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EVALUATION OF XANTHAN GUM AS A HYDROPHILIC MATRIX FOR CONTROLLED-RELEASE DOSAGE FORM PREPARATIONS

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ABSTRACT

Xanthan gum was evaluated as hydrophilic matrix for controlled release preparations. Different parameters were considered: direct and wet granulation, gum concentration, effect of addition of binders, pH, ionic strength, rotation speed and surfactant. Suitable controlled release profile could be obtained. Practically no influence of the parameters studied was noted, with the exception of gum concentration, the rotation speed and presence of ion in the dissolution medium. The release rate profiles were evaluated by different kinetic equations: Zero order, First order, Higuchi equation and RRSBW equation and the data statistically analyzed with F-Ratio. Without binder, in aqueous medium, zero order kinetics were found from the origin of the release rate profile. With binder and dissolution media with electrolytes or buffer solutions, generally zero order kinetics were also found after an initial period of about half an hour. The release kinetics were independent of the method of preparation and compression force.

INTRODUCTION

Xanthan gum is a hydrophilic polymer, produced by the microorganism Xanthamonas Campestris. In solution this polymer is known to tolerate high concentration of electrolytes. The viscosity is also nearly independent of pH and temperature [1]. For these reasons, it seemed an interesting polymer for the preparation of hydrophilic matrix tablets. According to our knowledge, until now, one work has been done with this polymer, using theophylline as active compound [2]. In our work, the attention was focused on the behaviour of the xanthan gum under different experimental conditions. In this study, caffeine was used as a soluble model drug. This compound is not influenced by the parameters investigated.

MATERIALS AND METHODS

Materials: Xanthan gum (Rheogel, Iranex, Rouen, France) was used as hydrophilic matrix, lactose (Bios, Brussels, Belgium) as filler, Kollidon® 25 (BASF, B-Brussels) and Avicel® PH 101 (FMC/Stokvis Chemicaliën, N-Barendrecht) as binders. Caffeine was taken as the model drug. In some formulations sodium lauryl sulphate (Flandria, B-Ghent) was used as wetting agent.

TABLE 1

Ingredients of formulations with percentages & methods of compression in tabular form.

Formula number	Caffeine %	Xanthan %	Kollidon®25 %	Avicel®PH101 %	Lactose %	Surfactant %	Alcohol ml/tab	Compression technique
F#1	66.67	33.33	-	-	-	-	-	Direct compression
F#2	66.67	16.67	-	-	16.67	-	-	Direct compression
F#3	66.67	12.50	-	-	20.83	-	-	Direct compression
F#4	66.67	6.67	-	-	26.67	-	-	Direct compression
F#5	66.67	5.83	-	-	27.50	-	-	Direct compression
F#6	66.67	4.17	-	-	29.17	-	-	Direct compression
F#7	66.67	5.83	-	10.00	17.50	-	-	Direct compression
F#8	66.67	5.83	-	20.00	7.50	-	-	Direct compression
F#9	66.67	5.83	10.00	-	17.50	-	-	Direct compression
F#10	66.67	5.83	20.00	-	7.50	-	-	Direct compression
F#11	66.67	5.83	25.00	-	2.50	-	-	Direct compression
F#12	50.00	15.00	15.00	-	20.00	-	-	Direct compression
F#13	50.00	25.00	15.00	-	10.00	-	0.10	Wet granulation
F#14	50.00	25.00	15.00	-	10.00	-	-	Direct compression
F#15	50.00	25.00	15.00	-	9.00	1.00	0.10	Wet granulation

METHODS

Compression of tablets: Tablets were prepared by wet granulation and direct compression at determined compression forces with an excenter press (Courtoy type R7, B-Brussels) using 13mm diameter die-punches. With wet granulation, a determined amount of alcohol was added. The slurry was granulated and after drying, passed through a sieve of 0.37mm and then compressed. The composition of the tablets is summarized in Table 1.

Preparation of dissolution media: Phosphate buffers USP XXII were prepared with the same ionic strength and different pH-values.

Dissolution Test: The release of drug from matrix tablets was measured according to the USP XXII apparatus (paddle) at 37 °C ± 0.5 using 1000ml of dissolution medium, at varying rotation speed and buffer composition. At determined time intervals, 5ml samples were taken, filtered through a glass filter and assayed spectrophotometrically, after appropriate dilution, with a Cary spectrophotometer at 273nm.

The total drug content of each tablet was determined by weighing the tablet and calculating the amount of active compound. The release rate experiments were carried out in triplicate.

Increase of viscosity as a function of time: One gram of xanthan gum was poured in solvent, mixed for 40 seconds with a ultra turrax (Janke & Kunkel, D- Staufen) to disperse it quickly and the increase in viscosity followed as a function of time using a Haake roto viscometer with a wing FLO 10, sensor 5 at 128rpm.

Data Analysis: The data were plotted according to the following different equations for describing the release kinetics of the drug.

Zero order : $\% F = a_1 + b_1 . t$ - (Equation 1)
First order : $\ln (100 - \%F) = a_2 - b_2 . t$ - - - - - - - - - - - - - - - - - - (Equation 2)
Square root or Higuchi equation : $\% F = a_3 + b_3 . \sqrt{t}$. - - - - - - - - - - - - - - - (Equation 3)
The RRSBW distribution: $\ln\ln [100/(100 - \% F)] = a_4 + b_4 .\ln t$ - - - - - - - - - - (Equation 4)
Where, % F = percent drug release at time (t) in minute
a_1, a_2, a_3, a_4 and b_1, b_2, b_3, b_4 are corresponding intercepts and slopes respectively.

Evaluation procedure: The graphs were verified for linearity by calculating slope, intercept and correlation coefficients using least square fit method. As we will see in results and discussions, linear plots and high correlation coefficients were observed with different models in many cases. Thus the mechanism of release of drug could not always be distinguished. Therefore, another method was selected for this purpose. The data were analyzed by rearranging the equations so that always the percent release of the drug is on the left side of the equations. The goodness of fit was evaluated by estimating the residual sums of squares of the deviations $\Sigma(F - \bar{F})^2$ where F is the observed and $\bar{F}$ is the least squares fit value of the percent of the drug released. For the comparisons, the sums were converted into variance estimates by dividing by the number of degrees of freedom, i.e. n-2. The equation with the least variance was considered to be the best fit and it's statistical significance from the others was shown by the F-ratio. The calculated F-values were compared to F critical at alpha = 0.05. In order to find the exact mechanism of release, the rate (dQ/dt) with F (cumulative amount released) and 1/F were also determined.

One way ANOVA was used to evaluate the influence of different parameters on the release of the drug from the matrix tablets.

RESULTS AND DISCUSSION

In all experiments sink conditions were maintained.

1. Effect of xanthan gum concentration on release rate of the drug: Tablets containing different concentrations of xanthan gum were prepared by direct compression (see Table 1). The release rates as a function of xanthan gum is given in Fig.1. From the Figure it is observed that the release rate is greatly influenced by the matrix concentration: a direct relationship is noted between the amount of gum in the formulation and release rate of the caffeine. With 33.33% gum and 66.67% active compound, a very slow release of the drug was obtained: only 15.1% of the drug was released in 240 minutes. Physically, a very thick layer of gel was formed in the first hour. Consequently, erosion of the tablet was inhibited and the release rate was delayed. By reducing the concentration of xanthan gum, the release rate was enhanced while the tablet properties were maintained. However, with 4.17% polymer, erosion of the tablet became quite noticeable. With a proportion of gum and lactose of 6.67 and 26.67% respectively, sufficient gel layer was formed after a few minutes. The best sustained release profile was obtained with 5.83% and 27.50% xanthan gum and lactose, respectively.

The data of Fig. 1 were plotted according to the Eq. 1 - 4. From the linear portions of the curves, slope, intercept and correlation coefficient(r) were calculated. The data are summarized in Table 2. With the zero order plot, linearity was noted with 4.17 and 5.83% polymer concentrations using all the data points. The data yielded an apparently straight line with zero order as well as with first order kinetics at high concentration of xanthan gum (16.67 and 33.33%). The correlation coefficients were high ($r > 0.997$). No linearity was noted with the Higuchi equation or the RRSBW fit. It is also mentioned by other authors that discrimination between two models is often difficult when the data are plotted according to the different equations [3-6]. A lot of authors decide the release rate process by simply comparing the correlation coefficients [3-5]. The model with the highest correlation coefficient is then selected. However, with these correlation coefficients, only

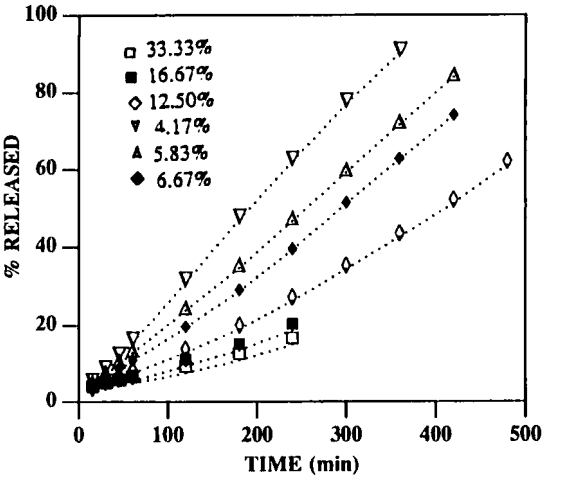

FIGURE 1

Effect of polymer concentration on release of caffeine from xanthan gum matrix tablets (compressed at 20KN) in water at 37°C and 50rpm, by paddle method.

the same model can be compared. To evaluate the data meaningfully and statistically, the dependent parameters must be in the same form (linear, logarithmic etc.).

Therefore, the equations were transformed, as mentioned in evaluation procedure, and the variances were calculated and compared. The best fit was obtained with the zero order equation (F-ratio). However, no significant statistical difference could be noted between the zero order and first order kinetics by the F-test. This can probably be explained by the fact that the drug is released very slowly from the tablets containing 16.67 and 33.33% xanthan gum.

The differences in data in ln scale are not very distinguishable. The RRSBW plot is an empirical function but shows generally the advantage that the whole dissolution curve can be described [7]. By plotting the data according to the Eq. 4, the slope(b_4) is said to be the shape parameter (b) and the ordinate intercept = -b.logTd with T_d = time parameter. This function can not be used for our data. This is not surprising as the RRSBW model can be used for first order and sigmoid curves but not for zero order kinetics [7].

In Fig.1 a small negative lag time was observed. Extrapolation of the lines passes the y-axis but the values are small (<1.4). This means that initially there is a burst of release of the drug. This can be explained by the fact that the formation of the gel layer takes some time while the active compound being on the surface, can be released immediately.

It was further tried if a linear relationship of matrix concentration with release rate of caffeine could be found by plotting ln k (zero order release rate constant) as a function of ln C % of corresponding polymer in the formulation. The result is shown in figure 2. The regression equation calculated from the data is : ln k = - 0.7593 ln C (%) - 0.3035 - - - - - - - - - - - - - - (Eq. 5). From Eq. 5 one can easily calculate the necessary concentration of gum in the formulation of a dosage form to get a specific amount of drug release at a specified time.

2. Effect of the rotation speed on the drug release from matrix tablets: For this experiment, tablets with the best release rate profile determined in 1. were used (e.g. tablets containing 5.83%

TABLE 2

Kinetics of caffeine from xanthan gum matrix tablets with regression analysis and F-test.

PARA-METER	ZERO ORDER				HIGUCHI			FIRST ORDER			F-RATIO
GUM %	SLOPE (k)	CORR. COEFF.	VARI-ANCE	DEG. FREE.	CORR. COEFF.	VARI-ANCE	DEG. FREE.	CORR. COEFF.	VARI-ANCE	DEG. FREE.	
33.33	0.055	0.998	0.124	5	-	-	-	0.998	0.187	5	ZERO/FIRST
16.67	0.072	0.999	0.123	5	-	-	-	0.998	0.232	5	ZERO/FIRST
12.50	0.108	1.000	0.551	5	-	-	-	-	-	-	-
6.67	0.171	0.999	1.715	7	-	-	-	-	-	-	-
5.83	0.196	1.000	0.595	9	-	-	-	-	-	-	-
4.17	0.252	1.000	0.556	8	-	-	-	-	-	-	-
ROTATION SPEED (rpm)											
30	0.156	0.999	0.867	9	-	-	-	-	-	-	-
50	0.196	1.000	0.595	9	-	-	-	-	-	-	-
80	0.216	0.999	0.301	8	-	-	-	0.998	0.969	4	ZERO/FIRST
100	0.295	0.999	0.751	4	-	-	-	0.999	0.960	4	ZERO/FIRST
PRESENCE OF IONS IN THE DISSOLUTION MEDIUM (0.1M*=0.1M HCl)											
0.00	0.062	0.999	0.153	9	-	-	-	0.997	0.477	9	ZERO/FIRST
0.1M	0.065	0.999	0.111	5	-	-	-	0.998	0.402	9	ZERO/FIRST
0.1M*	0.060	0.997	0.410	5	1.000	0.162	9	0.997	0.716	6	HIGUCHI
0.2M	0.118	0.999	0.848	7	-	-	-	-	-	-	-
0.4M	0.790	0.996	11.63	4	-	-	-	-	-	-	-
COMPRESSION TECHNIQUE (in aqueous, 0.1M NaCl and 0.2M NaCl solutions respectively)											
D.COM	0.062	0.999	0.153	9	-	-	-	0.997	0.477	9	ZERO/FIRST
WT.GR	0.064	0.998	0.360	9	-	-	-	0.997	0.603	8	ZERO/FIRST
D.COM	0.067	0.999	0.111	5	-	-	-	0.998	0.402	9	ZERO/FIRST
WT.GR	0.064	0.998	0.453	7	-	-	-	0.997	0.455	9	ZERO/FIRST
D.COM	0.156	0.999	0.711	9	-	-	-	-	-	-	-
WT.GR	0.154	0.999	0.235	8	-	-	-	-	-	-	-
COMPACTION FORCES (in 0.2M NaCl solutions)											
50KN	0.135	1.000	0.488	9	-	-	-	-	-	-	-
100KN	0.136	0.999	0.712	9	-	-	-	-	-	-	-
pH OF THE DISSOLUTION MEDIUM											
WATER	0.064	0.998	0.360	9	-	-	-	0.997	0.693	8	ZERO/FIRST
1.2	0.060	0.997	0.410	5	1.000	0.162	9	0.997	0.716	6	HIGUCHI
5.8	0.058	0.997	0.429	6	0.997	0.663	8	0.998	0.452	9	FIRST/HIGU/ZERO
6.4	0.057	0.997	0.558	6	0.998	0.378	6	0.998	0.463	9	FIRST/HIGU/ZERO
6.8	0.063	0.997	0.585	7	0.998	0.320	5	0.999	0.371	9	FIRST/HIGU/ZERO
7.4	0.059	0.998	0.399	6	0.997	0.528	8	0.999	0.395	9	FIRST/HIGU/ZERO
SURFACTANT (sodium lauryl sulfate)											
1.0 %	0.061	0.998	0.387	9	-	-	-	0.998	0.636	7	ZERO/FIRST
0.0 %	0.065	0.998	0.360	9	-	-	-	0.997	0.693	8	ZERO/FIRST

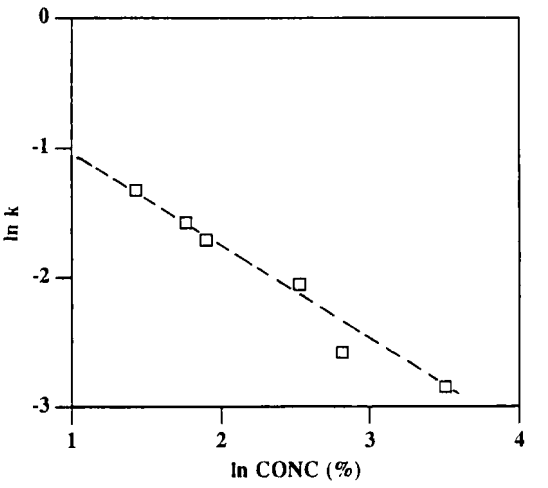

FIGURE 2

Relationship of matrix concentration with release rate of caffeine from xanthan gum matrix tablets.

xanthan gum, F#5). The rotation speed was changed from 30 to 100rpm. The results are shown in Fig. 3. For the sake of clarity, the data in the beginning of the plots of Fig. 3 are omitted but are taken into account for the statistical evaluation. A great positive influence of the rotation speed was noted: nearly a two-fold amount of the drug was released at 100rpm than at 30rpm at similar experimental conditions. As the stirring speed increased, the thickness of the hydrated gelatinous layer surrounding the intact tablet core was noticeably decreased under the elevated stirring conditions, resulting in a more rapid release of the drug from the matrix tablets.

When we observe the whole release rate profile, the shape of the curves was changing: from a linear curve at 50rpm, they become more curved at the higher rotation speeds, e.g. 80 and 100rpm. The data can again be interpreted by zero order kinetics for the whole curve at 30 and 50rpm, and up to nearly 60% at the higher rotation speeds. With the first order plot, linearity was also found up to 60% of the drug released. When the Higuchi equation was tried, the graph obtained at 80 and 100rpm, profiles with two linear phases were noted. There was an initial linear phase for the early time points. A break in the curve occurred at 20% where a second phase with a more positive slope described the data for the remainder of the experiment. This initial linear portion of the biphasic response can be explained as follows: when the dissolution process starts, several processes are operating: water penetrates the tablet, the drug must dissolve, the dissolved drug must leave the tablet and dissolve in the dissolution medium. This takes some time. So the release of active compound can be delayed. At later times, when the gel layer is fully formed and diffusion is in equilibrium, then only the Higuchi equation applies. Harris and McGinity [8] found a similar plots using montmorillonite as matrix compound. The best fit was obtained with zero order plots (least F-ratio).

However, a significant difference between the models could not be observed by the F-ratio's (see table 2). Therefore, to get more meaningful information, the method of Schwartz [9] was tried: the release rate plotted versus % F or 1/ %F gives linearity for first order and the Higuchi equation, respectively. When plotting the rate as a function of % F a constant rate was obtained, suggesting a zero order release process occurred.

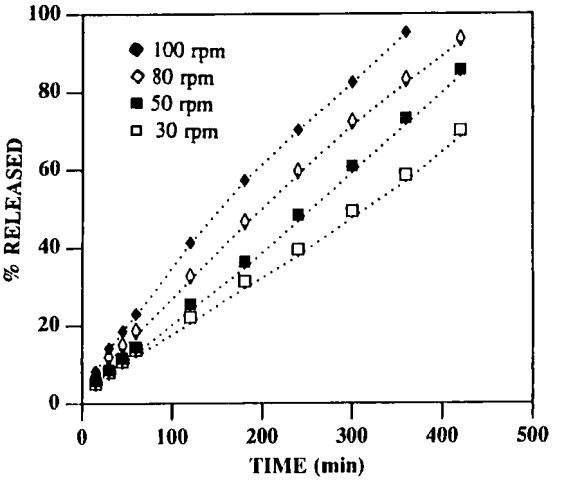

FIGURE 3

Effect of rotation speeds on the release rate of caffeine from xanthan gum matrix tablets, F#5, (compressed at 20KN), in water at 37°C, by paddle method.

3. Effect of ionic strength of the dissolution medium: The ionic strength in the stomach is fairly constant. For that reason it is important that controlled release tablets are resistant in media of 0.1 ionic strength and somewhat higher. To evaluate this parameter, tablets containing 5.83% xanthan gum (F#5) were tried in 0.1M NaCl solution. With these tablets, a dramatic effect was noted when 0.1M NaCl was used as dissolution medium: a very rapid disintegration of the tablet was observed; in fact, in a few minutes, the tablets completely disappeared in the medium. This dramatic effect of ionic strength was not expected, as it is well known that xanthan gum can tolerate salts in very high concentrations [1]. However, after a certain time, swollen particles of the gum were found in the dissolution medium itself, suggesting a decrease in the swelling rate of xanthan gum in the presence of salts.

To overcome this problem, two binders were added to the matrix tablet, i.e. Avicel and kollidon in different concentrations, with the aim of maintaining the tablets in the beginning of the dissolution experiment, and to allow sufficient time for swelling of the gum. With 10% Kollidon (F#9), instantaneous disintegration occurred in 0.1M NaCl dissolution medium; with 20% Kollidon (F#10), results were not very improved. It was noted that increasing the binder, even in high concentration e.g. 25% (F#11), was not enough to hold up the tablets to their original size and shape. Therefore, the matrix concentration was also increased in the formulations. Comparatively better results were found with 15% xanthan gum and 15% (F#12) binder in the formulation when using 0.1M NaCl as dissolution medium. The tablet, however, rapidly released the drug at the beginning of the experiment, i.e. more than 40% release of caffeine was noted in the first half an hour, followed by a linear release profile. However, when using 0.2M NaCl, the tablets instantly disintegrated in the dissolution medium. Finally, by adding more gum, e.g. 25% (F#14) good release rates were noted in the same dissolution medium.

Comparing Avicel with Kollidon, practically no difference in release profile was noted. However, the physical appearance of wetted tablets was, visually, better with Kollidon. The results obtained from the experiment carried out with different ionic strengths with the same formulation

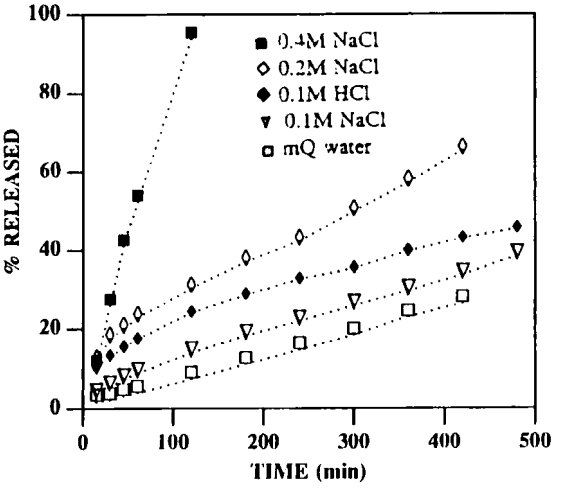

FIGURE 4

Effect of ionic strength of dissolution media on the release rate of caffeine from xanthan gum matrix tablets, F#14, (compressed at 50KN) at 37°C, by paddle method (50rpm).

(F#14) is shown in Fig. 4. From Fig.4, the influence of ionic strength on release rate is obvious. Up to 0.2M NaCl, sustained release behaviour was found. In 0.4M NaCl, dissolution was too fast.

The shape of the curves was also changing as a function of the ionic strength: in water, linearity was observed from the beginning of the experiment. In the salt solutions, linearity was observed only after about 100 minutes. This initial increase of dissolution is attributed to a decrease of swelling rate under the influence of the salts. When we observe the dissolution profiles carefully, the slope of the linear portions are nearly the same in water as in 0.1M NaCl solution. This observation is confirmed by the calculation of the slopes (see Table 2). The higher ionic strengths, however, show increasing release rates. Release rate profiles with this same slope can be explained by the fact that at 0.1 ionic strength, only the rate of hydration is retarded in comparison with water, but not the hydration itself. At the time that the gel layer is formed, the release rate in solution with 0.1 μ should then be the same as in water. This last suggestion agrees with results from literature: it is well known that the viscosity, and thus, the hydration of xanthan gum are not much influenced by high amounts of electrolytes [1].

The suggestion that the rate of hydration is retarded in NaCl solutions was proved by measuring the viscosity increase of xanthan gum in buffer solutions as a function of time with and without addition of salts. The end-viscosity was retarded in the dissolution media when salt was added; i.e. the end-viscosity of xanthan gum was noted in 5 minutes, while the end-viscosity with addition of salt was not yet reached in 20 minutes (data not shown).

4. Effect of wet granulation and direct compression: Tablets with different compression forces were prepared using direct compression and wet granulation techniques and dissolution experiments were performed in water, 0.1M and 0.2M NaCl solutions. Practically no influence was noted. The data are presented in Table 2. However, the physical appearance of the tablet manufactured by wet granulation was better. The results were independent of compression forces.

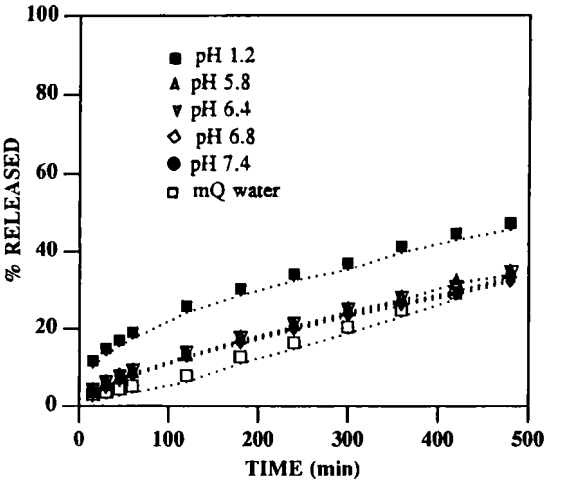

FIGURE 5

Effect of pH of the dissolution media on the release rate of caffeine from xanthan gum matrix tablets, F#13, (compressed at 50KN) at 37°C, by paddle method (50rpm).

5. Effect of pH of the dissolution medium: The experiments, performed in the dissolution media of different pH values e.g. pH 1.2, 5.8, 6.4, 6.8 and 7.4, are illustrated in Fig. 5. Figure 5 indicates that there is no influence of pH on the release property of caffeine. Exception was noted with 0.1M HCl: where at the beginning of the experiment the release rate was increased, due to a slower, visually observed swelling of the polymer, after 100 minutes, the kinetics were nearly the same as with the other pH values, indicated by the same slope (see Table 2). When the results obtained in the buffers were compared with those in water as dissolution medium, the release rate is somewhat higher in the buffers (see Fig. 5), obvious due to the ionic strength of the buffer solutions ($\mu = 0.1145$). As seen in Table 2, the release rate did not follow the same release rate profile in the different media. Especially in 0.1M HCl (pH 1.2), the curve is best fitted with Higuchi equation. This is further confirmed by plotting rates as a function of 1/% F. A change in pH of the dissolution medium can exert an influence on the solubility of the drug or on the hydration of the polymer. The solubility of the model drug was not changed as a function of pH. The influence of pH is noted with several polymers used as matrix. Nearly all gums possessing a carboxyl acid function (e.g. Carbopol) are influenced in a great extent by change in pH. Although xanthan gum is an anionic polymer, containing a carboxylic acid function, the stability of this polymer to pH and ionic strength is high and is attributed to the rod shape of the molecule and the importance of hydrogen bonding intermolecularly [1].

6. Effect of surfactant on the release of caffeine from xanthan gum matrix tablets: The importance and influence of surfactants on release rate of drugs is well known: in the gastro intestinal tract, many surface active compounds are present, lowering the surface tension and possibly influencing the release rate. To simulate this behaviour in dissolution experiments, surfactants are sometimes added in the dissolution medium. Some authors recommend the addition of surfactants [10]; other authors, however, are from the opposite opinion [11]. Surfactants also can improve wettability of tablets and increase the penetration of solvent in tablets. The influence of 1% sodium lauryl sulfate, incorporated in tablets was evaluated. No effect was noted when water or a phosphate buffer of pH 6.8 were used as dissolution media. Data are shown in table 2.

7. Effect of compression forces on release rate of caffeine from matrix tablets: The effect of various compression forces on the release characteristics of caffeine were studied by changing the compression forces from 10 to 100 kN. The experiments were performed with tablets containing binder and those without binder using water, 0.1M and 0.2M NaCl, as dissolution media. With all these tablets, no influence of compression force was noted. Part of these results are shown in Table 2. Many times it has been published that compression force has not much influence on the release rate [12]. However, it is important that the compression force is high enough to inhibit partial or total disintegration of the tablet, and from the industrial point of view, it is important to know the influence of this parameter.

CONCLUSIONS

Xanthan gum seems to be an interesting macromolecule for the preparation of hydrophilic matrix tablets. The release of the drug from xanthan gum matrix tablets is independent of compression force (from 10KN to 100KN), compaction technique, pH of the dissolution medium and presence of surfactant. The presence of ions and rotation speed of the dissolution medium have a great influence on release rate profile of the drug from xanthan gum matrix tablets. In aqueous medium release rate kinetics almost follow zero order and in the presence of ions, release of soluble drug (caffeine) follow zero and/or square root of time kinetics.

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