Incorporation of calcium salts into xanthan gum matrices: hydration, erosion and drug release characteristics

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Abstract

Xanthan gum, a hydrophilic biopolymer with modified release properties, was used to produce directly compressed matrix tablets containing a model drug, Sodium p-aminosalicylate. Three formulations were prepared, each containing a different calcium dihydrate salt: Calcium Chloride, Calcium Sulfate or Dibasic Calcium Phosphate. The aim of the investigation was to relate the calcium ion content and solubility of the calcium salt to the *in vitro* drug release profile of the xanthan matrices. Tablet hydration, erosion and drug release were determined in distilled water using the BP paddle method. The data showed that the overall drug release was the greatest with addition of calcium Sulfate, followed by Calcium Chloride and dibasic Calcium Phosphate. The chloride salt formulation displayed the greatest percentage erosion due to rapid mass loss during the initial phase, followed by those with sulfate or phosphate salts. As xanthan gel viscosity increased and drug release was also found to be lower. It can be concluded that drug release is influenced by the solubility of the salt present in the formulation, since these parameters determine the viscosity and structure of the gel layer.

Keyword: Xanthan gum, drug release, salt effect, Sodium p-aminosalicylate

Introduction

Matrix tablet systems are prolonged release formulations. Matrix tablets that are primarily diffusional dependant are composed of a water insoluble polymer, which forms a porous matrix containing dispersed drug particles. Comparatively, hydrophilic colloid matrix systems are intended to modulate drug release through diffusion and erosion mechanisms. This system comprises of a water swellable hydrophilic polymer that forms a hydrated

matrix layer on contact with water. The rate of drug release is dependent on the penetration of water through the hydrated matrix layer, into the non-hydrated core and the diffusion of dissolved drug through the matrix. The outer hydrated layer will erode as it becomes more dilute and a new gel layer will form as the succeeding surface becomes hydrated. Historically, cellulose ether derivatives such as hydroxypropylmethyl cellulose (HPMC) have been used in matrix formulations due to their rapid hydration when in contact with water[1]. However, there is increasing interest in alternative natural polymers such as xanthan gum (XG).

Xanthan gum is a high molecular weight anionic polysaccharide gum, produced by pure-culture aerobic fermentation of a carbohydrate with the gram-negative bacterium, *Xanthomonas compestris*[2]. The polymer has extensive use in the food and cosmetic industries as a viscosity increasing agent and within the pharmaceutical industry as a hydrocolloid to thicken, suspend and stabilize water based systems[3]. Moreover, XG based matrix tablets have been proven to sustain drug release in a predictable manner due to XG's gelling properties. The primary structure of the gum contains repeated units of five sugar residues; two D-glucose units, two D-mannose units, and one D-glucuronic acid. The polymer backbone is identical to the structure of cellulose and consists of β-D-glucose units linked at the one and four positions. The side chain found on alternating anhydroglucose units is composed of: β-D-mannose-β-D-glucuronic acid-α-D-mannose. This trisaccharide side chain is the characteristic, which distinguishes xanthan from cellulose[2]. Depending on the bacterial strain and fermentation conditions used, the terminal mannose residue may carry a pyruvate moiety and the non-terminal mannose unit carries an acetyl functional group. The anionic character of XG is attributed to the pyruvate and glucuronic acid groups in the structure[3].

Drug release from xanthan gum matrix tablets is believed to be a complex interaction between; diffusion, swelling and erosion mechanisms[3-5]. When the hydrophilic polymer comes in contact with an aqueous medium the liquid penetrates and the matrix gradually hydrates and swells from the periphery to the centre of the tablet. Subsequently, the diameter of the tablet progressively increases and a gelatinous mass forms. This phenomenon occurs due to the formation of hydrogen bonds between XG and water, which causes the uncoiling of XG molecules. XG tablets consist of three regions: the highly swollen

outer gel layer, which acts as a diffusional barrier to retard drug release and further uptake of water; the moderately swollen, rubbery middle layer and the inner dry glassy core[4]. The thickness of the outer gel layer determines the diffusional path length of a water soluble drug and controls its release through Fickian diffusion during the initial phase[5]. However, as XG is hydrophilic in nature the polymer undergoes a relaxation process after hydration. This results in slow direct erosion of the outer layer, which affects the dimension of the matrices and thus influences subsequent drug release[6]. Soluble drugs are released through a combination of swelling and erosion mechanisms; however, for insoluble drugs matrix erosion is the most predominant release factor[3]. Furthermore, as swelling and erosion occur simultaneously, both mechanisms will control the overall drug release rate. Hence, a precise balance between the two factors is required to optimise drug release[5]. Sustained release XG matrix tablets have been investigated in numerous studies[4, 7-9] and provide evidences of XG's ability to prolong drug release. Talukdar, et al. (1998) reported that XG matrix tablets containing 50mg of indomethacin had the same *in vitro* drug release profile and displayed superior therapeutic efficacy *in vivo* compared to the reference product Flexin®[8]. The results showed XG tablets could reach the minimum effective concentration earlier and remained in range longer than the marketed equivalent. Furthermore, a gamma-scintigraphic study of the gastrointestinal transit of XG matrix tablets supports the viability of XG as a controlled release agent[7]. In order to improve sustained release performance of matrix system, XG has been used in combination with other natural excipients; chitosan, guar gum, karaya gum, galactomanan and sodium alginate[2]. The synergistic interactions between galactomannan and xanthan have been investigated in the formulation of directly compressed theophylline tablets[4,9]. Vendruscolo et al. (2005) found that drug release decreased with increased XG concentration. The authors conclude that tablets containing 8% XG and 8% galactomannan provide the most appropriate sustained release properties, with approximately 90% drug release at the end of 8 hours[9]. The work conducted by Jian et al. (2012) supports the theory that binary mixtures of xanthan gum and galactomannan matrix tablets retard diffusion of theophylline[4].

Numerous variables have been investigated which can change the drug release characteristics of XG matrix such as pH, temperature, ionic strength of the medium and the presence of divalent counterions within the tablet. The work conducted by Talukdar & Kinget (1995) showed that the swelling rate of XG system in an acidic medium was significantly lower than in neutral or alkaline solutions[3]. This phenomenon occurs because XG is an acidic polymer with a pKa of 3.1, thus at lower pH values the polymer is less soluble and swelling rate is suppressed[3]. Hence, as the swelling capacity of the polymer will be different in the stomach and the intestine, the drug release will be affected.

Drug release from XG matrix tablets is also sensitive to the presence of ions in the release medium; this is of particular importance because the ionic strength of the GI fluid varies[3]. Baumgartner et al. (2008) and Jaipal et al. (2013) illustrate that as the concentration of calcium ions within the matrix tablet increases, drug release also increases[10-11]. The effect of bivalent cations on the flow behaviour of XG solutions has been investigated in several studies[3, 10, 12-13]. At increased ionic strength the ordered structure of XG predominates and this impacts the viscosity of the XG gel[12]. Also, depending on the initial concentration of XG, increasing ionic strength can either increase or decrease the overall hydrogel viscosity. Wyatt et al. (2011) shows that the critical xanthan concentration at which the addition of salt neither increases nor decreases viscosity is approximately 0.2% at zero shear rate viscosity in 50mM of Sodium Chloride. At XG concentrations greater than 0.2% the viscosity increases as salt content rises[14]. Whereas, when XG concentration is below the critical concentration, the solution viscosity decreases with increasing salt content. Therefore, the critical XG concentration will vary depending on the salt concentration and type of salt compound. In a similar way to the ionic strength of the medium, temperature also controls the equilibrium between ordered and disordered chains of XG in aqueous solution[13]. At high temperature a disordered structure of XG predominates, whereas, at lower temperate a single double helix conformation is assumed. This is of particular importance because the conformational state of XG impacts the rheological properties of the polymer [13].

This work will incorporate different inorganic calcium salts; Calcium Chloride ($CaCl_2.2H_2O$), Calcium Sulfate ($CaSO_4.2H_2O$) and Dibasic Calcium Phosphate ($CaHPO_4.2H_2O$) into XG based matrix tablets containing a model hydrophilic drug, Sodium p-aminosalicylate. The primary objectives for this work are to investigate the effect of calcium salts on the erosion and swelling properties as well as dissolution profiles of xanthan matrix tablets. A comparison of the influence of calcium salts on the viscosity of XG hydrogels is also explored.

Materials and Methods

Materials

Xanthan gum was supplied by A+E Connock (Perfumery & cosmetics) LTD. (Hampshire, England). Sodium p-aminosalicylate as dihydrate salt was provided by Sigma-Aldrich chemical company, Inc, (Milwaukke, USA). Avicel PH-101 NF was supplied by FMC Biopolymer (Philadelphia, USA). Magnesium stearate Eur. Ph was provided by Medex UK (Northampton, UK). Calcium Sulfate dihydrate Ph. Eur NF was supplied by JRS Pharmaceuticals (Rosenberg, Germany). Calcium Chloride dihydrate was provided by Fisher scientific UK Ltd. (Leicestershire, UK). Dibasic Calcium Phosphate dihydrate USP/BP was supplied by Penwest Phamacuticals LTD. (Surrey, UK). The basic properties of the calcium salts are provided in Table 1.

Preparation of matrix tablets

Three xanthan gum based tablet formulations were prepared by the direct compression method (Table 2). To produce tablet with a semi-automatic mode, excipients such as magnesium stearate and microcrystalline cellulose were added. For each formulation, 100g were thoroughly mixed for 5 minutes at 30 rpm using a tumbler mixer (Model: Glen Creston LTD, Stanmore UK). Subsequently, the powder mix was manually fed and automatically compressed using a single punch (10 mm flat faced punch) tableting machine (Model: Manesty machines LTD, Liverpool England, type: F3) to attain a target tablet weight of 390mg.

Calibration plot for Sodium p-aminosalicylate

A stock solution (1mgml^{-1}) was prepared by dissolving appropriate quantity of Sodium p-aminosalicylate then made to the required volume with distilled water. A series of calibration standards ranging between 0.005mgml^{-1} and 0.03mgml^{-1} then prepared and triplet samples of the standard solutions were analyzed using a UV spectrophotometer (Model: M501, Spectronic Camspec Ltd, Leeds, England) at λ_{max} of 300nm[15]. The mean

absorbance value for each standard solution was then plotted against the corresponding concentration and the calibration equation determined.

Characterization of physical tablet properties

a. Uniformity of mass

Randomly selected tablets (n=20) from each formulation were individually weighed on an electronic balance and the average mass determined. The BP states '*not more than 2 of the individual masses deviate from the average mass by more than 5% and none deviates by more than 10%'* [16].

b. Uniformity of drug content

Randomly selected matrix tablets (n=5) from each formulation were individually weighed then crushed using a pestle and mortar. The resulting powder was dissolved in appropriate quantity of distilled water. To ensure full dissolution of the drug in the powder mix the samples were sonicated for 30 minutes and the solution was diluted to a final concentration of 0.02mgml^{-1}. The samples were measured at λmax of 300nm using a UV spectrophotometer (Model: M501, Spectronic Camspec Ltd, Leeds, England). Subsequently the average drug content was calculated using the calibration equation for Sodium p-aminosalycilate. The BP states *'The preparation complies with the test if each individual content is between 85 percent and 115 percent of the average content. The preparation fails to comply with the test if more than one individual content is outside these limits or if one individual content is outside the limits of 75 percent to 125 percent of the average content'* [16].

c. Tablet tensile strength and porosity

The diameter and thickness of randomly selected tablets (n=10) were measured using a vernier caliper and the corresponding crushing load was recorded using a tablet hardness tester (Model: Schleuniger & Co, Switzerland, model: 2E). Subsequently, the individual tablet tensile strength was calculated using the equation (1).

$$\sigma = \frac{2F}{\pi DT} \quad \text{..... (1)}$$

where σ, is tensile strength (Pa); F, is force (N); D, is diameter (m) and T, is thickness (m)

The densities of the tablet excipients were determined in a triplicate using a helium multipycnometer (Model: MVP-6DC, Quantachrome instruments, Boynton Beach, USA). Subsequently tablet porosity can be predicted by Equation 2.

$$e = \left[1 - \left(\frac{P_a}{P_t}\right)\right] * 100 \text{ ..... (2)}$$

Where e, is tablet porosity (%); P_a, is the apparent density of (gcm^{-3}) and P_t, is the density of powder (gcm^{-3})

Swelling and erosion studies

The swelling and erosion experiment was conducted using a fully calibrated dissolution apparatus (Model: DT6, Copley Scientific LTD, Nottingham, England) and the BP paddle method, with a paddle rotating rate of 50rpm in 1000ml of distilled water (37^{o}C ± 5 ^{O}C). For the test three tablets from each formulation were weighed and placed into the dissolution medium. Subsequently, at specified time intervals (0.5, 2, 4 and 6 hours) the tablets were carefully withdrawn using a spatula and the excess medium removed using tissue paper. The weight of the hydrated tablet was recorded and the corresponding swelling index was calculated (Equation 3) [10]. The tablets were then placed in a drying cabinet (Model: LEEC, Nottingham, England) at 70^{o}C to remove the moisture, and to reach constant mass before being reweighed and the percentage erosion determined (Equation 4) [10].

$$Swelling\ index\ (\%) = \frac{m_t - m_r}{m_r} * 100 \quad \text{..... (3)}$$

Where: m_t, is the mass of the hydrated tablets after the determined time of swelling (g) and m_r, is the mass of the swollen tablet after it has been dried in the oven (g)

$$Erosion\ index\ (\%) = \frac{m_0 - m_r}{m_0} * 100 \quad \text{..... (4)}$$

Where: m_0, is the mass of the dry tablet before swelling (g)

'In vitro' drug release profile

The dissolution test was carried out using the same conditions as described in the swelling and erosion experiment. Three tablets from each formulation were individually weighed before placing them into the dissolution medium at 37^{o}C ± 0.5^{o}C. Distilled water was used as the dissolution medium. During the dissolution test, a sample (10ml) was periodically withdrawn and replaced with equal volume of distilled water. The extracted sample was analyzed spectrophotometrically (Model: M501, Spectronic Camspec Ltd, Leeds, England) at 300nm, and the concentration of drug in the sample was derived from the calibration curve. The *in vitro* drug release data was reanalyzed using zero order kinetics, first order kinetics, Higuchi, Hixson-Crowell and Korsmeyer Peppas mathematical models. For zero order kinetics the cumulative fraction released is a function of time[17]. First order kinetics describes a system, which is dependent on the concentration of the dissolved substance[18]; for this model natural logarithm of unreleased fraction of drug is plotted against time. The Higuchi model describes a diffusional based drug release from matrix systems and relates drug concentration to the square root of time[18]. For systems in which the surface area and diameter of the particles or tablets change with time the Hixson-Crowell model can be utilised[18], for this model data is plotted as cube root of unreleased fraction versus time. The Korsmeyer-Peppas model describes drug release from a polymeric system where complex release mechanisms involved, for this model fraction release is plotted against time and to determine the mechanism of drug release data up to 60% of drug release was fitted to equation 5[17].

$$\frac{M_t}{M_\infty} = kt^n \quad \text{..... (5)}$$

Where: M_t, is the amount of drug released at time t; M_∞, is the amount of drug released at infinite time; k, is the rate constant; n, is the diffusion exponent used to characterise the transport mechanism.

Xanthan hydrogel for rheological investigations

To simulate the swollen outer layer of the XG matrix tablets, four gels (1%) were prepared. Three of the gels contained a calcium salt (Chloride, Sulfate or Phosphate, at a ratio of 1:5 of

calcium salt: XG that is equivalent to the tablet formulation, Table 2) and the fourth gel contained no salt. The hydrogels were prepared by adding the XG and dihydrate salt to distilled water and the samples were then mixed using a homogeniser (Model: Silverson, Machines Ltd, Waterside, Chesham, UK) for 15 minutes. The gels were stored at room temperature to allow for complete hydration before used. After equilibrating the samples at 37^{o}C and the flow properties of the gel preparations were measured using a digital viscometer and spindle number 64 (Model: LVDV-IP, Brookfield Engineering Labs, Massachusetts, USA). The shear rate ranged from 4.18s^{-1} to 25.08s^{-1} and the spindle speed ranged from 20 rpm to 120 rpm. The apparent viscosity of the sample was plotted against shear rate and the flow properties were then described using the power law equation (Equation 6).

$$\eta = k(\dot{y})^{(n-1)} \quad \text{..... (6)}$$

where η, is the viscosity (Pa.s); k, is the consistency index (Pa.s); $\dot{y}$, is the shear rate (s^{-1}), n; is the flow behaviour (power law) index.

Scanning electron microscope imaging

The morphological differences between the dry matrices and the swollen then dried matrices (4hrs) were analyzed using a scanning electron microscope (Model: S3000N, Hitachi High Technologies, Wokingham Berkshire, UK). The samples were prepared by cutting the tablets in half, mounting them onto a metal stages and coating the samples in gold-palladium using a coating unit (Model: SC760, Quorum Technology, Sussex, England).

Statistical analysis

Statistical analysis was performed using SPPS software (version 20.0, SPSS Inc. Chicago, USA). Data was determined using one-way ANOVA followed by a *post hoc* test. A p-value of <0.05 was considered as significant.

Results and discussions

The results show that all formulations comply with the BP uniformity of mass and uniformity of content requirements (Table 3). The tensile strength readings of the formulations are relatively low while the 'zero pressure' porosities of the three batches are similar[19].

Dynamic swelling and erosion studies

Figure 1 shows the swelling index of F1 (677%), F2 (868%) and F3 (745%) following six hours in contact with distilled water. F1 (containing soluble chloride salt) shows the lowest swelling capacity, which is consistent with radial and axial swelling results (data not presented). Comparatively, F3 has a lower swelling index than F2, which can be attributed to the hydrophobicity of the matrix tablet. The extent of matrix erosion was deduced from tablet's weight loss once it had been dried in the oven. The process of matrix erosion arises when the outer gel layer becomes fully hydrated and the polymer chains preserving the layer relax and disentangle. As a result, the surface of the matrix tablet wears away due to loss of structural integrity[20]. Figure 2 displays the erosion profiles of the three formulations. After six hours in contact with the medium, F1 showed the highest erosion index (37%) when compared to F2 and F3. Erosion in the first thirty minutes of the experiment was found to be statistically faster for F1 ($p < 0.05$), which was then followed by a reduced erosion rate in the later periods. Hypothetically, the initial rapid erosion of F1 occurs because the chloride salt readily dissociates when the water molecules influx into the tablet, due to its hydrophilic nature. Consequently, the calcium ions leach into the solution and the tablets gel layer is easily erodible, since the calcium ions are unable to interact with the XG polymer chains. As time progresses the gel layer proliferates until it is fully formed and can encapsulate the calcium ions. Subsequently, the gel is strengthened through interactions with the calcium ions and thus further erosion is reduced. A delay in gel layer formation was also reported[21]. Comparatively, the Sulfate and Phosphate salts present in F2 and F3 respectfully are less hydrophilic and as a result undergo less initial erosion, allowing for the fully hydrated gel layer to develop. The rate of erosion can be deduced from the gradient of the curve (Figure 2); the data indicates that F2 (3.1 hr^{-1}) has a higher rate of erosion than F3

and F1, which have similar rates (2.9 hr^{-1}). This trend can be explained by the viscosity of the gel layer as described later.

Rheological characterisation of XG hydrogels

The rheology of XG solutions in the presence of mono- and divalent ions is dependent on xanthan concentration. The effects of salt concentration on flow behaviour can be attributed to the molecular conformation states of XG. Xanthan gum is known to exist in two different conformational states: ordered and disordered. In salt free solution the disordered conformation predominates, in which the pyruvate unit on the side chains are ionised, highly solvated and repel mutual charges and thus project away from the backbone and the molecule occupies a larger hydrodynamic volume. Strong Coulombic repulsions between like charges along the polyelectrolyte backbone also stretch and elongate the individual chains[22]. It is believed that the pyruvate unit forms the principle electrostatic interaction towards the metal due to their negative charges and positioning at the outer ends of the side chains, which confers only minor steric hindrance. Comparatively, the uncharged acetyl groups and the glucose units play a less significant role in complex formation[12]. The addition of small counter ions like Ca^{2+} will reduce the charge of xanthan chain[10]. Thus, at low polymer content the viscosity of XG solutions will decline upon the addition of salts, which increases ionic strength[12, 22]. Bergmann et al (2008) observed a viscosity decrease in a 0.15% XG solution when ion content was increased[12]. This phenomenon occurs because in dilute solutions charge screening with calcium ions decreases the polymer's interaction with water; allowing the XG chains to assume ordered helical molecular conformations which occupy a smaller hydrodynamic volume leading to a decrease in viscosity[22]. Comparatively, at higher XG concentration, the interaction between the polymer molecules increases as salt content increases[3, 10, 22]. This effect outweighs the reduction in hydrodynamic volume of the molecules, and hence viscosity increases. It has been hypothesized that the increase in viscosity is caused by ion bridging, in which either an inter-molecular or intra-molecular crosslink is formed; subsequently increased interaction between the polymer chains induces a more rigid network[22]. A threshold in salt content

exists where changes in viscosity of the XG solution is limited, i.e. beyond this point, further addition of salts will have little influence on the rheological properties of the gel[3, 14, 23-24].

Like Talukdar and Kinget (1995) a 1% gel was chosen for the rheological experiment. The viscosity measurements of XG hydrogels containing the respective salts were measured at 37°C[3]. Figure 3 represents the apparent viscosity of the 1% XG solutions at different shear rates. The rheological behaviour of all the samples is characteristic of pseudoplastic or shear thinning fluids; that is to say, the apparent viscosity progressively decreases as shear rate increases[24]. This observation is in accordance with published data, which explored the rheological properties of XG[13, 22-23, 25]. XG solutions exhibit this behaviour because the molecules in solution can self-associate and form non-permanent aggregates through hydrogen bonding and polymer entanglement[13, 24]. This highly ordered network results in high viscosity at low shear rates. When the shear rate is increased the aggregates are disrupted and hence viscosity decreases[13].

The power model output values for the consistency index (k), the flow behaviour index (n) and the coefficient of determination (R^2) are listed in Table 4. For a Newtonian fluid the power law index is equal to 1; for a shear-thinning fluid it is between 0 and 1; and for a shear thickening fluid it is greater than 1[26]. All samples exhibit a good fit to the power law equation and as all n values are less than 1, the samples are shear thinning fluids. The concentration of hydrogel used in this experiment was 1% which would be considered a high XG content; therefore in accordance with previously published works the viscosity of the hydrogel should increase as calcium ion content rises[3, 10, 22]. The results in Table 4 are to some extent in agreement with these literatures, in that F1 has a higher calcium ion content (Chloride salt contributes to 0.340 mmol of Ca^{2+} per tablet) compared to F2 (Sulfate salt contributes to 0.291mmol of Ca^{2+} per tablet) and exhibits higher viscosity, due to increased interactions between XG and calcium ions. The data also illustrates that the presence of salt in the XG solution increases viscosity. This is indicated by the lower k value for the 1% XG hydrogel in which salt was absent, compared with the hydrogels in which salt was present. The results for F3 are unique and are not in accordance with hypothesis that increasing calcium concentration increases the viscosity. Dibasic Calcium Phosphate is practically insoluble in water (Table 1) because of the strong ionic interaction between the phosphate and calcium ions. The formulation F3 (phosphate salt contributed to 0.290mmol of Ca^{2+} per

tablet) has the lowest amount of calcium ions in solution, which are able to interact with the XG, yet it has the highest viscosity. Consequently, it can be postulated that another mechanism is behind the unique rheological behaviour of this hydrogel. Dario et al. (2010) evaluated the effect of Calcium Phosphate on the flow behaviour of 0.4% XG solutions[13]. The authors reported that the addition of insoluble calcium salts ($CaCO_3$ and $Ca_3(PO_4)_2$) increased the k values of XG hydrogels; which supports the rheological properties of F3. In current study, based on the solubility data of the calcium salt (Table 1), the amount of dissociated Ca^{2+} ions from the phosphate salt was in excess quantity relative to the pyruvate units of the 1% gel preparation. Hence the presence of solid salt particles in solution may be enough to increase the k value. It has also been hypothesized that xanthan chains in the solution could bind to the surface of the insoluble calcium particles, building a complex network, which increases viscosity[13].

'In vitro' drug release studies

The release profiles of Sodium p-aminosalicylate from the formulations is displayed in Figure 4. The data indicates that F2 released the highest fraction of drug followed by F1 and F3. Statistical analysis showed difference in terms of the overall fraction released for the samples after 6 hours in contact with the dissolution medium ($p < 0.05$). *Post hoc* test using Games-Howell analysis demonstrated that the overall fraction released for F3 was also significantly lower than F2. Drug release from XG matrices begins after the medium comes in contact with the tablet and drug at the surface of the unit is dissolved. Figure 4 shows that for the first hour of the experiment, the hydrophilicity of the salt governs the release rate; with F1 having the highest fraction of released drug followed by F2 and F3. This trend suggests that the presence of a more water soluble salt in the formulation will induce a faster rate of drug release during the initial phase, through salt dissociation into the medium. Furthermore, there is a point where the drug release profiles of F1 and F2 intercept; at this point the calcium ions within F1 have had sufficient time to interact with the XG molecules and strengthen the gel layer. Hence, erosion of the matrix is reduced and percentage drug release is lower. Overall, F2 generates the most rapid drug release because the formulation has the least viscous gel layer (Table 4) and highest swelling capacity (Figure

1), which makes the matrix more susceptible to erosion[3]. Comparatively, F1 has the lowest swelling capacity as is highlighted in the swelling studies (Figure 1), thus intuitively F1 should have the greatest release rate owing to a shorter diffusion pathway. However, experimentally this is not the case because the gel layer is more viscous than that of F2 resulting in lower drug diffusivity. Conversely, the presence of the hydrophobic phosphate salt in F3 produces a formulation with a highly viscous gel layer coupled with modest swelling capacity. Accordingly, the core of the tablet remains dry after six hours in contact with the medium, which accounts for the lowest overall drug release. Overall, in relation to drug release the rheology results show that the apparent viscosity of the gel layer governs the erosion rate of the tablet and hence determines drug release kinetics. F2 produces the most rapid drug release because it has the least viscous gel layer, which can erode more readily. F1 presents a moderate viscosity and therefore intermediate drug release property whereas F3 has the lowest rate of drug release underpinned by the most viscous outer gel layer as described above.

The drug release kinetics of the matrices is strongly associated with the structure of the polymer network in the gel layer and the arrangement of water molecules within it[10]. In an attempt to determine the most suitable mathematical model the *in vitro* data was analyzed using zero order kinetics, first order kinetics, Higuchi, Hixson-Crowell and Korsmeyer Peppas kinetic theories. From the kinetic modelling results presented in Table 5, the correlation coefficient values indicate that all the formulations show good conformity to the Korsmeyer Peppas model, nonetheless F2 and F3 also fit to the first order and Higuchi square root kinetic models, respectively. The Higuchi mathematical model is commonly used to describe drug release from modified release dosage systems in which drug release is primarily diffusional based and matrix swelling and dissolution are negligible[18]. Therefore, the Higuchi model is not most appropriate representation of drug release from the XG formulations, since drug release from these matrices is considered multifactorial and involves; liquid penetration, polymer swelling, drug diffusion and matrix erosion. On the other hand, first order kinetic model is partially appropriate as it was described for porous matrix where drug release is proportional to the amount of the drug remaining in its interior and was independent from swelling and erosion as observed for XG system[18].

The *in vitro* drug release data was analyzed using the simple power law developed by Korsmeyer et al. (1983), which best describes the drug release data from the swollen tablet matrices[27-28]. Based on the value of the diffusion exponent (n), drug transport in cylinder geometry is classified as either Fickian drug release ($n = 0.45$), non-Fickian also known as anomalous transport ($0.45 < n < 0.89$), or case II transport ($n = 0.89$)[29]. Fickian diffusional transport describes molecular diffusion due to a chemical potential gradient. Case II transport is a drug release mechanism associated with stresses and state of transition in the hydrophilic glossy polymers, which swell in water or physiological fluids. Anomalous transport occurs due to a coupling of Fickian diffusion and polymer relaxation[10]. The drug release mechanism from the XG matrices was found to be non-Fickian anomalous transport for all formulations based the n-value obtained from the Korsmeyer-Peppas model (Table 5). This signifies that diffusion, polymer erosion and relaxation are the predominant mechanisms of drug release; this finding has also been reported in other literature sources [4,9,10-11,30]. According to Baumgartner et al, (2008) the higher the ionic strength the more pronounced the contribution of Fickian diffusion[10]; thus F1 obtained the lowest n value because the formulation had the greatest calcium ion content.

Scanning electron microscope (SEM) images of the matrix tablets at various time points were taken in order to visually explain the drug release properties of the three formulations. The micrographs of the dry matrix tablets indicates F1 has large airspaces between the particles indicating increased porosity visually, whereas F2 and F3 appear to have a more densely packed arrangement of particles (Figure 5). Interestingly, after four hours in contact with the medium the internal spaces of the three tablets have very different structural arrangements. This is partly attributed to the polymer relaxation and formation of gel layer upon absorption of dissolution medium[31]. F1 appears more 'spindly' which is likely due to the interaction between the XG polymer chains and calcium ions. Comparatively, F2 has a more hollow appearance owing to the formulation elevated degree in swelling; consequently at the four hours' time interval the highest fraction of released drug was observed. Whereas F3, had the lowest drug release, which was supported by the SEM image in which the tablet core appeared intact. Additionally, the images of the diffusion layer highlight the degree of erosion the tablets endured. Remarkably, the diffusion layer of F3 appears structurally sound and visually highlights the hydrophobicity of the preparation, as

well as the effectiveness of the gel layer as a barrier to water penetration and drug molecule diffusion. Presence of bulking agent such as lactose In XG tablets as well as addition of soluble calcium ions to the dissolution medium for sodium alginate/XG blend tablets have shown to alter the drug release profiles of propranolol HCl [31,32]. This is owned to the hydrophilic property of lactose, and to influence of calcium ions on the gel integrity, respectively. From the SEM, adding calcium salts of different solubility profiles is also responsible for the difference in appearances of the tablets upon immersion in the dissolution medium.

Conclusions

Overall, the experiments have shown that incorporating $CaCl_2.2H_2O$, $CaSO_4.2H_2O$ or $CaHPO_4.2H_2O$ into XG matrix tablets can modify the drug release behaviour of the formulation. It was hypothesized that the more hydrophilic and higher calcium salt content, the quicker the expected drug release. This is because the salt can readily dissociate into Ca^{2+} ions that can then interact with XG at a molecular level, and subsequently shorten the length of the diffusion pathway. Nonetheless, the sulfate salt had the fastest overall rate of drug release and the phosphate salt had the lowest. This phenomenon has been attributed partly to the viscosity and structure of the gel layer; with $CaSO_4.2H_2O$ having the least viscous layer followed by $CaCl_2.2H_2O$ and $CaHPO_4.2H_2O$ while strong surface structure was observed in those tablets containing $CaHPO_4.2H_2O$. It can be pre-assumed that the water solubility of the calcium salt plays a role in governing drug release from XG matrices; since this physical property determines the properties of the gel layer. Previous works have incorporated other matrix controlling agents such as chitosan, alginate to modify drug release profiles in addition to xanthan gum. This study shows that by adding readily available inorganic calcium salts, matrix properties can be manipulated. In summary, it can be concluded that the type of calcium compounds incorporates into XG matrices will impact the drug release properties of the formulation.

Declaration of interest

All the authors pf this manuscript report no declaration of conflict of interest.

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Table 1 Properties of inorganic calcium salts

Calcium salt	Molecular mass	Water solubility (gL^{-1})
$CaCl_2.2H_2O$	147.00*	950*
$CaSO_4.2H_2O$	172.17*	2.1*
$CaHPO_4.2H_2O$	172.09*	0.3**

*Data taken from the handbook of pharmaceutical excipients 6th edition [33-35]

** Data taken from Allwood and Kearney (1998) [36]

Table 2 Composition of tablet formulations

Ingredient/ID	Tablet composition (mg)		
	F 1	F 2	F3
Xanthan gum	250	250	250
Sodium p-aminosalicylate	50	50	50
Calcium Chloride dihydrate	50	-	-
Calcium Sulfate dihydrate	-	50	-
Dibasic Calcium Phosphate dehydrate	-	-	50
Avicel PH101	30	30	30
Magnesium stearate	4.5	4.5	4.5

Table 3 Physical properties of tablets. Data expressed as Mean ± SD.

Tablet Property	Formulation ID		
	F1	F2	F3
Mass (mg)	390 ± 0.005	386 ± 0.011	390 ± 0.002
Drug content (mg)	50.752 ± 0.576	50.952 ± 0.193	50.910 ± 0.244
Tensile strength (MPa)	0.539 ± 0.029	0.768 ± 0.026	0.876 ± 0.035
Porosity (%)	33.47 ± 1.09	34.85 ± 1.18	34.96 ± 0.27

Table 4 Rheological parameters determined using the power law equation for XG solutions prepared using different salts (based on downward curve)

Equation component	Formulation ID			
	F1	F2	F3	Control (salt absent)
K	12.008	11.757	13.869	10.515
n	0.163	0.158	0.140	0.150
R^2	0.9998	0.9998	0.9996	0.9999

Table 5 Parameters derived from kinetic models for drug release from XG matrices

Kinetic model/ID	Correlation Coefficient (R) and rate of release (k)		
	F1	F2	F3
Zero order	0.9785; 0.090 hr^{-1}	0.9721; 0.108 hr-1	0.9852; 0.088 hr^{-1}
First order*	0.9970; -0.18 hr^{-1}	0.9978; -0.25 hr^{-1}	0.9986; -0.17 hr^{-1}
Higuchi	0.9980; 0.29 $hr^{-1/2}$	0.9955; 0.35 $hr^{-1/2}$	0.9996; 0.28 $hr^{-1/2}$
Hixson-Crowell**	0.9926, -0.048 hr^{-1}	0.9930, -0.062 hr^{-1}	0.9960, -0.044 hr^{-1}
Korsmeyer Peppas***	0.9998	0.9977	0.9995
n***	0.51	0.62	0.53
k***	0.30 hr^{-n}	0.31 hr^{-n}	0.27 hr^{-n}

* based on ln unreleased fraction vs. time

**based on $(\text{unreleased fraction})^{1/3}$ vs. time

*** where n = diffusion exponent and k = rate constant

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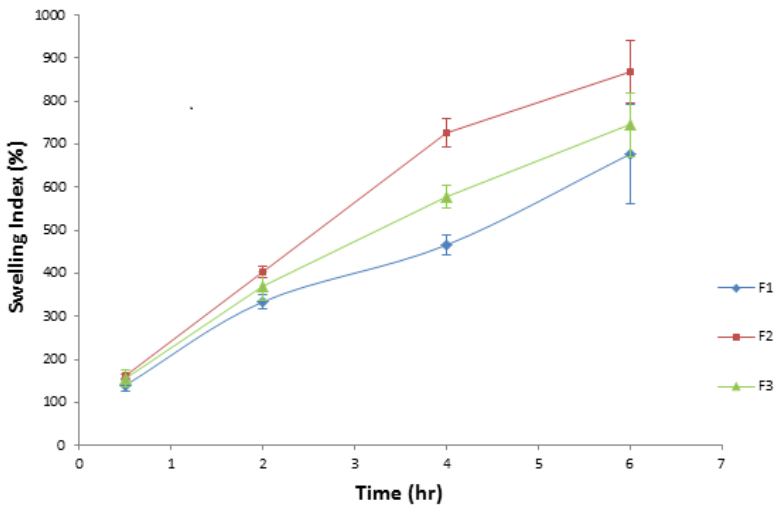


Figure 1 Influence of calcium salts on the swelling profiles of XG matrix tablets in distilled water

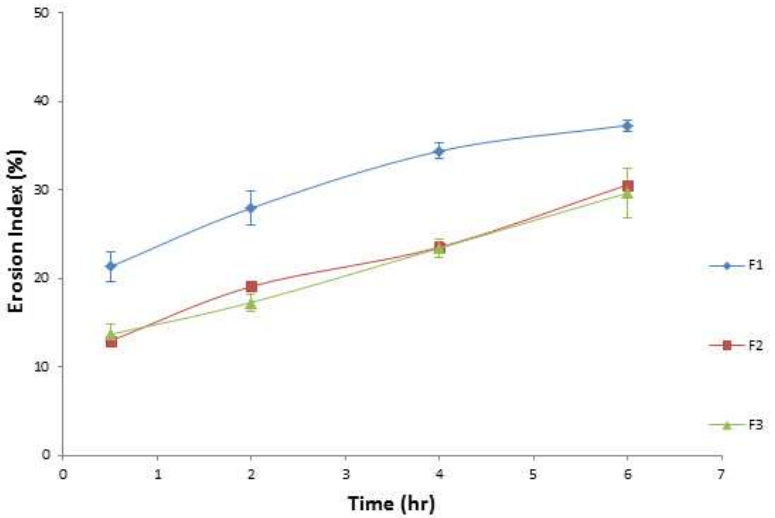


Figure 2 Influence of calcium salts on the erosion profiles of xanthan gum matrix tablets in distilled water

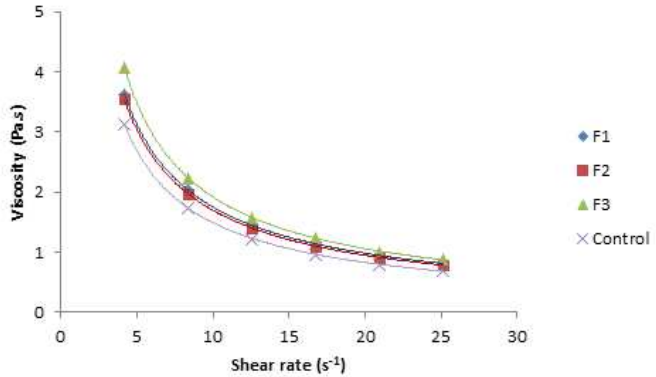


Figure 3 The apparent viscosity of 1% XG hydrogels as a function of shear rate at 37°C

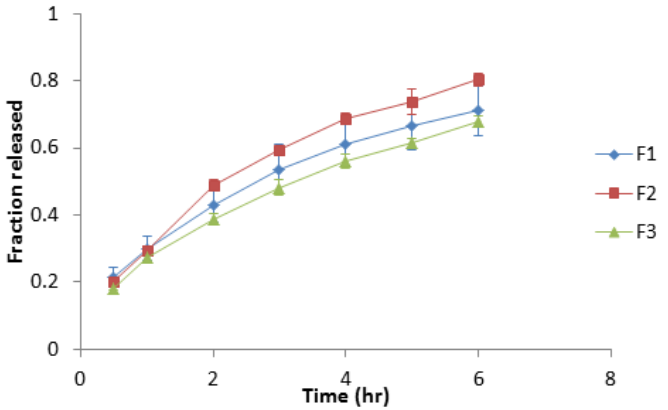


Figure 4 Drug release profiles of Sodium p-aminosalicylate from the XG matrices

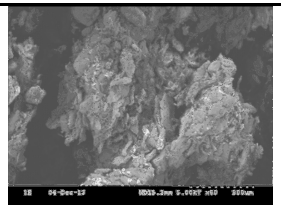
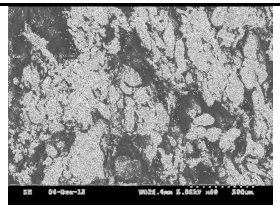
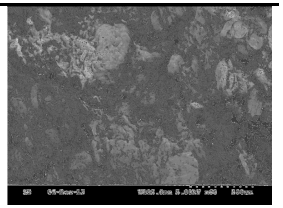
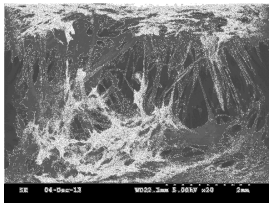
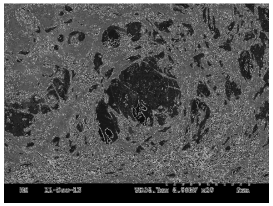
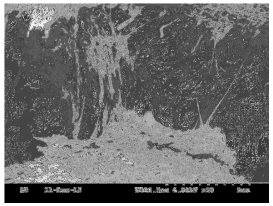
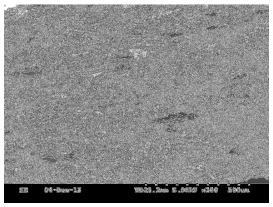
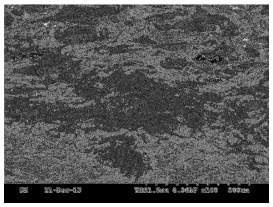
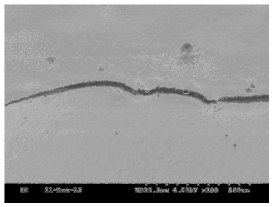
	Formulation		
	F1	F2	F3
Dry matrix tablet			
4 hours			
4 hours-diffusion layer			

Figure 5 Micrographs of the dry matrices and the swollen then dried matrices removed at four hours