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EVALUATION OF XANTHAN GUM IN THE PREPARATION OF SUSTAINED RELEASE MATRIX TABLETS

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ABSTRACT

The objective of this study was to evaluate xanthan gum as a matrix former for the preparation of sustained release tablets. Preliminary experiments indicated that a fine particle size of xanthan gum produced the slowest and most reproducible release profiles. Based on single surface experiments and tablet erosion studies, it was concluded that release of a soluble drug (chlorpheniramine maleate) and an insoluble drug (theophylline) from tablets containing low concentraions of xanthan gum was mainly via diffusion and erosion, respectively. Drug release from tablets containing xanthan gum was slightly faster in acidic media due to more rapid initial surface erosion than at higher pH. After hydration of the gum, drug release was essentially pH-independent. The amount released was directly proportional to the loading dose of drug and inversely proportional to gum concentration in tablets. Release profiles of chlorpheniramine maleate and theophylline remained unchanged after three months storage of the tablets at 40°C/80% RH and 40°C. Model tablets containing 5% xanthan gum exhibited release profiles similar to tablets containing 15% hydroxypropyl methylcellulose.

INTRODUCTION

Xanthan gum (XG), a high molecular weight biopolysaccharide, is widely used in liquid preparations as a suspending agent. XG functions as a hydrophilic colloid to thicken, suspend and stabilize water-based systems. It is used in combination with other gums and sugars in sustained release lozenges[1]. Other patents disclosed the use of xanthan gum alone or in combination with other matrix forming polymers in sustained release tablets[2,3]. Guley et al[2] used combinations of xanthan gum, hydroxypropyl methylcellulose, hydroxypropyl cellulose and ethylcellulose in coated tablets for sustained release. The tablets contained 30-72 wt % of a mixture of polymers.

Clare et al[4] disclosed hydrocolloid blends containing guar gum, carboxymethyl-cellulose, locust bean gum and XG for controlled release of calcium ions in alginate print paste compositions. Sudgen[5] used combinations of locust bean gum and XG in buccal tablets containing a phenothiazine compound for controlled release up to 2 hours. Recently, Calanchi et al[6] disclosed the use of XG in matrix tablets.

Since the matrix forming ability of XG has not been studied in detail, we evaluated the properties this gum for the preparation of prolonged release tablets.

MATERIALS AND METHODS

Materials

The following materials were used: Xanthan gum, NF (Keltrol^{R} and Keltrol TF^{R}, Kelco Div., Merck and Co.); sodium alginate, NF (Keltone^{R} LV, Kelco Div., Merck and Co.); acetaminophen (Compap-L^{R}, Mallinckrodt Inc.); benzocaine, USP; benzoic acid, USP; chlorpheniramine maleate, USP (Sigma Chemical Co.); theophylline anhydrous, USP (Knoll Pharmaceuticals.); lactose, NF (Fast-Flo^{R}, Foremost Whey Products.); dicalcium phosphate, USP (Emcompress^{R}, Edward Mendell Co., Inc.); magnesium stearate, NF; and microcrystalline cellulose, NF (Avicel^{R} PH101, FMC Corp.)

Methods

A. Preparation of a blend for direct compression.

For preliminary evaluation, XG was screened through 40, 80, 200 and 325 mesh screens. Remaining ingredients were screened through a 40 mesh screen. Prototype

TABLE 1

Prototype Tablet Formulations

	%	mg/tablet		
Ingredient		**Expt1**	**Expt2**	**Expt3**
Acetaminophen	66.67	500.0	-	-
Chlorpheniramine maleate	1.07	-	8.0	-
Theophylline (anhydrous)	26.67	-	-	200.0
Xanthan gum	5.0	37.5	37.5	37.5
Lactose	-	205.0	697.0	505.0
Magnesium Stearate	1.0	7.5	7.5	7.5

formulations are shown in Table 1. All tablets weighed 750 mg. All ingredients except magnesium stearate were blended in the Twin Shell Blender for 15 minutes. Magnesium stearate was added and blended with the premix in the Twin Shell blender for an additional 5 minutes.

B. Tablet Compression.

Tablets were prepared by direct compression using a Stokes B2 press. 12 mm round flat face tablets were made. The compression force was kept constant. Tablet weight, thickness and hardness were recorded. Tablets containing model drugs and various concentration of XG were tested by the USP basket dissolution method.

A two factor central composite design was used to study the effect of filler excipient and concentraion of gum on drug release from tablets. The two factors selected for this study were:

1. Concentration of XG - X1
2. Ratio of filler excipients - X2 (soluble diluent lactose and insoluble diluent unmilled dicalcium phosphate)

Table 2 describes how the factor levels were determined. For the base experiment, 12% XG, 30% lactose and 30% dicalcium phosphate (DCP) were used; the lubricant level and compression force were kept constant. This design is based on a factorial design with additional points added to estimate curvature of the response

TABLE 2

Factorial Design: Variable Levels (eu-Experimental unit).

Independent Variables	-1.414 eu	-1 eu	0 eu	+1 eu	+1.414 eu
X1:Conc.of XG (1eu=5%)	4.9	7	12	17	19.1
X2:Conc.of lactose (1eu=15%)	8.8	15	30	45	51.2

surface. The model used is typically a second order polynomial. A total of 9 experiments were run. The base level experiment (# 9) was run in triplicate to estimate experimental error.

C. Dissolution Testing

The USP apparatus 1 (basket) at 100 rpm and apparatus 2 (paddle) at 50 rpm were evaluated. The USP basket at 100 rpm gave more reproducible results as demonstrated by a smaller relative standard deviation and was used in all determinations. The dissolution medium consisted of either Simulated Gastric Fluid without enzyme (SGF, pH 1.2) or Simulated Intestinal Fluid (SIF, pH 7.5). Also selective formulations were tested for dissolution using a pH change method by transfering the baskets after 2 hours in SGF to SIF. Samples were collected throughout the dissolution study at various time intervals and assayed by a suitable method (HPLC or spectrophotometry). Three tablets were tested from each formulation in each dissolution medium. Sink conditions were maintained in all experiments.

D. Drug Release Study from a Fixed Surface Area.

The method used here was similar to that of Goodhart et al[7] and Kopcha et al[8]. A tablet was compressed in a 12 mm diameter die at a compression force of 3000 pounds for 30 seconds on a hydraulic press (Carver Press). The other side of the die was sealed with a waxed cork to keep it dry. The tablet in a die was placed in a USP dissolution vessel containing 500 mL water at 37°C exposing the upper surface to the paddle at a

distance of 2.5 cm. The paddle was rotated at 50 rpm. Samples were collected at various time intervals and assayed. This apparatus (stationary tablet in a die/rotating fluid) was calibrated by using benzoic acid tablets compressed in a die. Stirring rate (paddle speed) was varied between 50 and 75 rpm. Fifty rpm was found to be adequate for uniform mixing without causing excessive erosion when tablets containing low amounts of XG were tested. Diffusion layer thickness (h_2) was calculated by use of the following equation derived by Khoury et al[9].

$$h_2 = (DC_sX)/Q \qquad \text{(Eq.1)}$$

where D is diffusion coefficient, C_s is solute solubility, X is area of dissolving surface, and Q is dissolution rate.

E. Matrix-tablet Erosion Studies.

Three matrix erosion studies were conducted in triplicate. The first study was conducted to show the matrix erosion (matrix tablet weight loss) in SGF and simulated intestinal fluid (SIF). Tablets containing 6.7% theophylline, 5% XG, 87.3% lactose and 1% magnesium stearate were subjected to dissolution in SGF and SIF using the USP basket method at 100 rpm. The tablets remaining in the baskets were taken out at each time-point and dried to constant weight in a hot air oven at 75°C ($\pm$ 5°C) and then weighed.

The second and third studies were conducted to evaluate mechanisms of release of a water-soluble drug (chlorpheniramine maleate) and a sparingly soluble drug (theophylline). Tablets containing 200 mg drug (26.67% of tablet weight), 10% XG, 62.33% dicalcium phosphate and 1% magnesium stearate were subjected to dissolution in purified water at 37°C using the USP basket method at 100 rpm. The tablets remaining in the baskets were taken out, dried and weighed as explained above.

F. Stability Studies.

Tablets containing drug (CPM and theophylline) and excipients were stored in high density polyethylene (HDPE) bottles at 40°C and 40°C with 80% relative humidity for three months. The samples were tested for dissolution by the pH change method as described above.

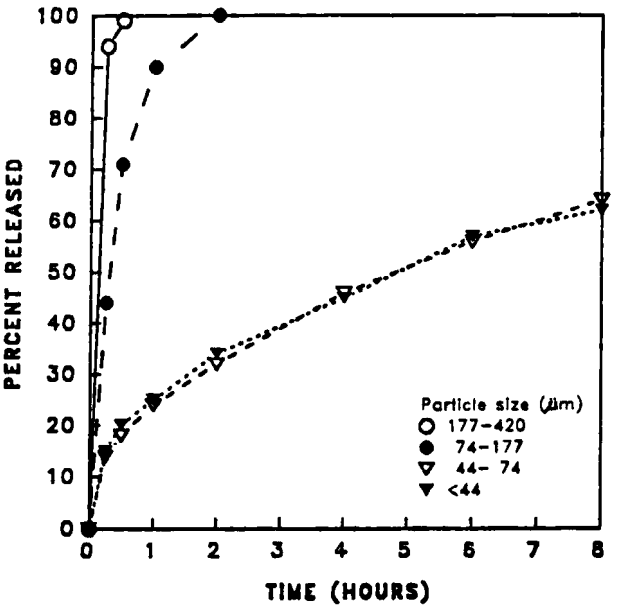

FIGURE 1

Effect of particle size of xanthan gum on acetaminophen release from tablets into simulated gastric fluid.

RESULTS AND DISCUSSION

A. Effect of Xanthan Gum Partical Size.

To demonstrate the effect of particle size, four different fractions of XG were used in directly compressed tablet formulations containing 500 mg acetaminophen (APAP) as model drug. As shown in Figure 1, the 200 mesh (40-74 μm) XG was found to be most effective in sustaining the release of APAP in SGF. Similar results were found for SIF. The coarser XG fractions (40 and 80 mesh) did not hydrate fast enough to form a protective gel layer and the tablet matrix was broken prematurely while the fine XG (200 mesh) provided sustained release. It is interesting to note that the tablets formulated with very fine (325 mesh) XG did not provide any additional advantage in slowing down the APAP release. The study was repeated using a soluble low dose model drug, chlorpheniramine maleate (CPM) 8 mg per tablet. The results were similar to the APAP study. The 200 mesh XG (Keltrol TF^{R}) was found to be most effective in sustaining

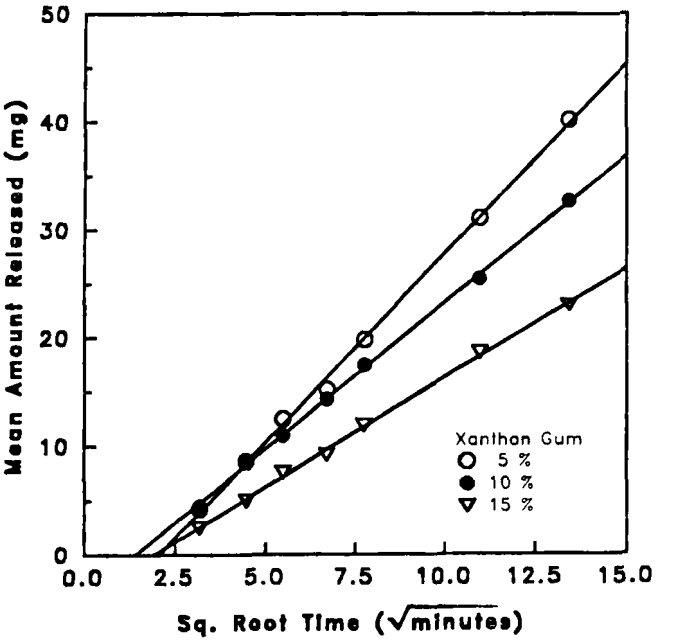

FIGURE 2

Effect of Xanthan Gum Concentration on Release of CPM from a Single Surface.

release of CPM in SGF and SIF. Based on this study 200 mesh XG was selected as a matrix former in tablets in succeeding experiments.

B. Release Mechanism from a Single Surface.

Figure 2 illustrates that release profiles of CPM from single surface of tablets containing 5, 10 and 15% XG were a linear function of the square root of time, following Higuchi's diffusion model. Water penetrates into the tablet hydrating the polymer and dissolving CPM which then diffuses out. As shown in Table 3, the release rate is decreased as gum concentration increases. This is believed to be due to an increase in viscosity of the hydrated layer as gum concentration is raised.

Release of theophylline from a single surface into water followed an apparent zero order rate (Fig. 3). Data derived from the experiments is listed in Table 4. In tablets containing 5% XG, the release profile up to 3 hours was linear. After about 3 hours, the

TABLE 3

Effect of Xanthan Gum Concentration on Release of CPM from a Single Surface.

Xanthan Gum (%)	Release Rate (mg $hr^{-1/2}$ $cm^{-2}x10^2$)	r^a	D^b ($cm^2sec^{-1}x10^6$)
5	5.11	0.9993	5.54
10	3.65	0.9979	3.96
15	2.78	0.9996	3.02

[a] Regression coefficient.
[b] Apparent diffusion coefficient.

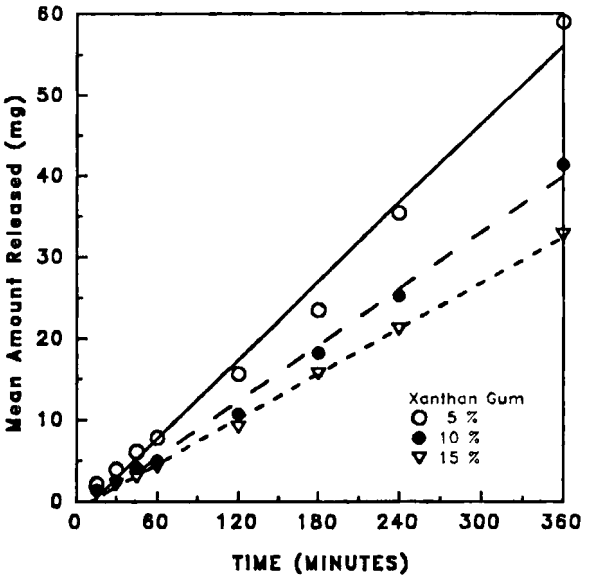

FIGURE 3

Effect of Xanthan Gum Concentration on Release of theophylline from a Single Surface.

TABLE 4

Effect of Xanthan Gum Concentration on Release of theophylline from a Single Surface.

Xanthan Gum (%)	Release Rate (mg $hr^{-1}cm^2x10^2$)	r^a
5	1.76	0.9942
10	1.23	0.9968
15	0.98	0.9989

[a] Regression coefficient.

swollen portion of the gel started eroding more rapidly due to the mixing action of the paddle, which resulted in faster release of theophylline after that time. In tablets containing 10% and 15% XG, the release was linear up to 6 hours. This experiment suggested that theophylline was released predominantly via erosion.

Release rates from single surface of the tablets containing various concentrations of CPM and theophylline were determined. Slopes of the amount released versus time were plotted against drug concentration. The plots were linear up to 26.7% drug.

In order to demonstrate the effect of solubility of the drug on release from single surface, release of benzocaine, a relatively insoluble compound, was measured for up to 90 minutes. The plot of amount released versus time showed zero order release suggesting that matrix erosion was the principal mechanism. The amount released in one hour is 1.55%, 3.9% and 9.4% for benzocaine, theophylline and CPM, respectively, indicating that the release rate increases with solubility of the drug in the release medium.

C. Release Profile Analysis from Tablets.

The well known Hixson-Crowell cube root dissolution model[10] was found to adequately describe the entire release profile (up to 95% cumulative release) over time. This equation has been used previously to describe release from matrix systems[11,12]. Equation 2 was used in this study:

$$W_o^{1/3} - W^{1/3} = K(t-t_o) \qquad \text{(Eq. 2)}$$

TABLE 5

Release Profile Analysis from Tablets.

Drug	Medium	K (%$^{1/3}$/h)[a]	t50%	t90%	r[b]
CPM	SGF	0.3331	1.46	6.04	0.9940
	SIF	0.2219	3.55	10.43	0.9982
Theophylline	SGF	0.1746	3.65	12.39	0.9930
	SIF	0.1225	6.89	19.34	0.9987

[a] Cube root release rate constant.
[b] Correlation coefficient, cube root model.

where W_o is initial percent of drug in the matrix, W is percent drug remaining in the matrix at time t, K is apparent release rate constant (%$^{1/3}$/h), t is time (hours) and t_o is lag time (hours). K was determined from the slope of a plot of cube root percent drug dissolved versus time.

The time for 50% and 90% of the drug to dissolve was calculated using the model fit of the data and therefore incorporated K. Table 5 summarizes data for two drugs in two media. The cube root model showed a better correlation in all cases than the square root of time relationship ($p < 0.05$).

Tablets containing XG underwent greater surface erosion at early times in SGF than in SIF (Table 5) as explained below. CPM release from the tablets was rapid initially due both to its higher solubility in SGF and more rapid initial surface erosion in this medium. Once the matrix hydrates and swells the rate of erosion slows down. The net effect of initial rapid erosion, diffusion and swelling of the matrix results in deviation in linearity from the Higuchi equation.

Thus the following processes are likely to operate: initial rapid drug dissolution from the surface accompanied by hydration of polymer to form a gel-like surface layer, dissolution of drug in the gel, permeation of drug through the gel, and slow dissolution of the gelled polymer of the outermost layer into the release medium. The combination of diffusion and erosion of matrices was also seen by Nakano et al[13]. and Lordi et al[14].

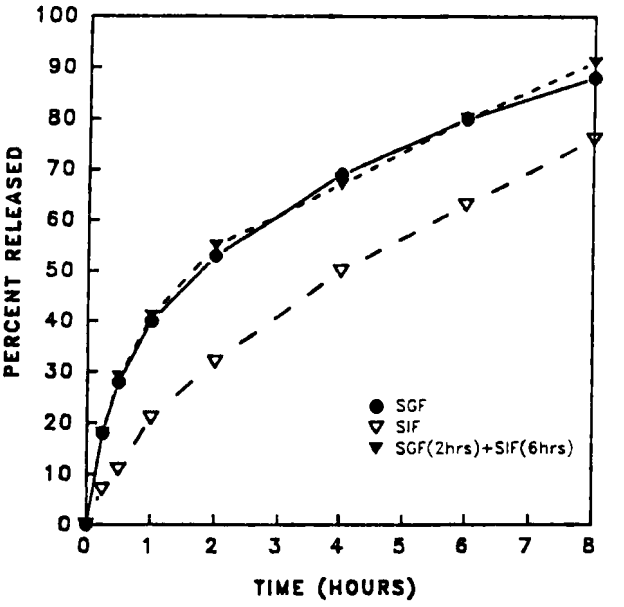

FIGURE 4

Effect of pH change on Release of CPM from Tablets containing 10% Xanthan Gum.

D. Effect of pH.

Tablets containing the model drugs CPM, theophylline and APAP were tested for release profiles in SGF, SIF and by changing pH (2 hours in SGF followed by 10 hours in SIF). As illustrated in Figure 4, CPM release was faster in SGF than in SIF. This can be explained as the result of higher polymer surface erosion, as shown below, in SGF and higher solubility of CPM in SGF than in SIF.

The release profiles of theophylline and APAP did not show a difference of more than 10% in both pH media. A matrix tablet containing XG forms a gel layer after hydration that is more resistant to attrition. This is true, regardless of the pH of release media. When the drug release was tested by changing pH, it was found that the release rate was very similar to that in SGF (Table 6). Table 6 also shows that although the release from XG matrix is less pH dependent than other anionic polymers, it is slightly higher in SGF.

TABLE 6

The Effect of pH on Release of Model Drugs from Tablets Containing 10% Xanthan Gum

CHLORPHENIRAMINE MALEATE

Medium	pH	K[a] (%$^{1/3}$/hr)	t50% (hr)	t90% (hr)	r[b]
SGF	1.2	0.2419	2.17	8.48	0.9846
SIF	7.5	0.1962	4.19	11.97	0.9981
SGF + SIF	1.2 &7.5	0.2584	2.12	8.11	0.9916

THEOPHYLLINE

Medium	pH	K[a] (%$^{1/3}$/hr)	t50% (hr)	t90% (hr)	r[b]
SGF	1.2	0.1183	6.08	18.97	0.9940
SIF	7.5	0.1133	7.96	21.40	0.9994
SGF + SIF	1.2 &7.5	0.1092	6.75	20.72	0.9963

ACETAMINOPHEN

Medium	pH	K[a] (%$^{1/3}$/hr)	t50% (hr)	t90% (hr)	r[b]
SGF	1.2	0.09660	8.42	24.22	0.9985
SIF	7.5	0.08636	9.78	27.46	0.9983
SGF + SIF	1.2 &7.5	0.09606	8.59	24.48	0.9963

[a] Release rate constant.
[b] Correlation coefficient, cube root model.

XG viscosity is relatively independent of pH[15]. It seems likely that the viscosity of the XG gel which forms on the tablet surface is also relatively independent of environmental pH.

E. Matrix Erosion Studies.

These studies measured the loss of weight from matrix tablets immersed in dissolution media as a function of time. Weight loss of XG-containing tablets was about

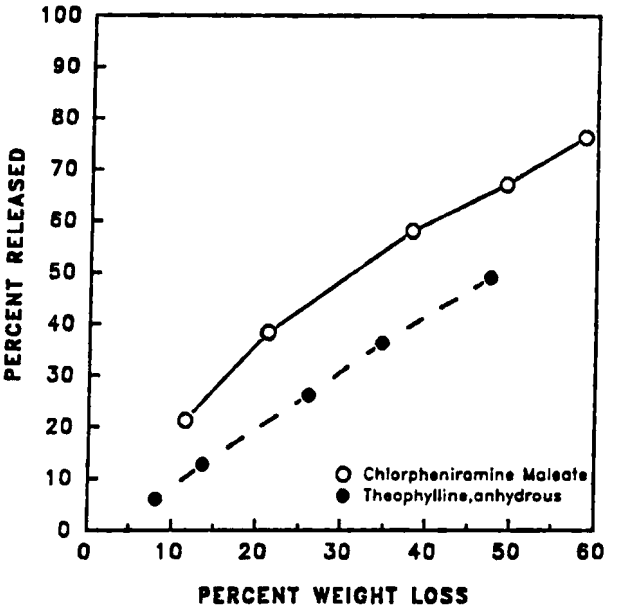

FIGURE 5

Matrix Erosion Study- Percent weight loss versus Percent drug released into water.

10 to 15% greater in SGF than SIF over a one-hour period. After one hour, the rate of weight loss was independent of pH.

A plot of percent weight loss versus percent theophylline released from tablets was linear (Fig. 5). Theophylline release was linearly correlated with time, confirming the importance of the erosion mechanism for this drug from tablets (Fig. 6). CPM release was faster than matrix erosion reflecting the introduction of diffusion to the release process. No linearity was observed when percent CPM release versus time was plotted (Fig. 6).

F. Effect of Gum Concentration and Excipients.

This study was designed to examine the effects of model soluble and insoluble excipients and gum concentration on release characteristics and hardness of the matrix tablets. The data collected for each formulation trial, as well as predicted values, r^2 value, regression F ratio and confidence values are presented in Table 7. All of these

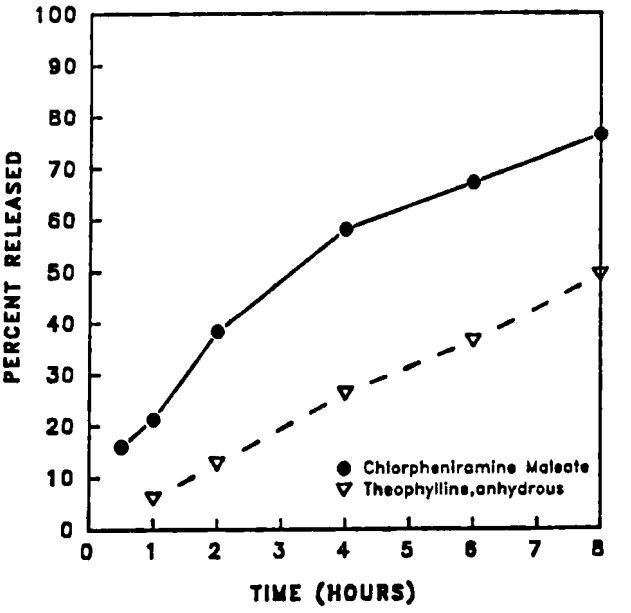

FIGURE 6

Matrix Tablet Erosion Study- Time versus Percent drug released into water.

values were statistically acceptable; they had confidence values for regression coefficients above 90% indicating a good fit.

Figure 7 covers the entire range of XG (4.9 to 19%) and lactose (8.8 to 51.2%), the remainder being dicalcium phosphate. The time for 90% dissolution increased with gum concentration as expected. But the curvature indicated that at low concentrations of lactose, T90% was slightly longer. For example, at 10% gum concentration, T90% was about 7 hours when lactose was used at a concentration of 51.2%. But when dicalcium phosphate was used at the same concentration, T90% was increased by 2 hours to 9 hours. Similar results were obtained with tablets containing theophylline.

Hardness of CPM tablets was plotted as a function of XG and lactose in Fig. 8. The tablet hardness increased slightly (by about 2 SCU) with increase in gum concentration from 5 to 10% and then decreased slightly when the gum concentration was further increased to 19%. This was true regardless of the model drug used. This indicates that compressibility of powder blends was affected at higher concentrations of gum.

TABLE 7
Effect of Xanthan Gum and Filler Excipients on Release of Chlorpheniramine Maleate from Tablets: Comparison of Actual (A) and Predicted (P) Responses

	T50% (hr)		T90% (hr)		Friability (%)		Hardness (SCU)	
Expt.	A	P	A	P	A	P	A	P
1	2.6	2.5	7.2	7.1	0.2	0.22	10	10
2	4.3	4.2	12.7	12.3	0.25	0.28	9	8
3	2.1	2.1	5.7	5.8	0.04	0.06	19	18
4	4.0	3.9	11.3	11.1	0.06	0.09	16	14
5	1.8	1.8	4.8	4.7	0.15	0.14	13	13
6	4.3	4.3	11.8	12.2	0.25	0.21	8	9
7	3.4	3.5	10.3	10.6	0.30	0.27	9	9
8	3.0	3.0	8.8	8.8	0.05	0.03	18	19
9A	2.8	2.7	8.0	7.8	0.06	0.10	15	15
9B	2.8	2.7	8.1	7.8	0.10	0.10	15	15
9C	2.5	2.7	7.3	7.8	0.13	0.10	14	15
r^2 =	0.9838		0.9870		0.9039		0.9467	
Regression F Ratio =	60.7		76.2		9.4		17.6	
Probability > F	0.0002		0.0001		0.0140		0.0034	
Confidence (%)	99.9		99.9		98.6		99.7	

Lactose has better compressibility than dicalcium phosphate. Therefore the tablets containing higher concentrations of lactose had greater hardness than the others.

Friability did not vary significantly as a function of gum concentration or the type of excipient. At the highest concentration of gum and dicalcium phosphate, friability

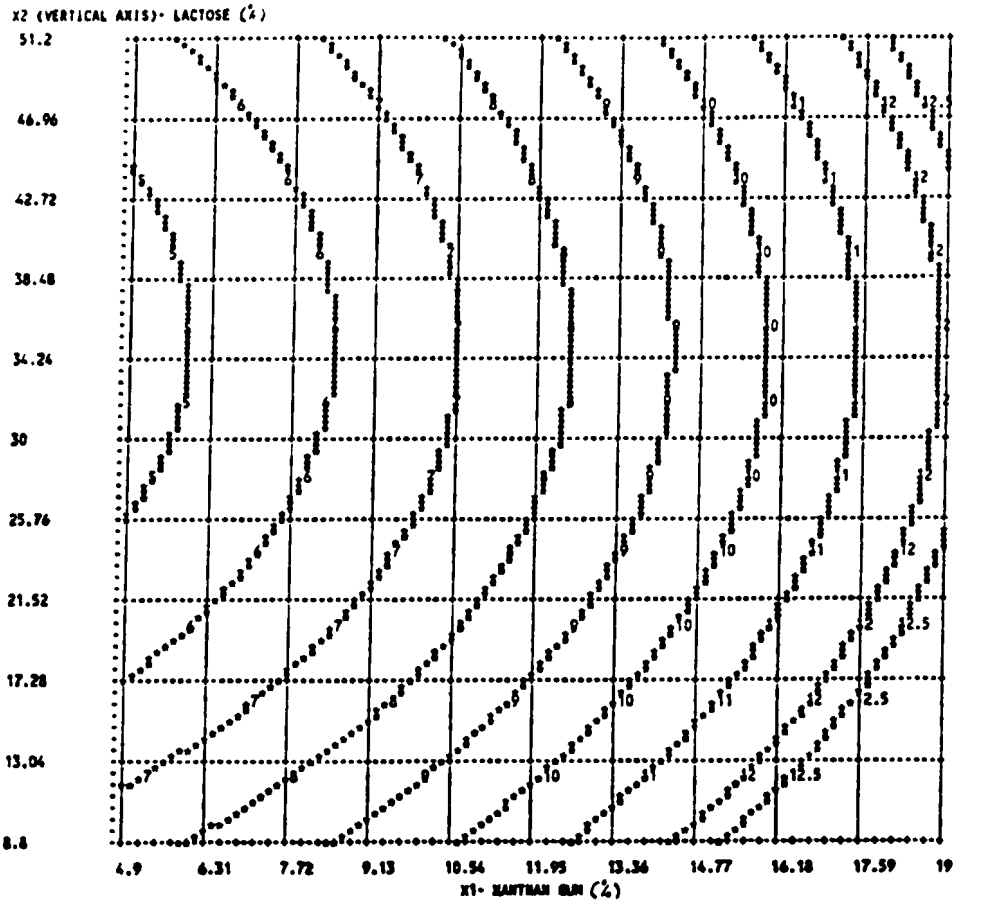

FIGURE 7

Interaction effects of Xanthan Gum concentration and lactose/dicalcium phosphate on time for 90% (T90%) CPM release.
T90% (hours): 5, 6, 7, 8, 9, 10, 11, 12, 12.5.

was increased by only 0.4%. No chipping or capping of tablets was seen in any of the experiments.

G. Accelerated Stability Studies.

The samples were stored at 40° C/80% RH in high density polyethylene bottles for 3 months to study the effect of accelerated conditions on drug release. Heat and humidity did not alter the dissolution profiles of CPM and theophylline ($P < 0.05$).

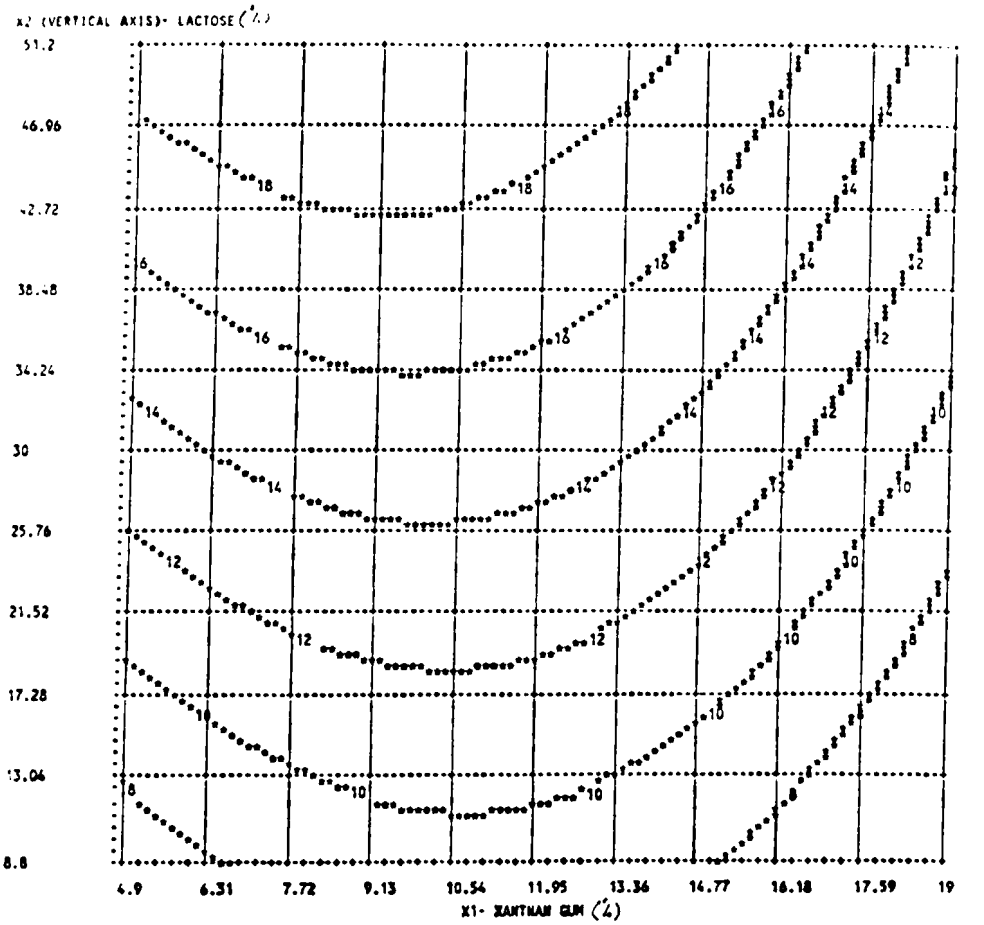

FIGURE 8

Interaction effects of Xanthan Gum concentration and lactose/dicalcium phosphate on Tablet Hardness.
Hardness (SCU): 8, 10, 12, 14, 16, 18, 20.

H. Comparison of Xanthan Gum with Hydroxypropyl MethylCellulose.

Our observations of release mechanisms from matrix tablets containing XG were qualitatively similar to those previously reported for hydroxypropyl methylcellulose (HPMC[16,17,18]). APAP tablets containing 5% XG showed similar release profiles in SGF and SIF (not shown) to those of tablets with 15% HPMC (METHOCEL^R K4MCRP) whereas tablets containing 5% HPMC disintegrated within one hour (Fig. 9). Drug

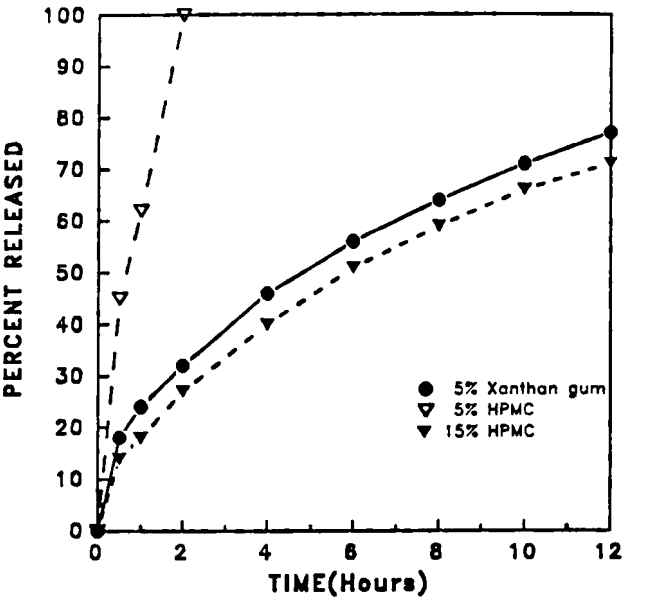

FIGURE 9

Comparison of acetaminophen release from tablets containing xanthan gum and tablets containing hydroxypropyl methylcellulose (METHOCEL^R K4MCRP) into simulated gastric acid.

release from the HPMC matrix is fairly independent of pH of the release medium, whereas drug is released at a slightly faster rate (5-10%) in acidic medium from XG matrix, due to more rapid initial surface erosion.

This experiment indicates that XG can be used in very small quantity (approximately 1/3 that of HPMC) to achieve a comparable sustained release profile. This is a distinct advantage in formulating high dose drugs without excessive increase in tablet weight.

CONCLUSIONS

Xanthan Gum was studied as a matrix former for sustained release tablets. It was very effective in prolonging release of soluble (CPM) and sparingly soluble (APAP, theophylline) drugs. The rate of release was slowed by decreasing the particle size of gum or by increasing gum concentration. The release of soluble drug was mainly via

diffusion, whereas sparingly soluble or insoluble drugs were released principally via erosion. Drug release from the XG matrix was slightly faster in acidic media, due to more rapid initial surface erosion. After hydration of the gum, drug release was essentially pH-independent. There were small differences in drug release from tablets containing a water-soluble (lactose) and insoluble (dicalcium phosphate) excipient. The release profiles remained unchanged after three months storage of the tablets containing the model drugs at 40°C/80% relative humidity and 40°C. XG is suitable for matrix tablets containing low or high dose drugs.

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