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COMMUNICATION

Release of Pentoxifylline from Xanthan Gum Matrix Tablets

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ABSTRACT

Pentoxifylline-controlled release tablets were prepared using xanthan gum. The effects of polymer concentration, rotation speed, ionic strength, and pH of the dissolution medium on the release of the water-soluble pentoxifylline were studied. The release rate decreased with increasing polymer concentration in the tablet, which was reflected in the increase in the mean dissolution time. A higher rotation speed and increased ionic strength of the dissolution medium resulted in a higher rate of drug release of xanthan-based tablets. A higher release rate of pentoxifylline was also observed using acidic dissolution medium.

Key Words: Pentoxifylline; Xanthan gum; Controlled release; Matrix tablets.

INTRODUCTION

The chemical name of pentoxifylline is [1-(5-oxyhexyl)-3,7-dimethylxanthine]. It has been approved for use in the treatment of intermittent claudication caused by chronic occlusive arterial disease from cerebrovascular disease.[1] Its major mode of action appears to be through increasing red blood cell deformability, by reducing blood viscosity, and by decreasing the potential for platelet aggregation and thrombus formation.[2,3] Because pentoxifylline is water-soluble[4] (solubility in water at 37°C is 191 mg/mL), and the peak of the plasma drug concentration occurs 1–3 hr after oral administration, it is difficult to maintain effective drug concentrations in the blood.[5] Pentoxifylline has a short elimination half-life (approximately 1 hr), and frequent dosing is necessary to maintain therapeutic plasma levels.[6] Therefore, a film-coated sustained release tablet has been commercially developed for effective therapy. Pentoxifylline is usually well tolerated when administered as a controlled release formulation.

Xanthan gum is a linear polysaccharide produced on a commercial scale by viscous fermentation of the bacterium *Xanthomonas campestris*. The molecule consists of a backbone identical to that of cellulose,

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with side chains attached to alternate glucose residues.[7] Xanthan gum is widely used as thickening agent in the food industry, and in the pharmaceutical industry, it is used as a hydrocolloid to thicken, suspend, emulsify, and stabilize water-based systems.[8] Xanthan gum has been also used as an effective excipient for sustained release formulations; it not only retards drug release, but also provides time-independent release kinetics.[9,10]

In this study, the use of xanthan gum as a hydrophilic matrix polymer for controlling the release of the water-soluble pentoxifylline was studied, together with the different factors affecting drug release from the hydrophilic matrix tablets.

EXPERIMENTAL

Materials

Materials used were pentoxifylline, xanthan gum, sodium chloride, sodium phosphate (Sigma Chemicals, St. Louis, MO), spray-dried lactose (FMC, Philadelphia, PA), and magnesium stearate—laboratory supply, NF grade. Dissolution apparatus included the VK 7000 (VanKel Industries, Inc., Cary, NC, USA), a Carver press (Fred S. Carver, Inc., Menomonee Falls, WI), and a UV/VIS spectrophotometer—HP8452 (Hewlett Packard, Avondale, PA).

Methods

Preparation of Tablets

Pentoxifylline controlled release tablets were prepared according to Table 1. The dry powder mixture of each tablet formula was blended and passed through a 250 μm sieve. Dry blend formulations were directly compressed with a Carver press into 580-mg caplets using 0.7962×0.2953-inch punch and die. Formulations were compressed at 3,000 pounds. The dwell time after target pressure was achieved was 10 sec.

Dissolution of Pentoxifylline Tablets

Dissolution of pentoxifylline from prepared tablet formulations was performed according to USP XXII Apparatus II. The tablet was placed into 900 mL of the dissolution medium maintained at 37.5°C. Three-milliliter samples were collected via an autosampler every 30 min for the first 4 hr, then at 2-hr intervals for the 24-hr dissolution study. Samples were then filtered through membrane filters (0.45 μm), and absorbance was measured at λ 274 nm. The percentage of pentoxifylline released was also calculated.

Table 1. Different formulations of pentoxifylline xanthan gum-based tablets.

Formula no.	Pentoxifylline (mg)	Xanthan gum (mg)	Lactose (mg)	Magnesium stearate (mg)
1	400	170	0	10
2	400	100	70	10
3	400	70	100	10
4	400	35	135	10
5	400	20	150	10

Effect of Different Formulation and Dissolution Variables on Drug Release

Pentoxifylline release from xanthan gum-based tablets was studied under different conditions of rotation speed of the dissolution apparatus, ionic strength of the dissolution media, and the pH of the dissolution media. Dissolution media were prepared by adding different amounts of sodium chloride to obtain different ionic strengths. The effect of pH was studied using 0.1 N HCl (pH 1.2) and phosphate buffer (pH 7.4).

Characterization of the Release Profile

The experimental results of the release studies were fitted according to the exponential equation[11]:

$$Qt/Q\infty = K \cdot t^n$$

where Q is the amount released at time t, $Q\infty$ is the overall released amount, K is a constant incorporating the properties of the macromolecular polymeric system and the drug, and n is a kinetic constant that depends on the transport mechanism. The exponent n gives information about the release mechanism, $n = 0.5$ characterizes the square root kinetics, $0.5 < n < 1.0$ indicates anomalous (non-Fickian transport), and $n = 1.0$ indicates zero-order kinetics. Drug diffusion and polymer

erosion control the release process in equal parts, if $n = 0.66$.[12]

To characterize drug release, the mean dissolution time (MDT) was calculated according to the following equation[13]:

$$\mathrm{MDT} = n/n + 1K^{-(1/n)}$$

RESULTS AND DISCUSSION

Effect of Xanthan Gum Concentration on Pentoxifylline Release

The release of pentoxifylline from tablets prepared with different concentrations of xanthan gum is shown in Fig. 1. It is clear that the release rate is greatly dependent on the concentration of gum in the formulation. Increasing the amount of gum in the formulation from 3.4% (formula 5) to 29.3% (formula 1) resulted in slower rate and extent release of the drug from the tablet. This slow release is because of the formation of a thick gel structure that delays drug release from the tablet matrix, where hydration of the individual xanthan gum particles results in extensive swelling. This causes initially well-separated particles to come into contact. As a result of the rheology of the hydrated product, the swollen particles coalesce. This results in a continuous viscoelastic matrix that fills the interstices, maintaining the integrity of the tablet and retarding further penetration of the dissolution medium. The increase in polymer concentration results in an increase of the MDT values, where for 3.4% xanthan gum concentration the MDT value was 2.36 hr, compared with 6.44 hr for the 29.3% concentration. The 3-fold increase in the MDT value with increasing polymer concentration can be ascribed to the entanglement density of the polymer at higher concentrations. These results are in accordance with the previous work of Talukdar et al.,[13] working on indomethacin controlled release tablets with xanthan gum.

Effect of Rotation Speed on Pentoxifylline Release from Tablets

Tablets prepared according to formulation 2, which gave the target profile for pentoxifylline controlled release tablets, were chosen for this study to determine the effect of rotation speed on drug release. The effect of rotation speed on drug release is shown in Fig. 2. It is shown that rotation speed has an influence on drug release, especially at higher rotation speeds, in which the rate of drug release was higher in the case of 100 rpm, compared with lower rotation speeds tested. This observation is attributed to the fact that,

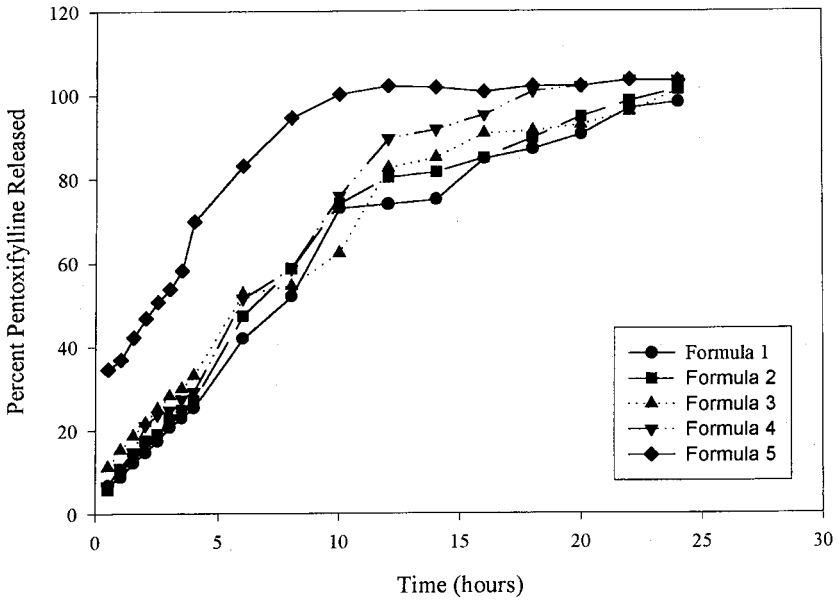

Figure 1. Release of pentoxifylline from different xanthan gum tablet formulations.

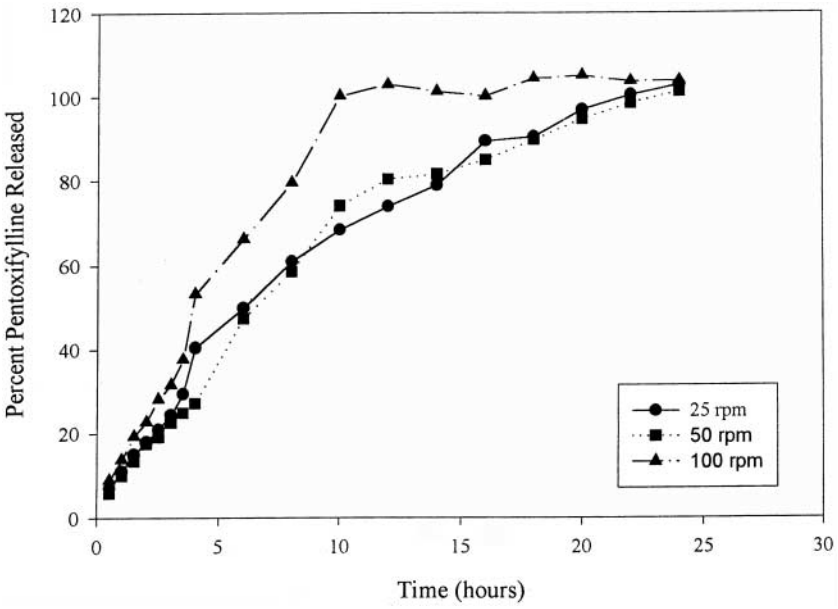

Figure 2. Effect of stirring rate on the release of pentoxifylline from xanthan gum-based tablets.

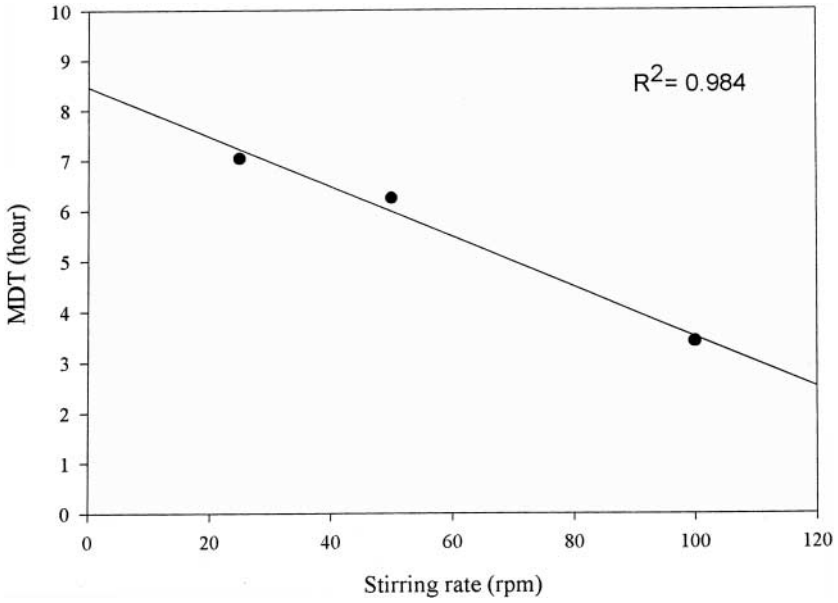

Figure 3. Correlation between stirring rate and MDT of pentoxifylline from xanthan gum-based tablets.

as stirring rate increases; the thickness of the hydrated gelatinous layer is considerably decreased, resulting in a faster release rate of the drug from the tablet matrix. A good correlation was found between the stirring rate and the MDT, where the correlation coefficient was found to be 0.984 (Fig. 3).

Effect of Ionic Strength of Dissolution Medium

The effect of ionic strength on the release of pentoxifylline from xanthan gum tablets (formulation 2) was studied at three different ionic strengths using 0.05, 0.1, and 0.2 M sodium chloride. The results

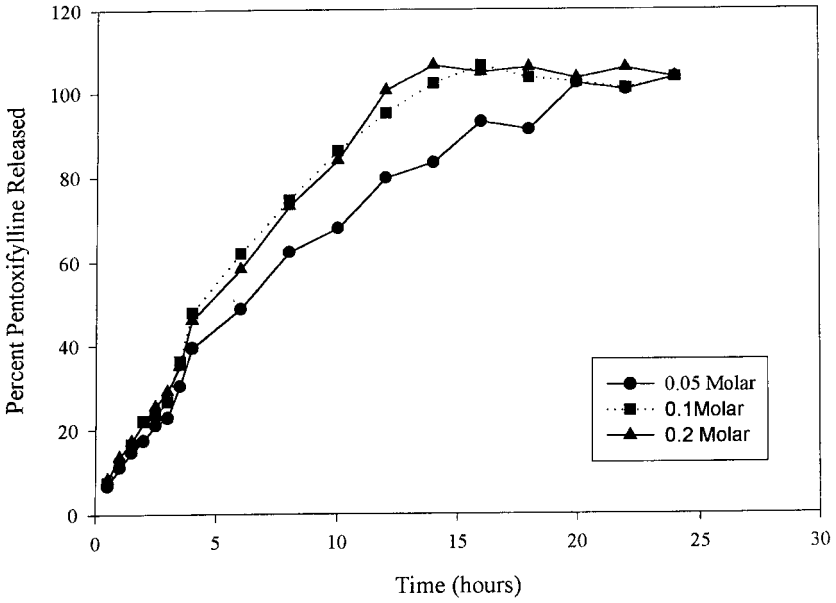

Figure 4. Effect of ionic strength on the release of pentoxifylline from xanthan gum-based tablets.

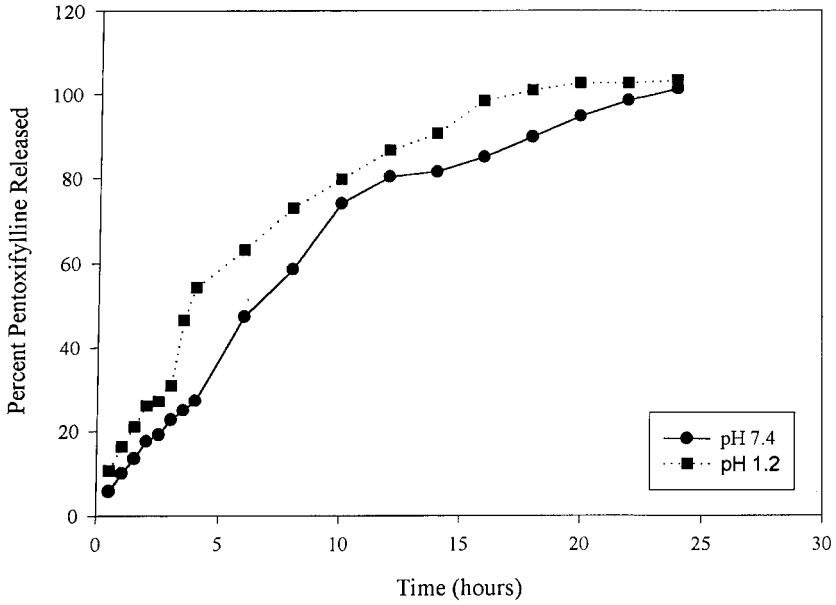

Figure 5. Effect of pH of dissolution medium on the release of pentoxifylline from xanthan gum-based tablets.

of the release study are illustrated graphically in Fig. 4, where it is clear that lower drug release was observed using 0.05 M sodium chloride. Using 0.2 M sodium chloride resulted in higher drug release. This higher release rate of pentoxifylline can be explained by the fact that, at higher salt concentration, the erosion process is reduced and the predominant process is the diffusion process, which allows the diffusion of the dissolved drug out of the matrix. This is indicated by the lower n values with higher salt concentration, where $n = 0.639$ for 0.05 M, compared with 0.567 in the case of 0.2 M sodium chloride.

The effect of ionic strength on matrix swelling and drug release from xanthan gum-based tablets was previously studied. It was found that, for water-soluble drugs, an increase in the ionic strength results in a decrease in matrix swelling and an increase in drug release as reflected by a lower MDT.[14]

Effect of pH of the Dissolution Medium

The effect of pH of the dissolution medium was studied on the release of pentoxifylline from tablet formulation 2. The release profile is shown in Fig. 5, where drug release is slightly higher in pH 1.2, compared with pH 7.4. The MDT for the release profile of formulation 2 in acidic medium is 5.2 hr, compared with 6.2 hr in pH 7.4. A similar increase in drug release was observed with chlorpheniramine maleate (another water-soluble drug), where drug release was faster in gastric fluid from tablets prepared using xanthan gum. In this case, the dissolution medium penetrates more rapidly, solubilizing a greater quantity of the drug that being highly soluble is then able to diffuse out of the tablet.[15] This effect of pH on drug release was also noted in several polymers, such as carbopol, which is influenced to a great extent by changes in pH.[16]

CONCLUSIONS

Xanthan gum-based tablets were found to be useful in controlling drug release of water-soluble pentoxifylline. Factors such as polymer concentration, stirring rate, ionic strength, and pH of the dissolution media appeared to play a role in the release of the drug from the tablets. Such factors need to be taken into account when designing controlled release tablets using xanthan gum.

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