); 0.04 M citrate buffer (pH 6.0); and 0.04 M phosphate buffer (pH 7.4 and 7.8). All media used for dissolution studies were adjusted to an ionic strength of 0.15 M with sodium chloride. Temperature was maintained at 37 °C by a thermostatted water circulator (Haake, model E1) during matrix dissolution.

Experiments were performed in triplicate using the USP rotating paddle dissolution method and a modification of the USP rotating basket method (USP dissolution apparatus model VK600 manufactured by VanKel Industries, Inc., Edison, NJ). Two methods were used because of the tendency of matrices exposed to solutions of higher pH to form a swollen, hydrated, gel-like layer that caused matrix adherence to the wall of the dissolution vessel when using the USP rotating paddle dissolution method. In the rotating basket method, the matrices are contained within fine mesh baskets so that contact between matrix and dissolution vessel surface is prevented.

The standard USP rotating basket method was modified by attachment of a Teflon paddle, of similar dimensions to those used in the USP rotating paddle method, to the rotation shaft just above the basket, as shown in Figure 2. The

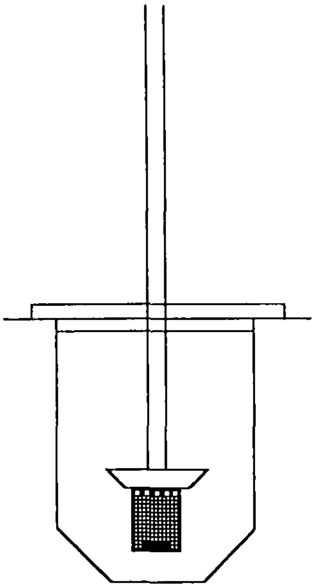

FIGURE 2

Diagram of the modified USP rotating basket dissolution apparatus. A Teflon paddle, of similar dimensions to those used in the USP rotating paddle dissolution method, is attached to the rotation shaft, just above the basket, in order to promote uniform solution mixing.

paddle was attached in order to provide more uniform solution mixing than could be obtained using the rotating basket alone. Rotation speed for each of the dissolution methods was set at 50 r.p.m.

Samples were removed from the vessels at selected intervals, and theophylline concentration was measured spectrophotometrically at a wavelength of 270 nm using a Cary 118 UV-Vis Spectrophotometer. Theophylline release rates for each pH were compared statistically using single classification analysis of variance (n=3).

RESULTS AND DISCUSSION

Percent theophylline release, over time, from 40% benzyl esterified alginic acid matrices is shown in Figure 3. From these curves, release is relatively rapid during the initial 10 to 20% release and then follows a somewhat linear release

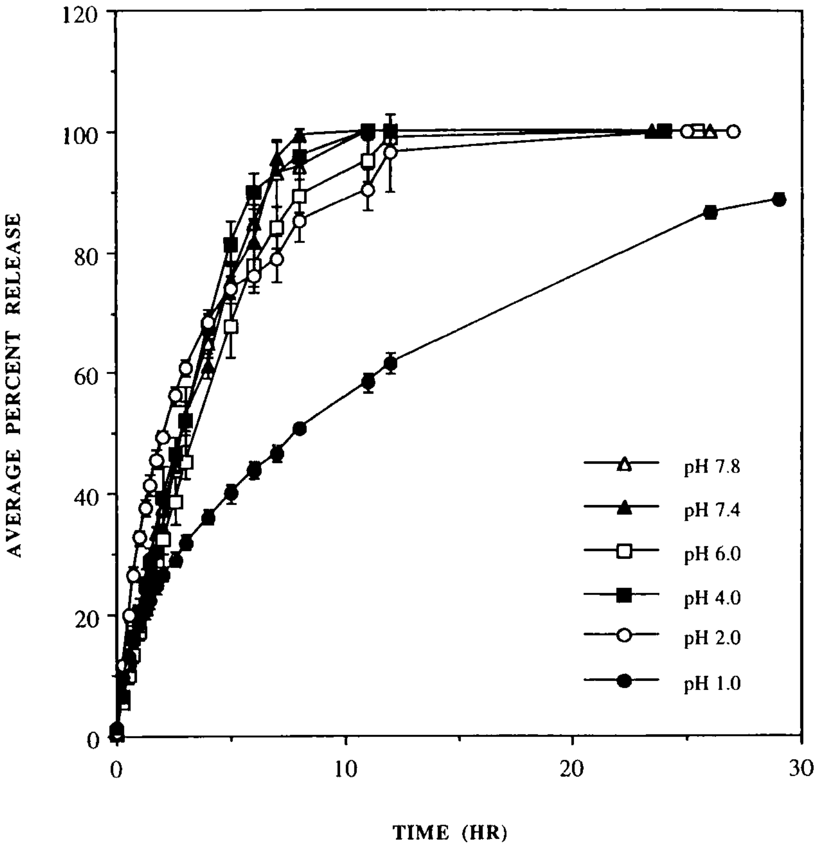

FIGURE 3

Percent theophylline release, over time, from 40% benzyl esterified alginic acid matrices.

pattern from approximately 20% to 80% release. These results are consistent with a burst effect, possibly associated with high drug loading in the matrix.

Mechanisms controlling release appeared to be pH dependent, because the release curves could not be easily fit to any one model. Therefore, release rates for each pH value were compared using a measure of the time for approximately 80% release ($t_{80\%}$).

The relationship between $t_{80\%}$ for theophylline release and pH, using the USP rotating paddle and the modified rotating basket dissolution methods, is illustrated in Figure 4. From this plot, theophylline release from 40% esterified

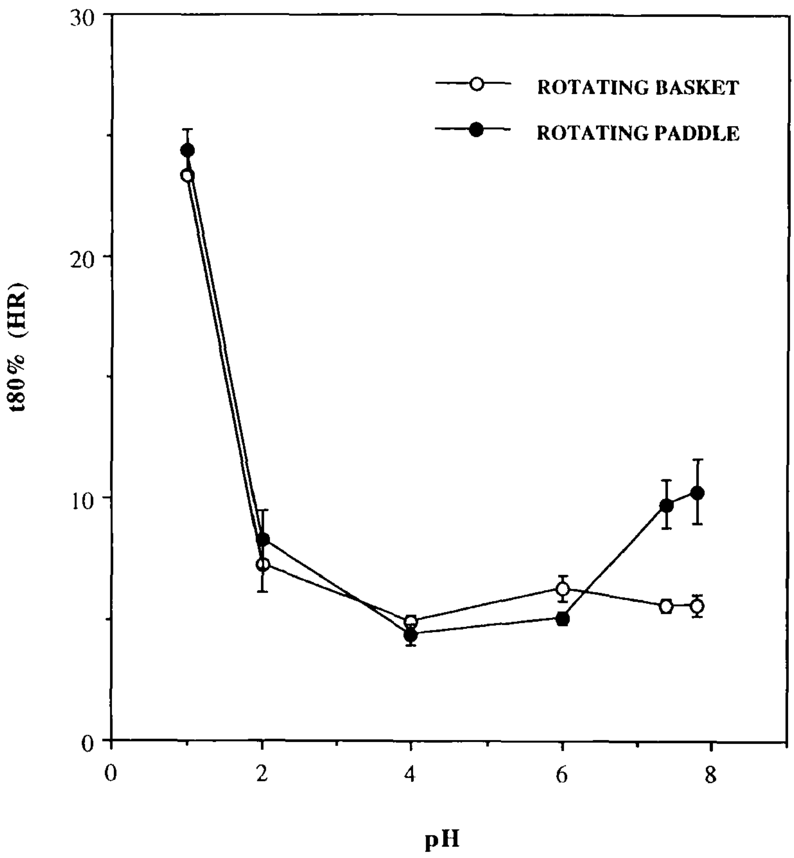

FIGURE 4

Effect of dissolution medium pH and in vitro dissolution method on theophylline release from matrices composed of the 40% benzyl ester of alginic acid.

alginic acid matrices is significantly slower at pH 1 than at pH 2 and above. Possible explanations for this behavior can be offered by examination of matrix physical appearance during dissolution in media of each pH studied.

A diagram of the physical changes observed over 24 hours in matrices exposed to different pH is shown in Figure 5. At pH 1, matrices appeared essentially unchanged throughout the dissolution period. Matrices in solutions of pH 2 showed some indentation and erosion, and by 24 hours, the matrix had collapsed. No polymer "gelling" was apparent in matrices exposed to these low pH conditions. At pH 4 and above, matrices began to show formation of a hydrated,

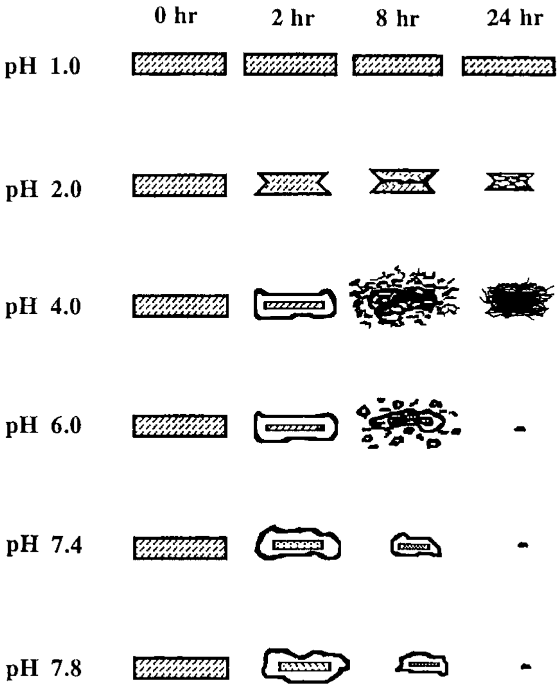

FIGURE 5

Physical changes observed over 24 hours in 40% benzyl esterified alginic acid matrices under various pH conditions.

gel-like layer, and within 8 hours, the matrices exposed to pH 4 and 6 had fragmented. The matrices studied at pH 7.4 and 7.8 did not disintegrate but did dissolve during the dissolution testing period.

These observations may, possibly, be explained by considering the ionization state of the polymer in the pH ranges investigated. As described previously, the mechanisms controlling theophylline release from these matrices appear to be pH dependent, and the pKa values of the two sugar residues of alginic acid lie between 3 and 4. At low pH, the polymer is in the acid form. It is hydrophobic and insoluble, and dissolution is probably limited by poor hydration of the polymer and subsequent slow diffusion of theophylline from the matrix. A small number of charges present on the acid groups at pH 2 may allow somewhat faster drug release due to greater solvent penetration into the partially esterified sodium alginate network, followed by greater ion exchange between sodium and hydrogen ions. Partial precipitation of the acid form of the polymer may then lead to collapse of the matrix. At intermediate pH, the polymer remains ionized and is more hydrophilic, potentially allowing various competing processes to arise: 1) increased osmotic pressure within the membrane, due to the presence of ionic charges on the polymer, leading to increased solvent penetration and higher hydrostatic pressure within the matrix, and 2) increased polymer hydration and transformation into a gel-like adhesive state. Upon matrix disintegration, surface area exposed to solvent increases, leading to more rapid drug release. Finally, at higher pH, the polymer is ionized, hydrophilic and soluble. It rapidly hydrates with solvent penetration and forms a swollen, adhesive layer maintaining matrix integrity. Release rate is then controlled by diffusion of the drug molecule through the hydrated polymer layer.

These explanations are consistent with the results of a study conducted by Bamba and Carstensen, et. al.,[27] in which the rate of drug release from gel-forming polymers was found to be controlled by competition between dissolution medium penetration into the polymer matrix and drug diffusion through the gelled polymer layer.

In addition, because of the presence of both fixed and freely mobile ionic charges in the polymer network, there is a higher concentration of total charges within the matrix, compared to the external dissolution medium, under intermediate to high pH conditions. The distribution of these charges is determined by Donnan equilibrium, and it has been suggested that the resulting osmotic pressure difference between the polymer and the external solution may cause increased polymer swelling, also potentially affecting rate of drug release.[28,29]

From Figure 4, it appears that release becomes slower above pH 6, using the USP rotating paddle dissolution method, but as described earlier, matrix adherence to the dissolution vessel wall was observed under these conditions. As a result, matrix surface area exposed to solvent was decreased, which could have slowed drug release. To resolve this question, studies were repeated using the modified rotating basket dissolution method to prevent matrix contact with the vessel wall. As Figure 3 illustrates, theophylline release rate at higher pH is faster with use of the rotating basket method than with use of the rotating paddle method. The $t_{80\%}$ values for release in media of pH 1, 2, and 4 are not statistically different between dissolution methods ($p<0.05$). This suggests that the slowed drug release rate observed at higher pH values, using the rotating paddle method, was caused by matrix adherence to the vessel wall, thus decreasing the effective matrix surface area available for release.

A question has been raised by Khan and Rhodes[30] as to the use of a fine mesh basket in dissolution studies that involve tablets containing adhesive, "gel"-forming polymers, such as the alginates, because these materials tend to block the pores of the basket and slow drug release. From our results, however, this did not appear to present a problem at pH 7.4 and 7.8 because the rotating basket method showed more rapid theophylline release than the rotating paddle method.

CONCLUSION

Release of theophylline from 40% esterified alginic acid co-compressed matrices is relatively independent of dissolution medium pH above pH 2. The differences in release rates that were observed may be due, in part to two factors: 1) the ionization state of the polymer under various pH conditions, and 2) dissolution method used, particularly at higher pH values.

Drug release from these matrices is slow in acid environment and much more rapid in intermediate and higher pH environments. These characteristics suggest potential development of this polymer for orally administered dosage forms containing drugs that are unstable in acid pH, are irritating to the gastric mucosa, or possess other properties such that release in a highly acidic environment is undesirable. The partially esterified alginates could, therefore, prove useful in the production of delayed release oral delivery systems for the optimization of drug therapy.

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