Starch-free grewia gum matrices: Compaction, swelling, erosion and drug release behaviour

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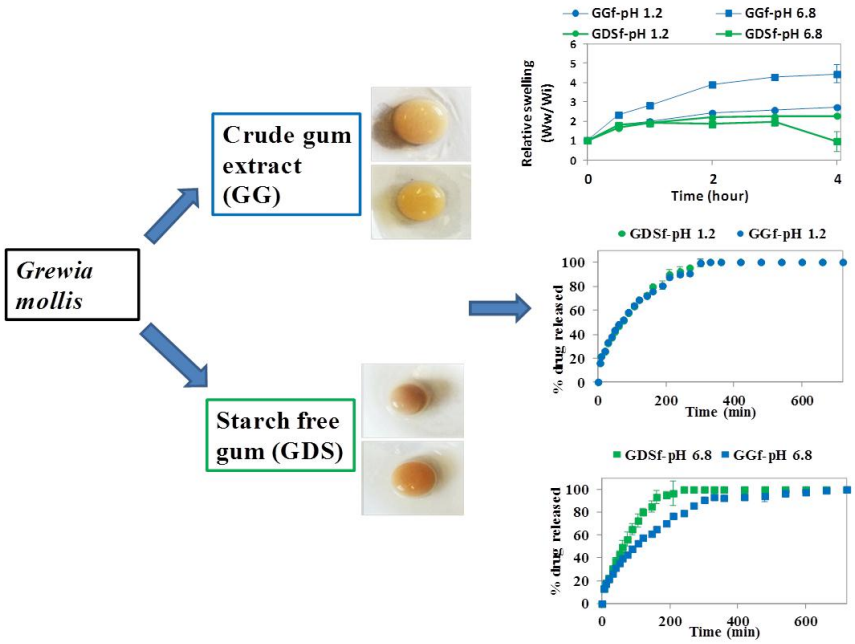
Abstract

Polysaccharides are suitable for application as hydrophilic matrices because of their ability to hydrate and swell upon contact with fluids, forming a gel layer which controls drug release. When extracted from plants, polysaccharides often contain significant quantities of starch that impacts upon their functional properties. This study aimed to evaluate differences in swelling, erosion and drug release from matrix tablets prepared from grewia gum (GG) and starch-free grewia gum (GDS) extracted from the stems of *Grewia mollis*. HPMC was used as a control polymer with theophylline as a model drug. Swelling, erosion, and *in-vitro* release were performed in deionized water, pH1.2 and pH6.8 media. The Vergnaud and Krosmeyer-Peppas model were used for swelling and drug release kinetics, respectively. However, linear regression technique was used to determine the erosion rate. GDS compacts were significantly harder than the native GG and HPMC compacts. GDS matrices exhibited the fastest erosion and drug release in deionised water and phosphate buffer compared with the GG and HPMC. At pH1.2, GDS exhibited greater swelling than erosion, and drug release was similar to GG and HPMC. This highlights the potential of GDS as a matrix for controlled release similar to HPMC and GG at pH1.2 but with a more rapid release at pH6.8. GDS may have wider application in reinforcing compacts with relatively low mechanical strength.

K***eywords*****:** HPMC K4M, grewia gum, starch-free grewia gum, matrix tablets, theophylline

Abbreviations: HPMC, Hydroxypropyl methylcellulose; GG, native grewia gum; GDS, starch-free grewia gum; GGp, native grewia gum polymer; GDSp, de-starched grewia gum polymer; HPMCp, hydroxypropyl methylcellulose polymer; HPMCf, hydroxypropyl methylcellulose formulation; GGf, native grewia gum formulation; GDSf, de-starched grewia gum formulation; HCl, hydrochloric acid; MDT, mean dissolution time; MDR, mean dissolution rate; DE, dissolution efficiency; DSC, differential scanning calorimetry; USP, United States Pharmacopeia

Graphical Abstract



Erosion, swelling and drug release from native and starch-free *Grewia mollis* matrices

1. Introduction

In the developing world, the pharmaceutical sector depends heavily on petrochemicals due to majority of excipients being imported. Consequently, this accounts for high prices that are beyond the reach of the majority of the local populations, despite the fact that the countries of the developing world are often rich in renewable sources of raw materials suitable for use in the industry. Such materials which are abundant in nature and, can also be cultivated, remain largely undeveloped. Plant polysaccharides are one particular resource that could be used as alternative excipients and have come under increasing research focus in the design of dosage forms for oral controlled release administration (Naggar et al., 1992; Bonferoni et al., 1993; Kristmundsdo´ ttir et al., 1995; Sujja-areevath et al., 1996; Talukdar et al., 1996; Khullar et al., 1998; Vervoort et al., 1998; Munday and Cox, 2000; Mughal et al., 2011; Nep 2015). These materials are hydrophilic in nature and when in contact with water they hydrate and swell. This property has been utilized in the formulation of dosage forms (Nakano and Ogata, 1984) where the powdered drug is embedded within the matrix of hydrophilic polymeric materials and compressed to produce matrix tablets. The release of drug from such hydrophilic matrices is described as a complex interaction between swelling, diffusion and erosion (Harland et al., 1988; Peppas and Sahlin, 1989; Colombo et al., 1990; Lee and Kim, 1991; Colombo et al., 1992; Colombo et al., 1995; Reynolds et al., 1998; Munday and Cox, 2000; Ghori et al., 2014a).

Swelling is the result of the gradual imbibing of water to form an increasingly hydrated gel layer which is the diffusional path length across which the pharmaceutical active is transported *via* mechanisms of diffusion and gel layer dissolution (Wan et al., 1991; Panomsuket al., 1996). For polysaccharide matrices, this process has been shown to follow square root of time kinetics (Munday and Cox, 2000; Kavanagh and Corrigan, 2004). However, at the interface between the gel layer and the surrounding medium, other

mechanisms, in addition to diffusion, also come into play during drug release from matrices. The polymer chains gradually disentangle from the interface by erosion, thus enhancing drug release. Erosion of the polymer has also been shown to follow cube root of time kinetics (Munday and Cox, 2000; Kavanagh and Corrigan, 2004).

Hydroxypropyl methylcellulose (HPMC) is the most widely used of the cellulosic controlled release agents, providing outstanding controlled release performance. It is a hydrophilic cellulose derivative that is non-ionic, with versatile matrix forming ability and is used to control the release of soluble and insoluble drugs. The different viscosity grades available afford the choice of material forming more or less viscous gels. Furthermore, the non-ionic nature of the material enables pH –independent release of drug from tablet matrices (Merchant et al., 2006; Sahoo et al., 2008; Mughal et al., 2011).

Grewia mollis is a shrub which grows wild or cultivated in the middle belt region of Nigeria (and other parts of sub-saharan Africa) where the inner bark from the stems of the shrub is pulverised and used as a thickener in various food formulations. The native gum extract has previously been identified to contain polysaccharides (Okafor, Chukwu & Udeala, 2001; Nep and Conway, 2011a) and has been evaluated as a pharmaceutical excipient in oral formulations, as a binder or sustained release matrix (Nep & Conway 2011b), as bioadhesive (Nep & Okafor 2006; Nep & Conway 2011c) or as a suspending agent (Nep & Conway 2011d).

Various extraction methods have been explored and shown to impact the functional properties of grewia gum extracts (Ogaji, 2011; Akdowa et al 2014). Furthermore, it has been reported that the native grewia gum (GG) contains a significant quantity of starch and the enzymatic removal results in a starch free material which differs from the native polysaccharide in the relative proportion of monosaccharides and physicochemical properties (Nep et al., 2015). Consequently, it is anticipated that the starch-free grewia polysaccharide

(GDS) may exhibit different functional properties as compared with the native polysaccharide, thus providing the potential to diversify the applications using extracts produced using different methods.

In the present study, matrix tablets of the starch-free grewia gum were compared with similar formulations of the native grewia gum to show the effect of starch digestion on the functional application in matrix tablet formulations.

2. Materials and Methods

2.1 Materials

Methocel (HPMC K4M) was a kind gift from Colorcon (UK) and was used as supplied from manufacturer. Lactose monohydrate (FlowLac® 100) was a kind gift from Meggle (Germany). Magnesium stearate was used as procured from Merck (Germany). Anhydrous theophylline (TCI Chemicals, Europe) was used as the model drug. Dissolution media were prepared according to the USP 2003 method using the following materials: potassium chloride (Acros Organics, UK) and hydrochloric acid (Fisher Scientific, UK) for pH 1.2, and potassium phosphate monobasic-white crystals (Fisher BioReagents, UK) and sodium hydroxide (Fisher Scientific, UK) for pH 6.8 media. Native grewia polysaccharide and starch-free grewia polysaccharide were extracted in our laboratory as previously reported (Nep et al., 2015).

2.2 Extraction of native grewia polysaccharide (GG) and starch free grewia polysaccharide (GDS)

The method of Nep et al., (2015) was adopted without modification. Briefly, the inner stem bark of *Grewia mollis* was dried and shredded. The material was then macerated in 0.1% sodium metabisulphite for 24 hours. The swollen gum was separated from the residue

by filtration through a muslin bag and the filtrate was precipitated from solution using absolute ethanol. Further purification was achieved by re-dispersion in water and final precipitation in absolute ethanol to give the gum fraction code named GGp which was then oven dried at 50 °C for 24 hours. The dried GGp was milled to a particle size of 200 µm undersize using a centrifugal mill (ZM 100, Retsch Germany) set at a rotation speed of 10,000 rpm equipped with a 200 µm mesh filter. The milled powders were then collected and stored in sealed plastic containers before use in tablet formulation. To obtain the starch-free grewia polysaccharide (GDSp), GGp was digested using 1 %w/v dispersion of GGp with Termamyl 120 L (1 %v/v) with stirring at 70 °C for 4 hours. Sample pH was adjusted to 4.5 with 2 M HCl to precipitate the enzyme and the sample was then centrifuged at 4400 rpm for 20 min. The supernatant was dialysed against deionized water for 72 hours using a cellulose membrane with molecular weight cut-off at 12500 Da. The material was then precipitated using 2 volumes of 95% ethanol followed by a solvent exchange using 1 volume of 95% propan-2-ol. The precipitate was oven dried overnight at 50 °C and subsequently, tested for starch using 1% v/v iodine in KI solution as described by Nep et al (2015). The starch-free grewia polysaccharide (GDSp) was size reduced to a particle size of 200 µm undersize and stored under the same conditions as the GGp.

Particle size was determined using the Sympatec laser diffraction particle size analyser (Clausthal-Zellerfeld, Germany) according to the methodology detailed in Asare-Addo et al., (2015). Chemical and physical characterisation of both GGp and GDSp batches used in this study are reported in Nep et al., (2015).

2.3 Tablet formulation, compression, hardness and dimensions

The pure polymers (GGp, GDSp and HPMC K4M) were compacted using a single punch tableting machine (Model MTCM-1, Globe Pharma US) at 6 different pressures (44.6, 70.0, 97.4, 125.7, 150.8, and 176.0 MPa) to determine the effect of compression force on the

hardness of the pure polymer compacts and the tablet matrices. HPMC was used as a control due to its popular use in extended release matrices as a result of its robustness, stability, regulatory acceptance and cost effectiveness (Tiwari and Rajabi-Siahboomi, 2008; Nokhodchi and Asare-Addo, 2014). In the present study HPMC K4M was chosen as it is a mid-range viscosity grade (~4000 cp) and is commonly used in matrix tablets (Ghori et al., 2014a). Tablets matrices, containing theophylline as a model drug, were formulated according to the unit formula in Table 1. Round convex tablets with a diameter of 10.0 mm and a target weight of 250 mg were prepared by blending the appropriate amounts of ingredients as shown in Table 1 for 10 min in a Turbula® (Type T2C, Switzerland) blender and tablets formed by compression at 125.7 MPa. The compressed tablets were allowed to recover for 24 h, the hardness of the tablets was determined on a hardness tester (PharmaTest, Germany) while the thickness and diameter of the matrix tablets was measured using a digital calliper (Toolzone, UK) .

2.4 Bulk, tapped density and porosity of polymers and formulation blends

The bulk and tapped densities of the pure polymers and formulation blends were determined by weighing 10 g of the material into a 100 mL measuring cylinder and, without disturbing the cylinder the volume was read to give the bulk volume of the powder. The measuring cylinder was than tapped until the volume of powder was constant. This represents the tapped volume of the polysaccharide gum powder. The bulk or tapped density was calculated as the ratio of the weight of powder to the bulk or tapped volume respectively. Porosity was determined according to equation 1.

$$Tablet\ porosity = \left[1 - \left[\frac{tablet\ weight / tablet\ volume}{true\ density\ of\ powder}\right]\right] X100 \quad (1)$$

2.5 True density of the polymers and formulation blends

The true density of the polymers and formulation blends was determined using Micromeritics Accupyc II pycnometer 100 (Micromeritics, USA). The test was carried out using a multi-run system (10 runs) with a standard deviation of 0.005%. The results are the mean and standard deviation of three determinations.

2.6 *In-vitro* release studies

An automated USP dissolution apparatus II (paddle method) was used to monitor the dissolution profiles of theophylline from the tablet matrices. The dissolution medium was 900 mL of deionized water, 0.1 N HCl (pH 1.2) or phosphate buffer (pH 6.8) equilibrated to 37 ± 0.5 °C with a paddle stirring speed of 100 rpm. Samples were withdrawn at selected time intervals from 5 min up to 720 min using a peristaltic pump and the absorbance measured using a UV spectrophotometer. The concentrations of theophylline in the samples was determined using the linear regression equation obtained from the respective UV standard calibration curve at 272 nm.

2.7 Dissolution parameters (dissolution efficiency (DE) and mean dissolution time (MDT))

The mean dissolution time (MDT), the mean time for the drug to dissolve under *in-vitro* dissolution conditions, is a model-independent method and is suitable for dosage forms having different mechanisms of drug release (Al-Hamidi et al., 2013; 2014; Mu et al., 2003; Khan, 1975). Also calculated was the dissolution efficiency (DE), which is the area under the dissolution curve up to a certain time *t*, expressed as a percentage of the area of a rectangle described by 100% dissolution in the same time *t* (Khan, 1975).

$$MDT = \frac{\sum_{j=1}^{n} t_j \, \Delta M_j}{\sum_{j=1}^{n} \Delta M_j} \quad (2)$$

Where j is the sample number, n is the number of dissolution sample times, t_j is the time at midpoint between t_j and t_{j-1} and ΔM_j is the additional amount of drug dissolved between t_j and t_{j-1}.

$$DE = \frac{\int_0^t y \times dt}{y_{100} \times t} \times 100 \quad (3)$$

Where *y* is the drug percent dissolved at time *t*

2.8 Similarity factor

Similarity between the drug release profiles was determined using similarity factor f_2 (Moore and Flanner, 1996; Polli et al., 2004; Asare-Addo et al. 2010).

$$f2 = 50\ log\left\{\left[1 + \frac{1}{n}\sum_{t=1}^{n} w_t(R_t - T_t)^2\right]^{-0.5} X\ 100\right\} \quad (4)$$

where *n* is the number of pull points for tested samples; w_t is the optional weight factor; R_t is the reference assay at time point *t*; T_t is the test assay at time point *t*.

Similarity factor was calculated using the drug release profile of HPMC K4M matrices as the reference. f_2 values ranging from 50-100 indicate similarity between the two profiles. The closer the *f2* value is to 100, the more similar or identical the release profiles. Values of *f2* less than 50 indicate dissimilarity between two dissolution profiles (Polli et al., 1997; Pillay and Fassihi, 1998).

2.9 Kinetics of drug release

The kinetics of drug release were analysed using the Korsmeyer-Peppas model Eq (5) as detailed in Siepmann & Peppas, (2001a) where, Mt/M^{∞} is the fraction of drug released at time t while K is a drug release constant incorporating the geometrical characteristics of matrix tablet, and n is diffusional exponent of drug release. For cylinders, i.e., the tablet matrices made in the present study, n values of up to 0.45 suggest Fickian diffusion, and values of above 0.89 suggest Case-II transport. A value between these two suggests anomalous transport occurring as reported in numerous studies (Siepmann and Peppas 2001b; Asare-Addo et al., 2013; Siahi-Shadbad et al., 2011; Ritger and Peppas 1987).

$$\frac{Mt}{M^{\infty}} = Kt^n \quad (5)$$

2.10 Swelling and erosion studies

Swelling and erosion were determined according to a method described by Tahara et al. (1995). A USP II dissolution apparatus (PharmaTest, Germany) was used and set to 100 rpm and equilibrated at 37 °C. The deionized water, pH 6.8, or pH 1.2 buffer were used as swelling/erosion media. The matrix tablets were supported on pins at the bottom of the dissolution vessel. Swelling/erosion media (900 mL) was measured into each of the six vessels of the bath and allowed to equilibrate for 30 min before starting the experiment. The experiment consisted of allowing the tablets to swell and/or erode in the medium at 100 rpm for 30, 60, 120, 180 or 240 min before they were removed into a pre-weighed weighing boat. The excess dissolution medium was drained and blotted from around the tablet without disrupting the tablet. The tablet and weighing boat were then weighed to establish the wet weight of the tablet. The mean weight was determined for each formulation and degree of swelling (S) was calculated using Eq. (6): (Ghori et al., 2014b)

$$S = \frac{Ws - Wi}{Wi} \times 100 \qquad (6)$$

Where *Wi* and *Ws* are initial dry and swollen weight of matrix tablet, respectively, at immersion time (t) in the swelling media. The degree of swelling was determined from the mean of three replicates and presented as degree of swelling (S, %) against time (t). Finally, the tablets were dried to a constant weight in an oven at 50 °C. The tablets were cooled to ambient temperature and then weighed until a constant weight had been achieved and this was termed as dried weight of matrix tablets. The degree of erosion (E) was calculated using Eq. (7) (Ghori et al., 2014a)

$$E = \frac{Wi - Wf}{Wi} \times 100 \qquad (7)$$

Where, *Wi* is the initial weight of the matrix tablets and *Wf* is the weight of the dried matrices at specific sampling times.

The swelling kinetics of all the matrix tablets was determined by fitting the swelling data to a mathematical swelling model described by Vergnaud (1993). This model has been used by several authors to explain the mechanism of swelling (Ghori et al., 2014c, Chaibva et al., 2010, Roy and Rohera, 2002, Ebube et al. 1997) and the generalised form of Vergnaud model is shown in Eq. (8)

$$M = Kt^n \qquad (8)$$

Where,

M = the amount of liquid transferred

t = time

K = the swelling constant.

n = exponent indicating the mechanism of water uptake.

Ebube et al. (1997) reported that a value of $n < 0.5$ is indicative of a diffusion-controlled mechanism in which the rate of diffusion is much slower than the rate of polymer hydration in a matrix tablet. However, when $n = 1$, water diffuses through the matrix at a constant velocity, with an advancing liquid front marking the limit of liquid penetration into the matrix. A value of $0.45 < n < 1$ indicates an anomalous behaviour in which diffusion of liquid and polymer hydration are of similar magnitude. Moreover, the authors showed that when a simple linear regression was applied to a plot of percentage matrix erosion vs time the slope represented erosion rate (k, % min^{-1}) (Ghori et al., 2014a).

2.12 Differential Scanning Calorimetry (DSC)

Free and bound water of the tablets using endothermic scanning of the melted free water was performed as reported previously (Asare-Addo et al., 2011; Kaialy et al., 2013). Briefly, flat faced 4 mm disks with target weights of 20 mg were produced from all pure polymers and formulation blends and compressed using a single punch tableting machine (as

before) at 2500 psi (150.8 MPa). The discs were placed in standard aluminium pans (40 µL) containing 25 mg of purified water, 0.1N HCl (pH 1.2), or phosphate buffer (pH 6.8) and sealed with a lid. The pure polymers were then allowed to hydrate for up to 30 min to determine the influence of time on bound and free water states. The tablet formulations were hydrated for 5 min before DSC analysis. This was to determine if the state of water in the matrices could relate to the dissolution profiles of the tablets formulations. DSC analysis was performed in three stages. First, the samples were cooled from ambient temperatures (~25 $^{\circ}$C) to -30 °C at a rate of 55 °C/min to freeze any unbound (free) water; secondly, sample was held at -30 °C for 5 minutes for equilibration and thirdly, sample was heated from -30 °C to 50 °C at 10 °C/min. The experiment was run under nitrogen atmosphere and at a flow rate of 50 cm^3. These experiments were carried out in triplicate.

3. Results and Discussion

3.1 Physical properties of formulation blends

Properties of the pure polymers and formulation blends or compacts are presented in Table 2. The results show that the bulk density of the pure polymers (GGp, GDSp and HPMCp) increased upon blending with other formulation ingredients. The GDSp and the formulation blend (GDSf) exhibited the highest porosity of all the formulation blends and formed the hardest compacts or tablets at any given compression pressure (Figure 1). Thus GDSp is a highly compactible polymer, forming matrices with greater hardness compared with GGp or HPMCp matrices. What is interesting also is that the de-starching process did not affect the true density of the GDS polymer as its true density remained the same as the GG (Table 1).

Particle size analysis showed the HPMC K4M to have a d_{10} value of 26.79 µm, d_{50} of 78.67 µm and d_{90} of 141.63 µm. The results also showed d_{99} to have a value of 171.10 µm

3.2 Swelling and erosion of matrices

Upon its initial contact with liquid media the liquid starts to imbibe into the dry matrix tablet and the change in overall weight of matrix tablet is reflected as swelling. The extent of swelling was determined by using Eq. 6 and plotted with respect to time and shown in Figure 2 (a-c). The matrix erosion, however, which is a fundamental property of matrix tablets which occurs when the polymer chains present on the surface disentangle and begin to dissolve. Eventually this leads to bulk surface dissolution of polymer chains which is widely considered as matrix erosion. In this study the degree of matrix erosion was calculated by using Eq. 7 and % erosion vs time was plotted (Figure 4 a-c).

The results show that GGf matrices exhibited the highest extent of swelling in all media. GDSf matrices swell within the first 30 min in deionized water but are rapidly eroded thereafter (Figure 2A). In pH 6.8 media, GDSf matrices were observed to swell rapidly in the first 30 min and thereafter plateau until 180 min when erosion of the tablets occurred (Figure 2B). However, the least extent of swelling was exhibited by HPMC (K4M) matrices in pH 1.2. Moreover, to study the mechanism of swelling Vergnaud model was used, Eq. 8 (Vergnaud 1993) and swelling parameters were enlisted in Table 3. The model, however, was not applicable to GDSf as these particular matrices start to erode quickly. In general the R^2 values were in the range of 0.953-0.991, which indicate that the data can be well described by this model. According to the swelling kinetics findings, GGF has the highest swelling rate (K_w) 64.16 % min^{-1} in water but HPMCf has highest K_w 25.59 and 32.00 % min^{-1} in pH 6.8 and pH 1.2 media, respectively. All the grewia gum matrices, however, showed a no significant difference in pH 1.2 media which might be attributed to its anionic nature. The polymer swelling kinetics can also be inferred from the value of swelling exponent (*n*)

According to the criteria laid out by Ebube et al., (1997) all the matrix tablets apart from GGf in pH 6.8 showed diffusion controlled swelling, where the rate of polymer relaxation is greater than the rate of liquid penetration in to the polymer matrix network. However, GGf specifically in pH 6.8 swelling media showed an anomalous polymer swelling behaviour in which the rate of water diffusion and polymer relaxation is of same magnitude. Eventually after the swelling phase the hydrophilic polymer based matrices underwent erosion. The rate of polymer erosion was determined by using the data in Figure 4 and the erosion kinetics parameters were enlisted in Table 3. The R^2 of erosion kinetics findings were in the range of 0.954-0.998, and therefore attributed to a good fit indicating that the findings can explain the erosion phenomena. In water HPMCf showed highest erosion rate (K_E = 0.354 % min^{-1}) while in pH 6.8 GDSf showed highest erosion (K_E = 0.297 % min^{-1}). However, in pH 1.2 media the matrices have not showed any substantial difference in the erosion rates. Hydration of polysaccharides matrices occurs when hydrogen-bonding forces maintain the integrity of the hydrophilic polysaccharide matrix during the course of the experiment (Munday and Cox, 2000). Therefore, for any given material, when the hydrogen bonding forces are weak in any given media, matrix erosion may prevail. This probably explains the relatively higher erosion rate of GDSf matrices in water and pH 6.8 in contrast to pH 1.2 (Figure 4). The GDSf matrices rapidly hydrate upon contact with water or pH 6.8 media but the gel layer formed was not durable or resistant to erosion at 100 rpm.

Furthermore, the hydration rate of polysaccharides depends on the nature of the substituent groups and the degree of substitution (Roy and Rohera, 2002). HPMC K4M is a non-ionic polymer and has been reported (Streubel et al., 2000; Tatavarti and Hoag, 2006; Tatavarti et al., 2004; Gabr, 1992) to exhibit pH independent drug release as a result of pH independent swelling and erosion of the matrices when drug solubility is pH independent.

Both GGp and GDSp have both been reported to be anionic polysaccharides (Nep et al., 2015). Consequently, a pH dependent swelling and erosion of the matrices may be expected. However, the percentage content of uronic acids in GDSp (64 %w/w) is higher than GGp (58 %w/w), and likewise GDSp has a greater degree of acetyl esterification (GDSp 49% and GGp 34%) (Nep et al., 2015). Sungthongjeen et al., (2004) has shown that the degree of esterification of pectins can modify drug release from pectin based matrices

The decrease in erosion rate of GDSf matrices in pH 1.2 media may be attributable to a decrease in the ability of GDSp to hydrate as the pH falls below the pKa of the uronic acids present in the polymer chains.

Images of matrices after 3 hours of swelling and erosion in the different media are shown in Figure 3, which clearly shows the relatively rapid erosion and dissolution of GDSf matrices in deionised water and pH 6.8 media as compared with GGf and HPMCf.

3.4 Drug release from matrices

The release profiles are presented in Figure 6. The dissolution parameters T_{50} and T_{100} are shown in Table 4. The profiles show that none of the matrices exhibited any initial burst release of theophylline despite the propensity for initial burst release of soluble drugs from HPMC (Tiwari et al., 2003; Gohel et al., 2009; Huand and Brazel, 2001). Initial burst release is attributable to the rapid dissolution of the drug from the surface and near the surface of the matrix which occurs while the polymer is undergoing hydration to form a protective gel layer.

The release of theophylline in deionized water was fastest from the GDSf matrices which released 100% of the drug within 120 min (Figure. 5A). This may be explained to be as a consequence of the excessive erosion and dissolution of the GDSf matrices in deionized water. Conversely, GGf matrices showed the slowest release of theophylline in deionized

365 water. Similarly, in pH 6.8 media, GDS matrices showed the fastest release of theophylline with 100% of drug released after 240 min (Figure. 5C), also attributable to excessive erosion of the matrices.

However, in pH 1.2 media, it was observed that the extent and rate of drug release from the different polymer matrices were more or less the same (Figure. 5B) with GDSf 370 matrices releasing 100% of drug only after 330 min. The present results show that GDSf matrices release 100% of the drug faster in pH 6.8 (240 min) than in pH 1.2 media (330 min) in contrast with HPMC K4M and GGf matrices.

The release of the drug from the polymer matrices was also compared using dissolution efficiency (DE), mean dissolution time (MDT) and similarity factor (*f2*). The DE 375 and MDT are presented in table 4. The results show that the DE for the matrices in pH 1.2 media was 86.91%, 87.27% and 87.58% for GGf, GDSf and HPMC K4M matrices respectively, and indicates that the efficiency of release of the drug from the matrices was essentially the same in this medium. This is also supported by the similarity factor (*f2*) for the matrices in pH 1.2 media (Table 4). The *f2* was 83.66 and 82.15 for GGf and GDSf matrices 380 respectively with HPMC K4M as the reference verifying GGf and GDSf's similar drug release in pH 1.2 media to HPMC K4M. However, at pH 6.8, and in deionized water, there was a larger difference in release. The higher DE of GDSf (95.01% and 89.9% in water and pH 6.8 media respectively) concurs with the high erosion of the material in both media. Conversely the lower values of DE for GGf may be attributable to the swelling of the 385 material which persisted over the duration of the release study.

3.5 Modelling of drug release

The release kinetics for the polymer matrices are presented in Table 4. The release of theophylline from HPMC K4M matrix tablets has been reported (Asare-Addo et al., 2011;

390 Sriamornsak et al., 2007) to fit well with both Higuchi equation and Korsmeyer–Peppas equation. The Higuchi model describes drug release that is largely governed by diffusion through water-filled pores in the matrices, while the Korsmeyer–Peppas model describes the combined effect of diffusion and erosion mechanisms for drug release (Korsmeyer et al., 1983).

395 Theophylline release from GDSf matrices in pH 1.2 and pH 6.8 media were typically non-Fickian with a best fit to Korsmeyer-Peppas model indicating that drug release was by a combination of diffusion and erosion. In deionized water the model could not be determined because there were insufficient data points on the release profiles between 10% and 60% release to provide accurate values. Similarly, the release was anomalous (non-Fickian) and
400 diffusion controlled release for GGf and HPMC (K4M) matrices in deionized water, pH 1.2 and pH 6.8 media. Interestingly, the release data of GDSf matrices fitted well with zero-order release model with a correlation coefficient (r^2) greater than 0.996 (not shown) probably due to the extensive swelling of the tablets in deionized water as shown in Figure 2a.

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3.6 DSC hydration results and theophylline release from matrices

Jhon and Andrade, 1973 classifies hydration water to three types, namely; Type I (freezing or free, bulk-like water) melts at the normal melting point of pure water (0 °C). Type II (freezing or bound water) weakly interacts with macromolecules and displays a lower
410 melting point than pure water (<0 °C). Type I and II can be classed as free or freezable water with type III being classed as bound water. Bound water has the ability to interact with the ionic and hydrophilic groups of polymers and shows non-freezing behaviour. Water penetrates into a tablet matrix during the first stages of dissolution and acts as bound water. Aoki et al., (1995) explained that during the next stages of dissolution, the water content of

the matrices increases and freezable water is detected at levels that are related to drug release. Figure 6 shows the percentage of bound water with increasing time (1, 5, 10, and 30 min) for the pure polymers in deionized water, calculated from the thermographs in Figure 7. All the thermographs for the pure polymers demonstrated a slight shift to the left with an increase in hydration time. The results showed HPMC K4M to bind more to water as compared with GGp and GDSp. There was also an increase in the amount of bound water occurring with an increase in time. Due to the first time point of dissolution being at 5 min, hydration values to determine bound and free water states were utilised for the formulation matrices to establish a correlation between free water state and drug dissolution. This however was difficult to establish. The results however showed that GDSf, GGf and HPMC K4M matrices bound to deionized water more than to the other two media used (Table 5). It can be seen that the amount of available water for hydration increased in pH1.2 or phosphate buffer (pH6.8) for all the matrices. Also, HPMC K4M generally binds more to water in all the tested media as compared with GGf and GDSf formulations. This was similar to the trend for the pure polymers. Interestingly, when comparing the amount of bound water at the same time point (5 min) for the pure polymer and formulation compact, it is observed that the incorporation of drug and the lactose significantly reduces the bound water percentage.

4. Conclusion

Starch-free grewia polysaccharide is a highly compressible and compactible polymer with superior compression and compaction properties to those of GG and HPMC (K4M). The results show that variations in release properties are also apparent, depending on the polymer and the dissolution media used. In pH 1.2 media, drug release from GGS was similar to GG and HPMC (K4M) matrices and exhibited greater swelling than erosion. Rapid release of drug was observed from the GDS matrices in water and at pH6.8, mainly due to erosion. This

was despite forming compacts with greater hardness than GGp or HPMCp. GG matrices on the other hand, slowed down drug release when compared with HPMC (K4M) attributable to the greater swelling of the material. Overall this study has demonstrated the potential of grewia gum as a matrix former that can modify the release of a water soluble drug as a potential alternative to HPMC. Furthermore, by using different grades of the raw material it is possible to achieve different types of drug release. In addition, the superior compaction properties of GDSp may provide a wider application as a binder to strengthen weak compacts.

Acknowledgement

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Tables

Table 1: Unit formula for matrix tablets by direct compression

Table 1: Unit formula for matrix tablets by direct compression

Formulation code	Theophylline (mg)	Native grewia gum (GG) (mg)	De-starched grewia gum (GDS) (mg)	HPMC K4M (mg)	Lactose (mg)	MgSt (mg)
GG	125	75	-	-	47.5	2.5
GDS	125	-	75	-	47.5	2.5
HPMC (K4M)	125	-	-	75	47.5	2.5

Table 2: Properties of the pure polymer, formulation mixes, polymer compacts and tablet matrices

	True density (g/cm^3)	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Tablet Porosity (%) at 13.79 MPa	Tablet hardness (N) at 13.79 MPa
GGp	1.59±0.00	0.37±0.01	0.81±0.03	52.08±1.92	81.75±5.40
GGf	1.53±0.02	0.43±0.01	0.74±0.00	42.77±0.24	88.94±1.13
GDSp	1.59±0.01	0.20±0.03	0.38±0.02	49.61±1.93	375.07±38.78
GDSf	1.53±0.02	0.35±0.01	0.65±0.01	42.30±0.46	148.79±6.38
HPMCp	1.36±0.03	0.31±0.01	0.46±0.04	40.91±2.47	146.17±5.46
HPMCf	1.45±0.02	0.36±0.01	0.65±0.01	39.98±0.29	97.77±1.50

Note: "p" and "f" next to GG, GDS or HPMC is for pure polymer and formulation blends respectively.

Table 3: Parameters for swelling and erosion kinetics

Matrices	Swelling kinetics parameters			Erosion kinetics parameters	
	n	K_w	R^2	K_E	R^2
GGf-water	0.3461	64.16	0.977	0.1603	0.954
GDSf-Water	-	-	-	0.1548	0.991
HPMCf-Water	0.2111	32.16	0.966	0.3546	0.957
GGf-pH 6.8	0.4781	24.95	0.978	0.1409	0.981
GDSf- pH 6.8	-	-		0.2973	0.954
HPMCf- pH 6.8	0.2334	25.59	0.953	0.1449	0.992
GGf-pH 1.2	0.3979	19.51	0.991	0.1611	0.998
GDSf- pH 1.2	0.3573	19.34	0.970	0.1812	0.979
HPMCf- pH 1.2	0.2058	32.00	0.990	0.1704	0.997

K_w= Swelling constant (% min^{-1}), *n* = Swelling exponent, K_E= Erosion rate (% min^{-1})

Table 4: Dissolution parameters from release profiles of GG, GDS and HPMC K4M formulation tablet matrices

Matrix	Media	T_{50} (min)	T_{100} (min)	DE (%)	MDT	*Diffusional exponent, n*	*Similarity factor (f2)*
GG	*water*	120	540	80.98	136.96	0.43	37.96
	pH 1.2	67	330	86.91	94.22	0.45	83.66
	pH 6.8	97	720	80.52	140.28	0.46	52.86
GDS	*water*	32	120	95.01	35.91	N/A	N/A
	pH 1.2	75	330	87.27	91.69	0.44	82.15
	pH 6.8	60	240	89.9	72.72	0.54	56.49
HPMC	*water*	60	270	88.65	81.72	0.47	-
	pH 1.2	60	330	87.58	89.41	0.46	-
	pH 6.8	70	360	86.45	97.57	0.49	-

Table 5: Bound water (%) of the pure polymer compacts (HPMCp, GDSp, GGp) and the formulated tablet matrices (HPMCf. GDSf, GGf) in all media at 5 min

Compact	*Water (%)*	*pH 1.2 (%)*	*pH 6.8 (%)*
GDSp	21.2±1.56	13.39±2.22	18.23±0.40
GDSf	11.93±0.03	6.03±0.84	7.01±0.06
GGp	24.84±1.59	17.34±0.80	17.87±0.12
GGf	13.39±0.41	5.01±1.85	5.47±0.11
HPMCp	27.43±0.88	18.46±0.18	22.22±0.42
HPMCf	13.02±2.22	9.8±1.87	8.98±0.73

Figures

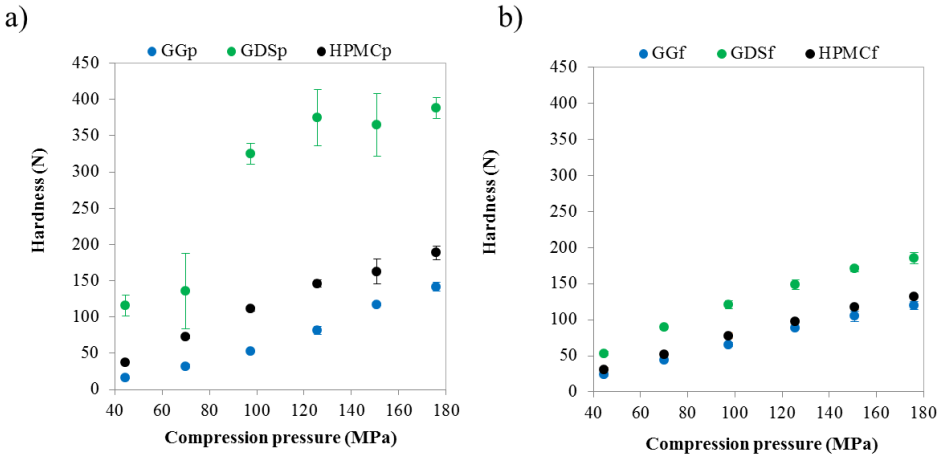

Figure 1: Dependence of hardness on compression pressure for the polymer compacts (HPMCp, GGp and GDSp) and formulation matrices (HPMCf, GGf and GDSf).

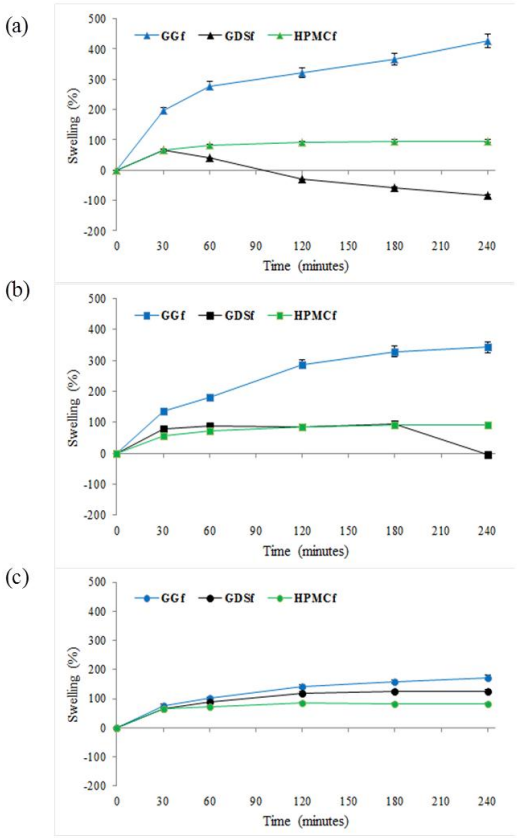

Figure 2: Swelling of HPMCf, GGf and GDSf matrices in A) deionized water B) phosphate buffer (pH 6.8) and C) 0.1N HCl (pH 1.2)

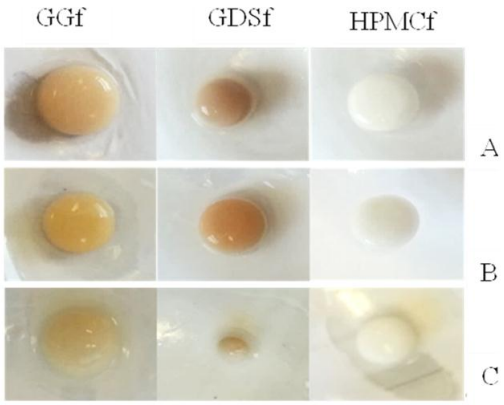

Figure 3: Photographs of the swelling and erosion of formulation matrices in (a) phosphate buffer (pH 6.8) (b) 0.1N HCl (pH 1.2), and (c) deionized water at 37^{o}C for 3 hours

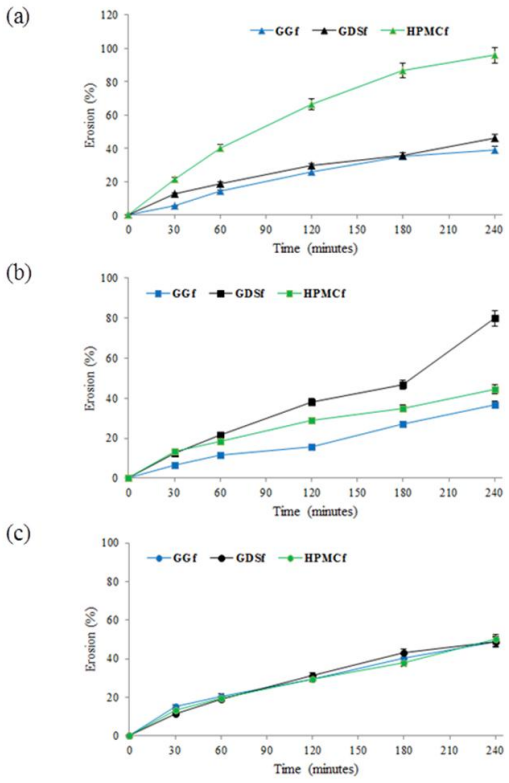

Figure 4: Dissolution medium uptake per unit polymer remaining **A.** for formulation matrices in different media, **B.** for formulation matrices in different media, plotted versus $t^{0.5}$ in water at 100 rpm. C. Dry weights of matrices in different media at 100 rpm fitted to cube root of time equation

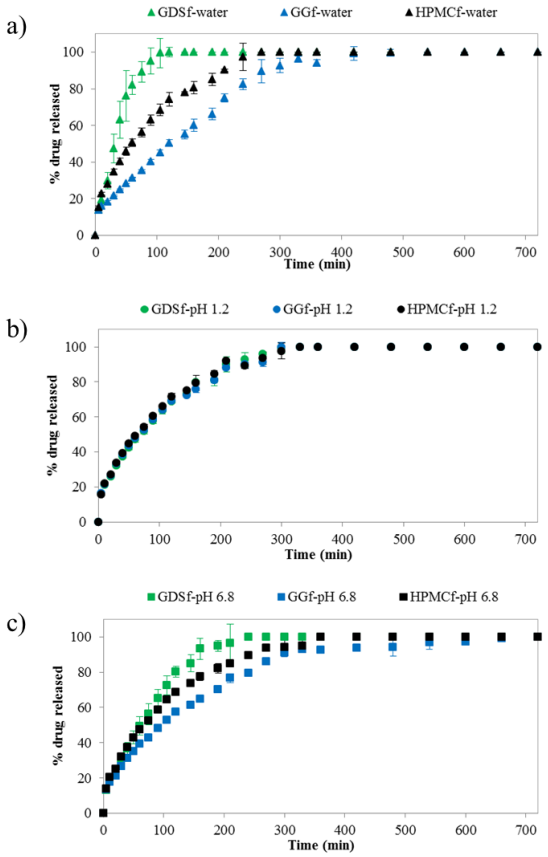

Figure 5: Release profiles of theophylline in: A. deionized water B. 0.1N HCl (pH 1.2) and C. phosphate buffer (pH 6.8) equilibrated to 37 °C and agitation speed of 100 rpm

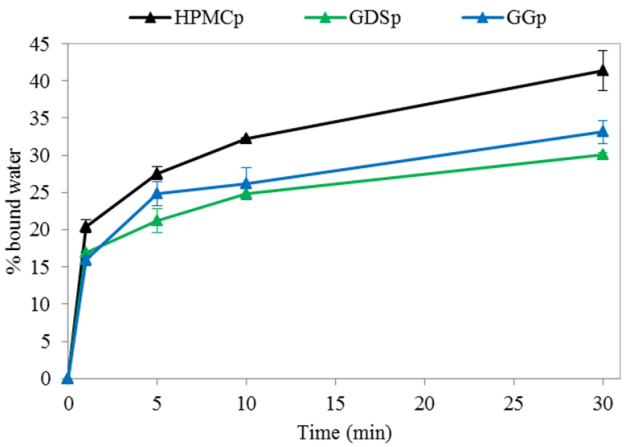

Figure 6: Representative bound water profiles of Pure Polymer compacts in distilled water

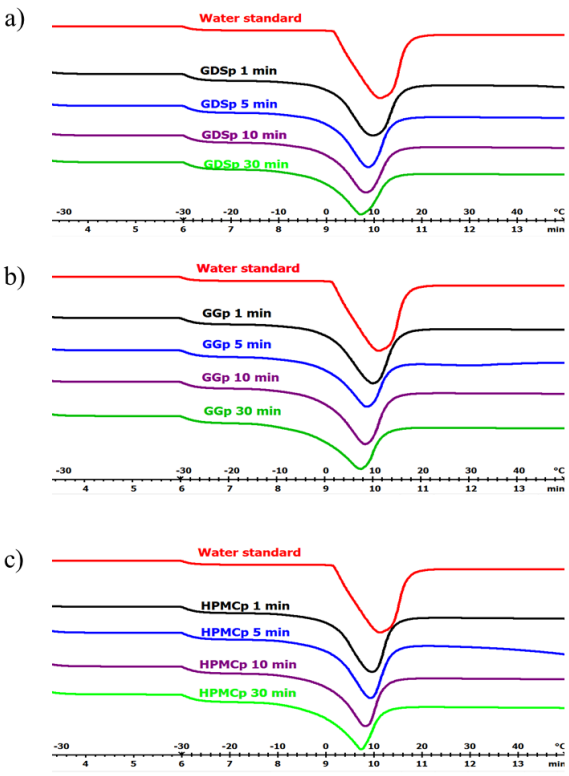

Figure 7: DSC Thermograms of the pure polymer compacts after hydration for 1, 5, 10, and 30 min in deionized water for A. GDS B. GG and, C. HPMC K4M