

Evaluation of The Formulation Variables on the Swelling and the Dissolution Properties of Controlled Release Xanthan Tablets of a Water-Soluble Drug

Wasfy Obeida^{*}, Aiman A. Obaidat

Department of Pharmaceutical Technology, Jordan University of Science and Technology, P. O. Box 3030, Irbid, JORDAN

Abstract

Direct compression tablets of xanthan gum containing a water-soluble drug were prepared at different polymer, diluent and drug ratios. An emphasis was directed towards incorporation of large quantities of the model drug. Also, the effects of formulation variables especially tablet excipients on the swelling properties and drug release kinetics were investigated. Swelling studies were conducted using USP disintegration apparatus in deionized distilled water at 37°C. Generally tablets containing high xanthan gum contents show higher rates and degrees of swelling. Drug release studies were conducted using USP XXII dissolution apparatus at 37°C. All tablets showed an extended drug release profile to various extents.

Key words: Xanthan gum, Chorpheniramine maleate, Swelling, Controlled release

Introduction

Systems prepared by incorporating drugs in hydrophilic polymeric matrices that swell in an aqueous medium are called swellable systems and have received considerable attention for controlled release preparation that might exhibit zero order release kinetics under specific conditions (Huber *et al.*, 1966; Lapidus and Lord 1968; Korsmeyer and Peppas 1981). In the swelling polymers, release of solute is controlled by one or more of the following processes; namely, the transport of the solvent into the polymer matrix, swelling of the polymer, diffusion of the solute out through the swollen polymer, erosion of the swollen polymer (Brazel and Peppas, 1999). A disadvantage of the use of hydrophilic polymers for controlled release of water-soluble drugs is the rapid dissolution of the surface drug and quick diffusion of drug through the outer hydrated gel layer. This causes initial rapid release followed by a period of slow release because of the increased path length of diffusion of the drug through the polymer as the hydration and swelling of polymer matrix progresses (Bavega *et al.*, 1987).

Xanthan gum is a highly ordered network through hydrogen bonds and polymer entanglement (Kang and Pettitt, 1993). It is commercially used in food industry for purposes of viscosity building and proven to be safe (Remington, 1995). Xanthan gum has been investigated by some workers and incorporated into tablet formulations to achieve sustained release action (Dhopeswarkar and Zats 1993, Bonferoni *et al.*, 1993, El-Gazayerly 2003).

^{*} *Corresponding author* : Email: obeidatw@just.edu.jo

The kinetics of drug release from matrices were examined for both freely water soluble (Higuchi, 1962) and poorly soluble drugs (Higuchi, 1963). A simple equation was derived (Korsmeyer *et al.*, 1983) that may be used to describe drug release from polymeric systems in which release deviates from fickian diffusion and follows a non-fickian (anomalous) behavior. Diluents such as anhydrous lactose, microcrystalline cellulose and dibasic calcium phosphate provide a ready to use product in which the formulator needs only to blend the desired active medicament with the diluents and then compress the mixture into tablets. The type and the ratio of the diluent can affect tablet compression properties as well as drug release rates and kinetics (Sung *et al.*, 1986; Ford *et al.*, 1987). The objectives of this study are (a) to study the effect of formulation variables on the swelling properties of xanthan gum tablets containing chlorpheniramine maleate as a water-soluble model drug (b) to evaluate the influence of diluents on swelling and release kinetics of chlorpheniramine tablets.

Materials and Methods

Materials: The following materials were used: Xanthan gum polymer, (Merck and Co.) Microcrystalline cellulose, (Avicel PH 101, Fluka Chemical), Lactose (anhydrous) (Central Drug House, India), Dibasic calcium phosphate, Magnesium stearate, (FMC Co.), Chlorpheniramine maleate, (Sigma Chemical Co.).

Instruments: Instruments and equipment used in this study include, Single punch tablet machine (ERWEKA, AR400), USP XX II dissolution apparatus (Vankel, VK 700, USA), UV spectrophotometer (Cintra 5, GBC scientific equipment), screw gauge micrometer, USP XXII Disintegration apparatus (ZT4, Erweka-Apparatebau, D-Heusenstamm), Hardness tester (COPLEY, model 2E \ 205), Roche type friabilator (Vankel), Standard Sieve set.

Tabletting: Tablets were prepared by mixing the polymer and the drug and half amount of the diluents for 3 min using V-shape blender after being passed through a 40-mesh screen. Then the other half of diluents was added to the blend and mixed for another 3 min. Magnesium stearate was passed through a 40-mesh screen and added to the previous blend and mixed for 6 min. The procedure was proved to obtain optimum mixing conditions. The mixture was then directly compressed into tablets 0.6 cm in diameter. Tablets were compressed to have low, medium and high crushing strengths. Friability tests were conducted for all tablet preparations.

Swelling studies: Swelling studies were conducted in a manner similar to the USP XXII disintegration tests to ensure efficient water contact. In this study, six tablets were placed in the disintegration apparatus, one tablet in each vessel, and allowed for direct contact with deionized distilled water (37 °C) at a rate of 32 cycles per minute. Initial diameter and thickness of each tablet were recorded prior to swelling and initial volume was calculated. The increase in tablet dimensions and therefore tablet volume was observed as a function of time until tablet achieved equilibrium (until maximum volume, V_{∞} was achieved). Six tablets were tested for each batch and tablet dimensions were measured at different time intervals using a screw gauge micrometer.

Dissolution studies: Six tablets of similar weight from each preparation were tested for the release of the drug using USP XXII rotating paddle apparatus at 100 rpm using 900 ml deionized distilled water at 37 °C. Samples were taken at 5 min, 30 min, 1 h, 3 h, 6 h, 7 h, 8 h and 12 h then filtered through 0.45 μ m Millipore filter and the concentration of the drug was measured spectrophotometrically at 260 nm. The sample taken was replaced by same volume of fresh medium. The percentage released was calculated and the average values were plotted against time to obtain the release profiles of the different formulations. Only medium hardness tablets (about 7 kg) were used in release studies.

Results and Discussion

Tablet formulations: Matrices of xanthan gum weighing about 250 mg and containing chlorpheniramine maleate at different loadings were compressed directly after mixing with different diluents. Powders were free flowing with good to moderate compressibility indices and tablets showed narrow range of weight variations with an acceptable friability. Tablets containing microcrystalline cellulose were found to be easier to compress compared to those tablets containing lactose and dibasic calcium phosphate that could be due the lower compressibility index of microcrystalline cellulose ($I = 23 \pm 1.2$) compared to the lactose ($I = 29 \pm 1.6$) and dibasic calcium phosphate ($I = 30 \pm 1.8$). Table 1 shows all tablet formulations and the percentages of components in each tablet. Crushing strengths were measured and found to be of low (3.5 ± 0.5), medium (7 ± 1.2) and high (12 ± 2.0) values for the three preparations. All tablets passed the friability testing with an average of (0.65 ± 0.15 %) loss after testing.

Table 1. The composition of different tablet formulations containing chlorpheniramine maleate at constant percentage of magnesium stearate (0.5%).

Tablet Formula symbol	% Xanthan gum	% Diluents	% Chlorpheniramine maleate
CPA 0	0	79.5 MCC ^a	20
CPA 1	15	74.5 MCC	10
CPA 2	15	64.5 MCC	20
CPA 3	30	59.5 MCC	10
CPA 4	30	49.5 MCC	20
CPA 5	30	49.5 MCC ^{2b}	20
CPA 6	15	74.5 LAC ^c	10
CPA 7	15	64.5 LAC	20
CPA 8	30	59.5 LAC	10
CPA 9	30	49.5 LAC	20
CPA 10	15	74.5 DBCP ^d	10
CPA 11	15	64.5 DBCP	20
CPA 12	30	59.5 DBCP	10
CPA 13	30	49.5 DBCP	20

a MCC (microcrystalline cellulose PH 101)

b MCC2 (microcrystalline cellulose PH 102)

c LAC (anhydrous lactose)

d DBCP (dibasic calcium phosphate).

Polymer swelling studies: Xanthan gum is a hydrophilic polymer due to the presence of hydrophilic hydroxyl groups. When the polymer comes in contact with water, forces of attraction, chiefly hydrogen bonding, starts between them so that forces holding polymer segments are much reduced in the presence of water molecules. Water molecules cause the polymer to hydrate, swell and increase in size as the water fills voids created by unfolding of

the tightly folded random coil of polymer (Mitchell *et al.*, 1993). Plots of normalized volume (V_t/V_0) of swollen tablet matrices of all preparations against time are shown in figures 1, 2 and 3, where V_0 is the initial tablet volume and V_t is the tablet volume at time t . The plots show rapid increase in tablet volume during the initial swelling period when compared to the equilibrium volume indicating fast hydration. After the initial swelling period, the swelling of tablets is retarded to reach a plateau where tablets achieve maximum swelling capacity or volume. This may be attributed to the fact that solvent fronts are meeting in the center of the tablet and there is no further unhydrated polymer to hydrate (Mitchell *et al.*, 1993).

Table 2. The slopes, intercepts and the linear regression coefficients from the swelling data of all tablets formulations of medium crushing strengths.

Tablet Formula symbol	Slope	Intercept	Regression coefficient
CPA 1	0.563	0.178	0.9965
CPA 2	0.544	0.234	0.9875
CPA 3	0.670	0.315	0.9877
CPA 4	0.685	0.696	0.9980
CPA 6	0.896	0.334	0.9898
CPA 7	0.796	0.432	0.9798
CPA 8	1.021	0.106	0.9915
CPA 9	0.885	0.543	0.9999
CPA 10	0.500	0.749	0.9891
CPA 11	0.444	0.666	0.9890
CPA 12	0.578	0.573	0.9988
CPA 13	0.663	0.869	0.9809

Swelling profiles (water uptake) seem to best fit the square root of time model for all the tablet formulations suggesting normal diffusion of water molecules into the polymer matrix. Table 2 shows the intercept, the slope and the linear regression coefficients of all tablet formulations having medium crushing strengths from plots of normalized amount against the square root of time. Generally tablets containing higher percentages of xanthan gum (30%) such as CPA3, CPA4, CPA8, CPA9, CPA12 and CPA13 show higher rates and volumes of swelling than those containing lower (15%) xanthan gum content at both high and low drug loadings as shown in Figures 1-3.

Tablets containing lactose swell more rapidly and to higher volumes compared to those containing microcrystalline cellulose and tablets containing dibasic calcium phosphate and this was more apparent at higher polymer content. This could be due to higher solubility of anhydrous lactose and its ability to attract water molecules towards tablet matrix allowing more efficient contact of xanthan gum and water.

Microcrystalline cellulose containing tablets swell faster and to higher extent than dibasic calcium phosphate containing tablets.

Tablet strength did not show a significant effect on swelling except for those containing lactose where swelling is affected to some extent by compression force. In the presence of a film of moisture, high forces of compression tend to force more soluble lactose into solution that would then recrystallize upon the relief of applied stress to form solid bridges of higher strength compared to tablets compressed at a relatively lower compression force. This would decrease water penetration and overall swelling. Higher drug loading resulted in slower rates of swelling and low swelling volumes compared with tablets of relatively low drug loading as shown in the

previous figures. This can be due to replacement of the polymer to the drug leaching out. This seems to be significant at drug loading close to that of the polymer (at high drug loading). On the other hand, the result indirectly suggests that the drug release at higher loading is faster than at lower loading and the voids created by the released drug and occupied by the polymer are more significant at higher drug loading.

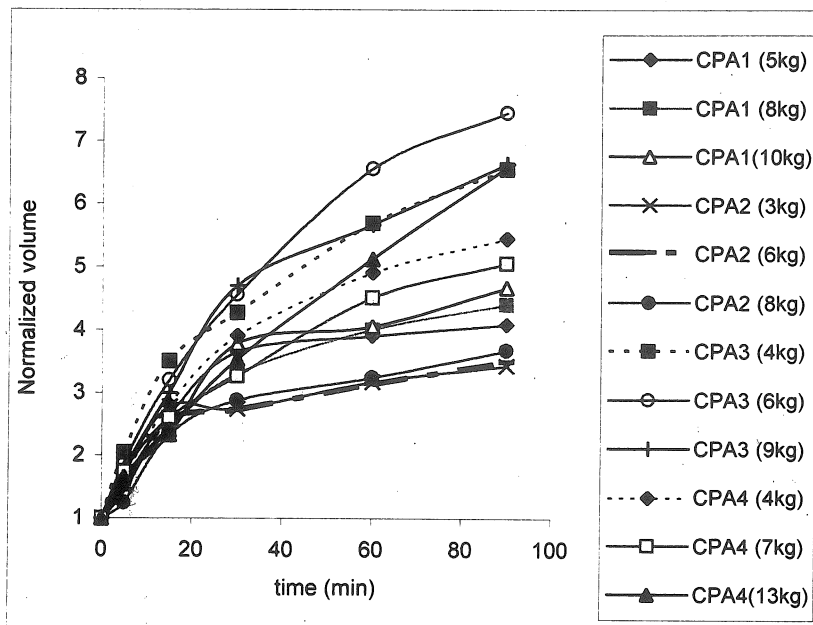


Figure 1. Normalized volumes of CPA1, CPA2, CPA3 and CPA4 tablets of different crushing strengths versus time in water at 37 °C.

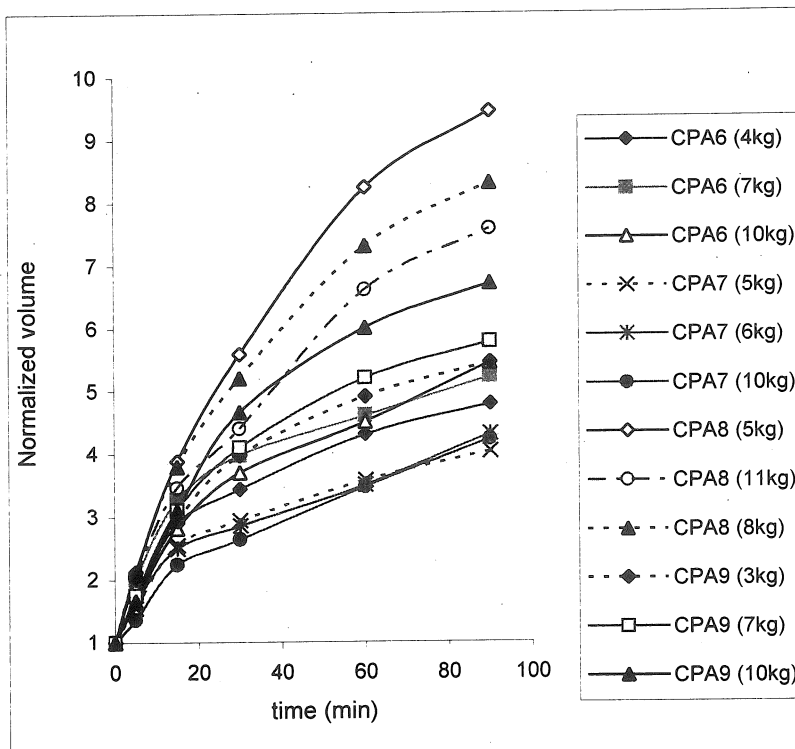


Figure 2. Normalized volumes of CPA6, CPA7, CPA8 and CPA9 tablets of different crushing strengths versus time in water at 37 °C.

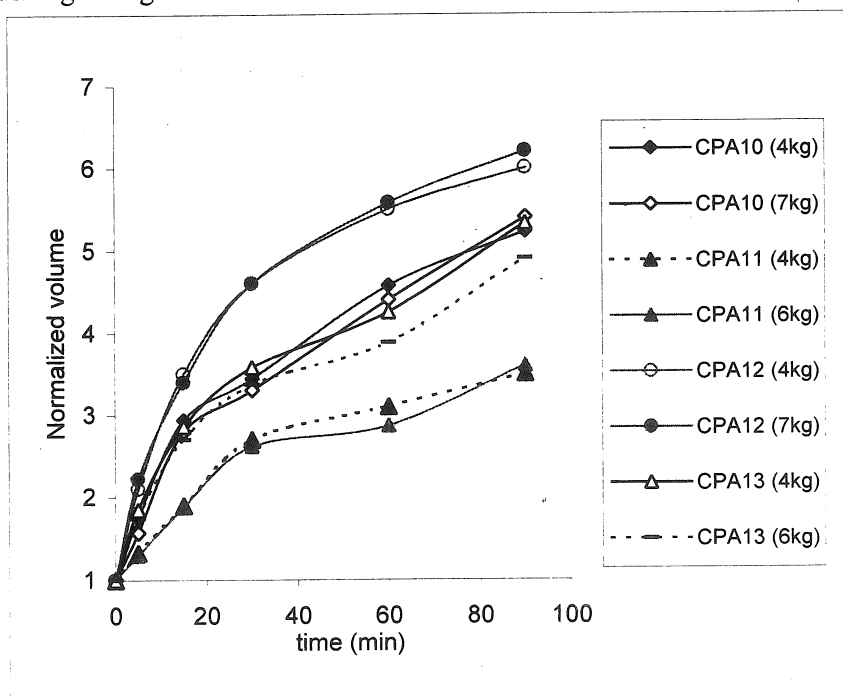


Figure 3. Normalized volumes of CPA10, CPA11, CPA12 and CPA13 tablets of different crushing strengths versus time in water at 37 °C.

Drug release studies: The release of drugs depends not only on the nature of the matrix but also on the solubility of the drug and the nature of the diluents in the tablet. Controlled drug release from swellable matrices is dependent on the formation of an external polymeric gel layer. The thickness and/or the viscosity of this layer are considered to be a major controlling element in the kinetics of drug release. In this study xanthan gum hydrophilic matrices were found to be effective in controlling and extending the release of a water-soluble drug, chlorpheniramine maleate.

Figures 4 - 6 show the drug release profiles of chlorpheniramine maleate from xanthan gum matrices containing microcrystalline cellulose, anhydrous lactose and dibasic calcium phosphate respectively at different ratios. Drug release from xanthan gum tablets was sustained compared to those tables without this polymer. Drug release profiles from xanthan gum tablets were extended with different half-life values depending on the formulation composition and most release profiles showed a square root of time dependence. Figure 7 shows the linear plots of the cumulative amount released versus the square root of time for a selected tablet formulations (for convenience) having medium crushing strengths and Table 3 lists the corresponding slopes, intercepts and the linear regression coefficient values for all tablet preparation. At late stages (> 80 %) of drug release, gel layer erosion and longer diffusion path-lengths predominate and release rates decrease with time.

Table 3. The slopes, intercepts and the linear regression coefficients from the drug release data of all tablet formulations of medium crushing strengths.

Tablet Formula symbol	Slope	Intercept	Regression coefficient
CPA 1	4.706	-21.68	0.9999
CPA 2	5.103	-10.14	0.9998
CPA 3	5.528	-50.04	0.9996
CPA 4	4.855	-47.34	0.9972
CPA 6	5.700	-44.82	0.9947
CPA 7	5.142	-25.27	0.9934
CPA 8	3.676	-35.82	0.9976
CPA 9	4.046	-25.60	0.9910
CPA 10	3.200	-15.77	0.9934
CPA 11	5.285	-27.72	0.9995
CPA 12	4.660	-17.74	0.9988
CPA 13	4.568	-24.46	0.9909

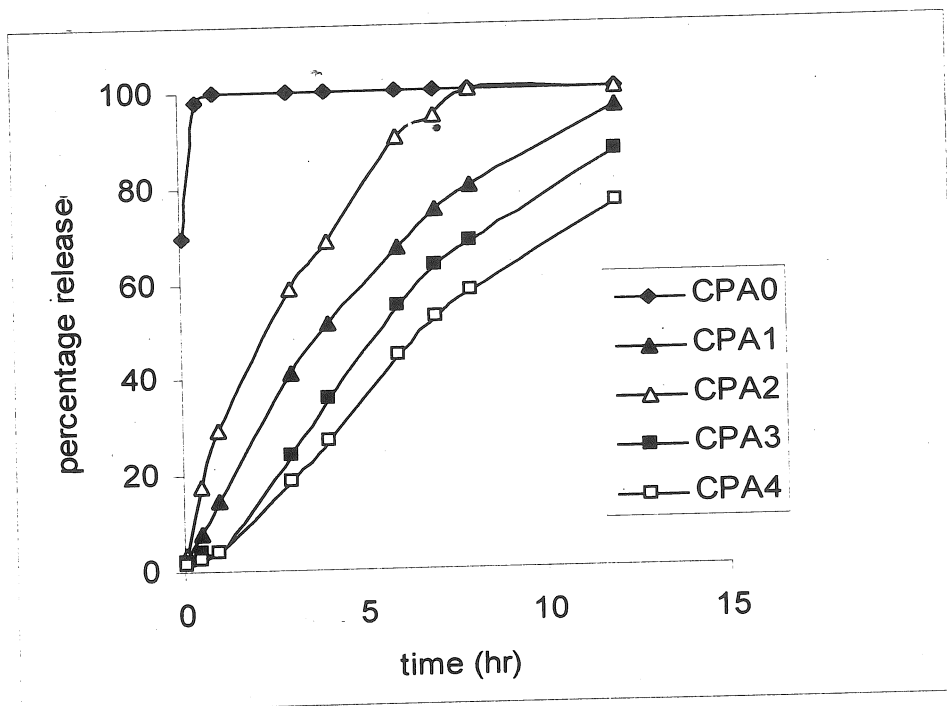


Figure 4. Drug release profile of chlorpheniramine maleate from xanthan tablets CPA0, CPA1, CPA2, CPA3 and CPA4 in water at 37 °C.

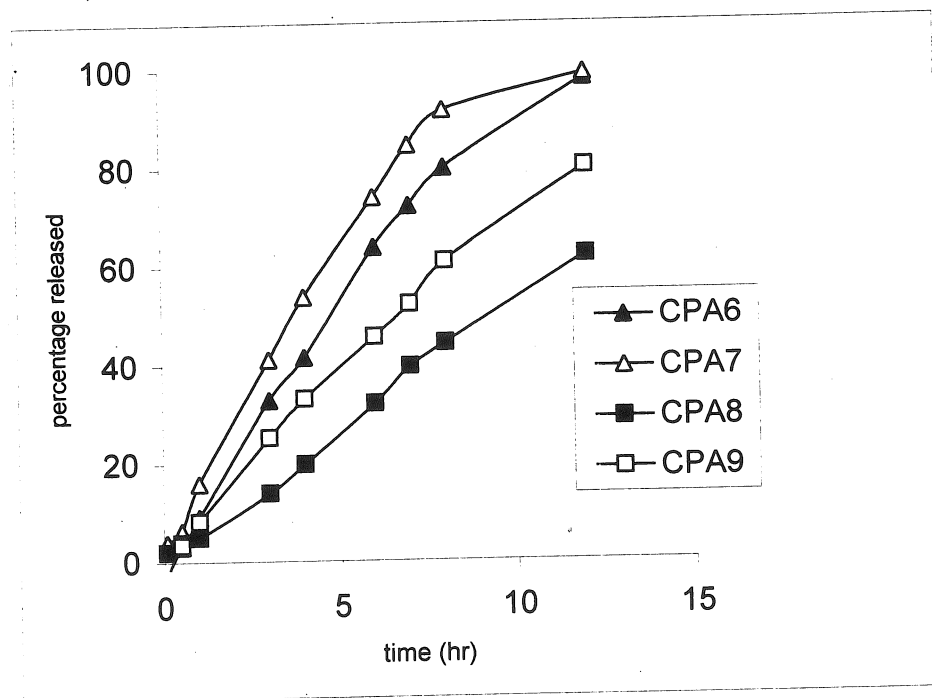


Figure 5. Drug release profile of chlorpheniramine maleate from xanthan tablets CPA6, CPA7, CPA8 and CPA9 in water at 37 °C.

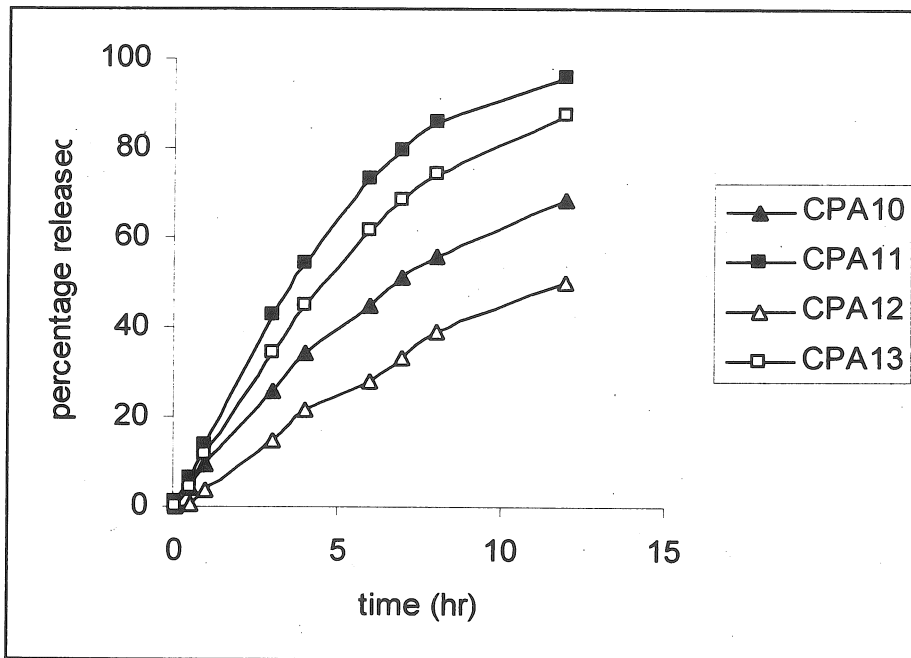


Figure 6. Drug release profile of chlorpheniramine maleate from xanthan tablets CPA10, CPA11, CPA12 and CAP13 in water at 37 °C.

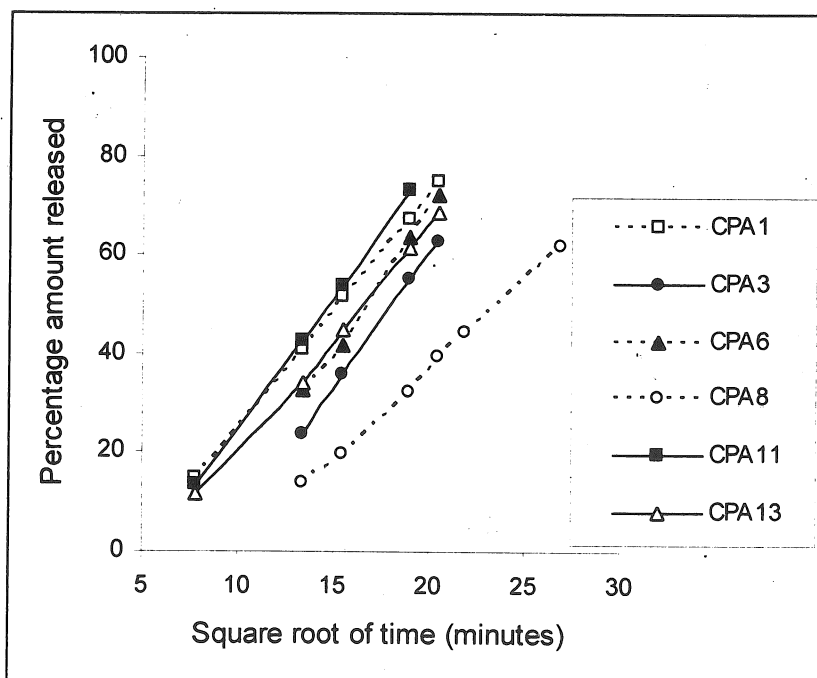


Figure 7. The amount of drug release versus the square root of time for some tablet formulations.

Tablet formulations containing the same diluents vary in the rate of release due to the different percentage of xanthan. For example, CPA3 and CPA4 showed more extended release profile due to the higher percentages of xanthan gum while CPA1 and CPA2 showed faster release rates.

Dibasic calcium phosphate containing tablets showed more extended release profiles of chlorpheniramine than other tablet preparations. In addition to the effect of xanthan gum gelling, we suggest that the sustained drug release profiles are due to the presence of dibasic calcium phosphate that is sparingly water-soluble so it can affect water penetration into the matrix and therefore drug release.

The relation between swelling capacities and drug release rates:

Xanthan polymer seems to be hydrated fast enough (as shown in Figures 1-3) allowing for the formation of a viscous polymer gel structure which delays drug release from tablets. Higher concentrations of xanthan result in the formation of continuous viscoelastic matrix that fills interstices, maintaining the integrity of the tablet. In addition, further matrix swelling is involved in controlling drug release into a near zero order kinetics for most of the times in the release profiles of lactose containing tablets. An apparent correlation was observed between the swelling capacity (maximum swelling volume) and drug release profiles within each set of tablet formulation. Swelling capacities were in the order of CPA4 > CPA3 > CPA1 > CPA2 and T50% values in the drug release profiles were in the same order. Similar results were also noticed for other tablet formulations containing anhydrous lactose and dibasic calcium phosphate. Lower swelling rates and swelling capacities of tablets containing dibasic calcium phosphate compared to the other tablet formulations were noticed. However, the release drug profiles were more extended than other tablet formulations. This can be explained based on the relatively hydrophobic nature of dibasic calcium phosphate that will affect water uptake and drug release.

In conclusion, tablets containing xanthan gum with several diluents and a water-soluble model drug, chlorpheniramine maleate, were prepared by direct compression. It was apparent from this study that xanthan polymer was capable of extending the release profile of chlorpheniramine maleate (aqueous solubility of 160 mg/ml) at low (15%) and high (30%) xanthan contents. Since chlorpheniramine maleate was used in high doses in this study, this indicates that xanthan gum can optimistically be used to extend the release of other water-soluble drugs that are usually used in high doses.

Swelling has been shown to follow square root of time kinetics and so does drug release from most preparations. Also this study shows that swelling kinetics of the tablet matrix and the rates of swelling in the initial times were important determinants of drug release kinetics.

Acknowledgement

This study was supported by a grant from Jordan University of Science and Technology (100/2003).

References

Bavega, K, Ranga Rao, V, Devi, P (1987). Zero-order hydrophilic matrix tablets of beta-adrenergic blockers. *Int. J. Pharm. Sci.* 39: 39 - 45.

- Bonferoni, M.C., Rossi, S., Tamayo, M., Pedraz, J.L., Domiquez-Gil., A., Caramella, C. (1993). On the employment of λ -carrageenan in a matrix system. I. Sensitivity to dissolution medium and comparison with sodium carboxymethylcellulose and xanthan gum. *J. Control. Release* 26: 119-127.
- Brazel, C.S., Peppas, N.A. (1999). Mechanisms of solute and drug transport in relaxing, swellable hydrophilic glassy polymers. *Polymer* 40: 3383-3398.
- Dhopeswarkar, V., Zats, J.L. (1993). Evaluation of xanthan gum in the preparation of sustained release matrix tablets. *Drug Dev. Ind. Pharm.* 19: 99 -1017.
- El-Gazayerly, O.N. (2003). Release of pentoxifylline from xanthan gum matrix tablets. *Drug Dev. Ind. Pharm.* 29: 241-246.
- Ford, J.L., Rubinstein, M.H., McCaul, F., Hogan, J.E., Edgar, P.J. (1987) Importance of drug type, tablet shape and added diluents on drug release kinetics from hydroxy propyl methyl cellulose matrix tablet. *Int. J. Pharm.* 40: 223 - 234.
- Higuchi, T. (1962). Analysis of data on the medication release from ointments. *J. Pharm. Sci.* 51: 802-804.
- Higuchi, T. (1963). Mechanism of sustained medication. Theoretical analysis of rate of release of solid drugs dispersed in solid matrices. *J. Pharm. Sci.* 52: 1145-1149.
- Huber, H.E., Dale, L.B., Christenseon, G.L. (1966). Utilization of hydrophilic gums for the control of drug release from tablet formulations. I. Disintegration and dissolution behavior. *J. Pharm. Sci.* 55: 974-976.
- Kang, K., Pettitt, D. (1993). Industrial gums: Polysaccharides and Their Derivatives, Third Ed.; Whistler R, Bemiller J, Eds; Academic Press, pp. 341-397.
- Korsmeyer, R.W., Peppas, N.A. (1981). Effect of the morphology of hydrophilic polymeric matrices on the diffusion and release of water soluble drugs. *J. Membrane Sci.* 9 : 211-227.
- Korsmeyer, R.W., Gurny, R., Doelker, E., Buri, P., Peppas, N.A. (1983). Mechanism of solute release from porous hydrophilic polymers. *Int. J. Pharm.* 15: 23-35.
- Lapidus, H., Lord, N.G. (1968). Drug release from compressed hydrophilic matrices, *J. Pharm. Sci.* 57: 1292-1301.
- Mitchell, K., Ford, J.L., Armstrong, D.J., Elliott, P.N.C., Hogan, J.E., Rostron, C. (1993). The influence of drugs on the properties of gels and swelling characteristics of matrices containing methylcellulose or hydroxypropylmethylcellulose. *Int. J. Pharm.* 100: 165-173.
- Remington (1995). *The Science and Practice of Pharmacy*, 19th Ed.; Mack Publishing Company: Pennsylvania.
- Sung, K.C., Nixon, P.R., Skoug, J.W., Ju, T.R., Ping Gao, Topp, E.M., Patel, M.V. (1986). Effect of formulation variables on drug and polymer release from HPMC-based matrix tablets. *Int. J. Pharm.* 142: 53-60.

Received: 06.12.2004
Accepted: 25.04.2005