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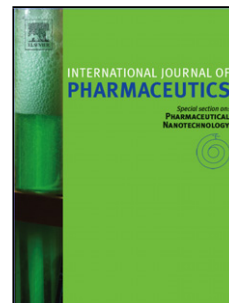
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# **The influence of hydroalcoholic media on the performance of Grewia polysaccharide in sustained release tablets**

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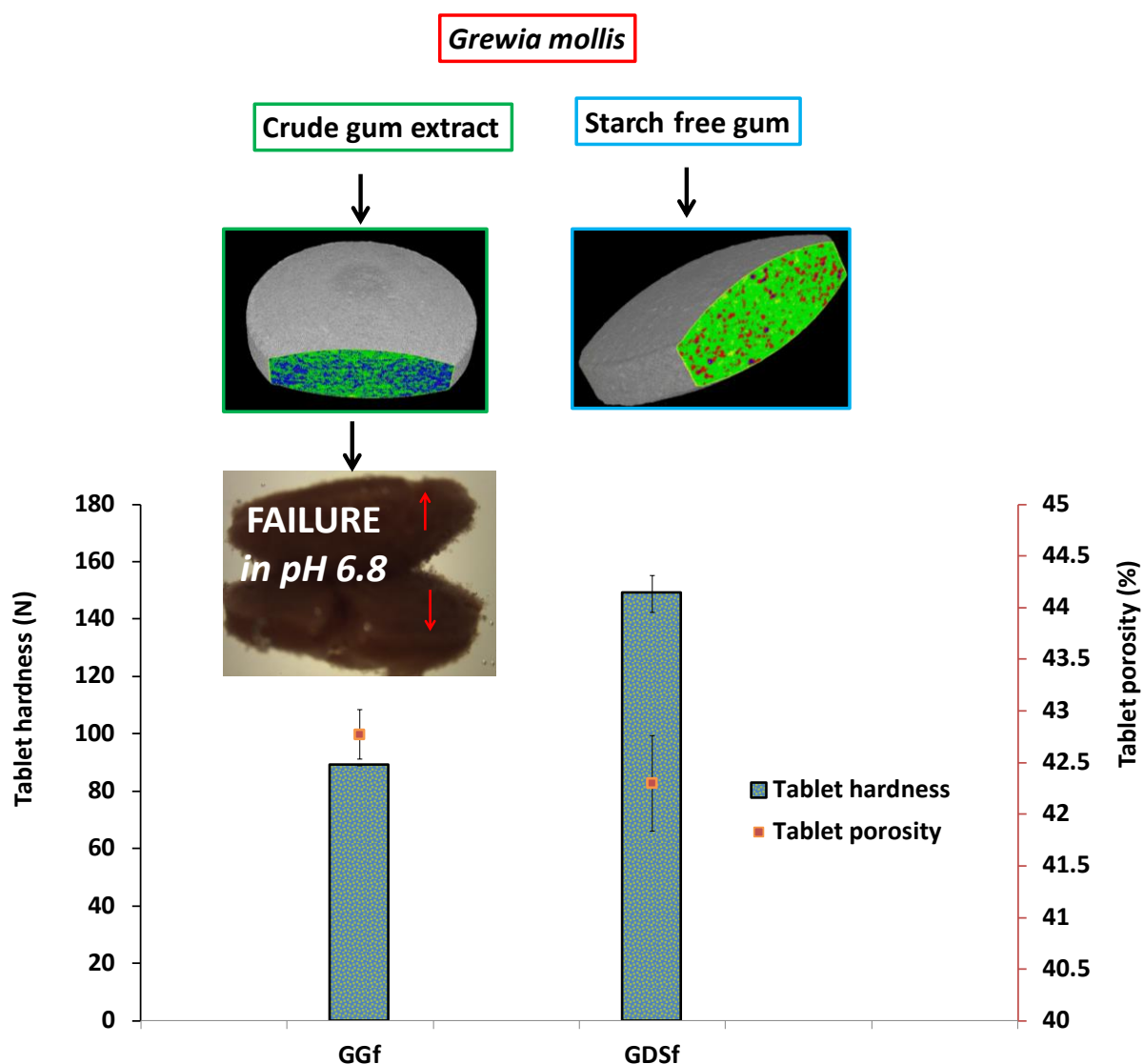
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## Graphical abstract



## Highlights

- Tomography showed differences in homogeneity of matrices depending on polymer grade
- Uneven mixing of polymer through tablet matrix contributes to cracking and splitting in alcoholic media
- The removal of starch from grewia gum improves mixing and resistance to damage

**Abstract**

Co-administration of drugs with alcohol can affect the plasma concentration of drugs in patients. It is also known that the excipients used in the **formulation** of drugs may not always be resistant to alcohol. This study evaluates effect of varying alcohol concentrations on theophylline release from two grades of *Grewia mollis* polysaccharides. X-ray microtomography showed that native polysaccharide **formulation** compacts were not homogenous **after the mixing process** resulting in its failure in swelling studies. Removal of starch from the native polysaccharide resulted in homogenous **formulation** compacts resistant to damage in high alcoholic media **in pH 6.8** (40 %v/v absolute ethanol). Destarched polymer compacts had a significantly higher hardness (375 N) than that of the native polysaccharide (82 N) and HPMC K4M (146 N). Dissolution studies showed similarity at all levels of alcohol tested ( $f_2=57-91$ ) in simulated gastric media (pH 1.2). The dissolution profiles in the simulated intestinal fluids were also similar ( $f_2=60-94$ ), with the exception of the native polysaccharide in pH 6.8 (40 %v/v absolute ethanol) ( $f_2=43$ ). This work highlights the properties of *Grewia* polysaccharide as a matrix former that can resist high alcoholic effects therefore; it may be suitable as an alternative to some of the commercially available matrix formers with wider applications for drug delivery **as a cheaper alternative in the developing world.**

**Keywords:** HPMC K4M, polysaccharide, matrix tablets, hydroalcoholic, **theophylline**

**Chemical compounds studied in this article**

Hydroxypropyl methylcellulose (HPMC) (PubChem [CID:57503849](#)); Lactose monohydrate (PubChem CID: 575038); Theophylline (PubChem CID: 2153); Ethanol (PubChem [CID:702](#)); Potassium Chloride (PubChem CID: 4873); Hydrochloric acid (PubChem CID: 313); Potassium phosphate monobasic (PubChem CID: 16218557); sodium hydroxide (PubChem [CID:14798](#));

**Abbreviations:** HPMC, Hydroxypropyl methylcellulose; GG, native Grewia gum; GDS, starch free Grewia gum; GGp, native Grewia gum polymer; GDSp, destarched 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

## 1. Introduction

There has been increasing research in the design of oral controlled release dosage forms focused on the use of polysaccharides derived from renewable sources. (Bonferoni et al., 1993; Khullar et al., 1998; Kristmundsdottir et al., 1995; Naggar et al., 1992; Sujjaareevath et al., 1996; Talukdar et al., 1996). The hydrophilic nature of these materials implies that when in contact with water, they hydrate and swell which makes them useful in the formulation of **oral controlled release** dosage forms. **The hydration and eventual swelling results in a gel layer that controls the mechanism of drug release** (Nokhodchi et al., 2014, 2012; Nakano and Ogato, 1984). Swelling of polysaccharide matrices has been shown to follow square root of time kinetics, with erosion of the polymers shown to follow the cube root of time kinetics (Kavanagh and Corrigan, 2004; Munday and Cox, 2000).

**Countries of the developing world are often rich in renewable sources of raw materials suitable for use in the pharmaceutical industry. Most of these countries however depend on imported excipients funded heavily by their petrochemical industries. The high costs of the pharmaceuticals produced means it is beyond the reach of the majority of the local population. Plant polysaccharides are coming under increased research interest and this is a resource in abundance in the developing world**

**(Nep et al., 2015). It is therefore important that these polysaccharides are fully characterised to determine their suitability as excipients in drug delivery.** *Grewia mollis* is a shrub that is cultivated in the middle belt region of Nigeria (and other parts of sub-Saharan Africa) and it also grows in the wild. When the inner bark from the stems of the shrub is pulverised, it can be used as a thickener in various food formulations (Nep et al., 2016). The polysaccharides identified to be present in the native gum extract (Nep and Conway, 2011a; Okafor et al., 2001) have been evaluated as a binder/ sustained release matrix (Nep and Conway, 2011b), bioadhesive (Nep and Conway, 2011c; Nep and Okafor, 2006) and as a suspending agent (Nep and Conway, 2011d). It has also been concluded that the extraction methods used can impact on the functional properties of *Grewia* gum extracts (Akdowna et al., 2014; Ogaji, 2011). The polysaccharides have been reported to consist of five neutral sugars namely, glucose (6.4 %), rhamnose (12.3 %), arabinose (0.5 %), xylose (0.3 %) and galactose (0.2 %) as well as galacturonic acid (16.3 %) and glucuronic acid (12.1 %) (Nep et al., 2016; Nep and Conway, 2011a; Okafor et al., 2001). Recently, Nep et al. (2015, 2016) successfully conducted the enzymatic removal of starch from *Grewia* gum (GG) resulting in a starch-free *Grewia* gum (GDS) which differed from the native polysaccharide in the relative proportion of monosaccharides and physicochemical properties (Nep et al., 2016). The same authors then evaluated the native gum and starch-free gum as potential hydrophilic matrix formers for sustained release applications (Nep et al., 2015). They found GDS compacts were significantly harder than the native GG and hydroxypropyl methyl cellulose (HPMC K4M) compacts. GDS matrices exhibited the fastest erosion and drug release in deionised water and phosphate buffer compared to the GG and HPMC matrices. At pH 1.2, GDS exhibited greater swelling than erosion. However, in both pH 1.2 and 6.8, drug release was similar to the GG and HPMC thus highlighting the potential of GDS as a matrix for controlled release similar to HPMC.

Polymer/polysaccharide excipients make up a large proportion of the tablet contents, and are responsible for controlling the rate of drug release; therefore, it is important to evaluate their resilience under harsh conditions that can be experienced in the gastrointestinal (GI) tract. In 2005, Palladone<sup>®</sup>, an extended-release narcotic analgesic capsule of hydromorphone hydrochloride, was withdrawn from the US market by the Food and Drug Agency (FDA) after clinical testing showed subjects who took the product with alcohol had increased levels of the drug in their blood leading to potentially fatal adverse reactions (FDA, 2005). **Alcohol-induced dose dumping can be a major challenge for drugs with narrow therapeutic index and drugs used in controlled release formulations as they generally contain higher drug doses than immediate release formulations (Rosiaux et al., 2013). If polymers are soluble in hydro-alcoholic media or solutions, it may cause drug release to occur faster instead of releasing drug in a controlled way. This is also true for drug reservoir systems which are surrounded by release-rate controlling polymeric films (Qiu et al., 2016). To combat the dose dumping issues, some authors have investigated and developed coating systems containing ethylcellulose and guar gum that show resistance at high (40 %) ethanol content (Rosiaux et al., 2013, 2013a; 2014). Others have also studied alcohol effect on hot-melt extruded pellets and film-coatings (Jedinger et al., 2015; 2016). There has also been a lot of interest in developing extended release matrices that are robust to alcoholic effects. Several authors have investigated release of drugs such as aspirin, felodipine, gliclazide, metformin hydrochloride and theophylline from matrix tablets and it was observed that even though the drug release kinetics were different, there was no dose dumping (Asare-Addo et al., 2013; Levina et al., 2007; Roberts et al., 2007). Readers are also referred to a recent review on the design of controlled-release formulation resistant to alcohol-induced dose dumping (Jedinger et al., 2014).**



In the present study, theophylline which is a bronchodilator used in the treatment of respiratory conditions such as bronchial asthma was used as the model drug. Theophylline is a partially water soluble drug with a narrow therapeutic index and its absorption is subject to formulation-dependent food-induced changes (Karim, 1986). All these make the management of theophylline dosing a bit difficult (Bettini et al., 1995). As such in this study, GG and GDS were extracted from *Grewia mollis* and characterised. The effects of the different grades of *Grewia* polysaccharides on the flow properties of the powder blend, the rheological properties and mechanical properties of the tablets were assessed. In addition, the release properties of the drug from the tablet matrices in different hydroalcoholic media were assessed.

## **2. Materials and Methods**

### **2.1 Materials**

Methocel (HPMC K4M) and lactose monohydrate (FlowLac® 100) were kind gifts from Colorcon (UK) and Meggle (Germany) respectively. Particle size analysis showed the HPMC K4M to have a  $d_{10}$  value of 26.79  $\mu\text{m}$ ,  $d_{50}$  of 78.67  $\mu\text{m}$ ,  $d_{90}$  of 141.63  $\mu\text{m}$  and  $d_{99}$  of 171.10  $\mu\text{m}$  using the Sympatec laser diffraction particle size analyser (Clausthal-Zellerfeld, Germany) according to the methodology detailed in a previous paper (Asare-Addo et al., 2015). Anhydrous theophylline was obtained from Tokyo Chemical Industry (UK) while the Magnesium stearate was used as procured from Merck (Germany). Dissolution buffers were prepared 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. Absolute ethanol (Fisher Scientific, UK), was used to produce the hydroalcoholic solutions in 5–40 % v/v with either 0.1 M HCl (pH 1.2) or phosphate buffer

(pH 6.8). GG and GDS were extracted in our laboratory as previously reported (Nep et al., 2015).

## **2.2 Extraction and characterisation of Grewia polysaccharide**

### **2.2.1 Extraction of native Grewia gum (GG) to isolate native Grewia gum polymer (GGp)**

The method of Nep et al., (2015) was adopted without modification (Nep et al., 2015). Briefly, the inner stem bark of *Grewia mollis* was dried and shredded. The shredded material was then macerated in 0.1% sodium metabisulphite for 24 hours after which GG was separated from the residue by filtration through a muslin bag and the filtrate precipitated from solution using absolute ethanol. This was purified further by re-dispersion in water and final precipitation in absolute ethanol to give the gum fraction code named GGp and then oven dried at 50 °C for 24 hours. The dried GGp was milled to a particle size of 200 µm undersize using a Retsch mill (ZM 1000, Retsch Germany) and stored in sealed plastic containers before use in tablet formulation.

### **2.2.2 Extraction of starch free grewia polysaccharide (GDSp)**

A suspension of GGp (1%w/v) as obtained in section 2.2.1, was digested with Termamyl® 120 L (1 %v/v) (Sigma, UK), under continuous agitation at 70 °C for 4 hours. Sample pH was adjusted to 4.5 with 2 M HCl to precipitate the enzyme and the sample centrifuged at 4400 rpm for 20 min. The obtained 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 obtained precipitate, given the fraction code name (GDSp), was oven-dried overnight at 50 °C and subsequently milled to reduce to a particle size of 200 µm undersize and stored under the same conditions as the GGp.

### 2.2.3 Thermogravimetric analysis (TGA)

Thermogravimetric analysis (TGA) was carried out using TGA (Mettler-Toledo Ltd, UK) under nitrogen atmosphere at flow rate of  $50 \text{ cm}^3 \text{ min}^{-1}$  with  $10 \text{ }^\circ\text{C min}^{-1}$  heating rate in the temperature range of  $25 \text{ }^\circ\text{C}$  to  $600 \text{ }^\circ\text{C}$  using  $70 \text{ }\mu\text{l}$  aluminium oxide crucibles.

### 2.2.4 X-ray powder diffraction (XRPD)

The methodology reported by Laity et al., (2015) was used to characterise the x-ray powder diffraction of GGp and GDSp (Laity et al., 2015). In brief, the samples were scanned in Bragg–Brentano geometry, over a scattering (Bragg,  $2\theta$ ) angle range from  $5$  to  $100^\circ$ , in  $0.02^\circ$  steps at  $1.5^\circ \text{ min}^{-1}$  using a D2 Phaser diffractometer (Bruker AXS GmbH, Karlsruhe, Germany), with a sealed microfocus generator operated at  $30 \text{ kV}$  and  $10 \text{ mA}$ , producing  $\text{CuK}_\alpha$  ( $\lambda X = 0.1542 \text{ nm}$ ) radiation and a Lynxeye ‘silicon strip’ multi-angle detector.

### 2.2.5 Rheological measurements

Samples of GGp, GDSp and HPMCP were each weighed and dispersed in different media - Media A ( $0.1 \text{ N HCl}$  (pH 1.2) with 0% ethanol); Media B ( $0.1 \text{ N HCl}$  (pH 1.2) with 40% ethanol); Media C (Phosphate buffer (pH 6.8) with 0% ethanol) and Media D (Phosphate buffer (pH 6.8) with 40% ethanol) to a final concentration of 2 % w/v. The samples were stored overnight under constant agitation at room temperature ( $\sim 22 \text{ }^\circ\text{C}$ ) to ensure full hydration of polymer. Viscosity measurements of the samples were performed at  $37 \text{ }^\circ\text{C}$  across shear rates ranging from  $1 \text{ s}^{-1}$  -  $1000 \text{ s}^{-1}$  for 5 min using a Bohlin Gemini rheometer fitted with a 55 mm cone and plate geometry with gap of 70 mm.

## 2.3 Tablet preparation and mechanical strength test

The formulation blends were prepared by mixing the appropriate amounts of ingredients (Table 1) for 10 min (**49 min<sup>-1</sup>**) using a Turbula<sup>®</sup> (Type T2C, Switzerland) blender. **Magnesium stearate was added after 8 min of blending all the other excipient and blended for another 2 min (49 min<sup>-1</sup>).**

### 2.3.1 Bulk, tapped, true density and porosity of polymers and formulation blends

The bulk and tapped densities of the polymers alone and in their 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 then 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. 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. Porosity was determined according to equation 1.

$$Tablet\ porosity = \left[ 1 - \left[ \frac{tablet\ weight / tablet\ volume}{true\ density\ of\ powder} \right] \right] \times 100$$

(1)

### 2.3.2 Tablet compaction

Round convex tablet matrices, with a diameter of 10 mm and a target weight of 250 mg, were prepared by compression at 125.7 MPa using a single punch-tableting machine (Model MTCM-1, Globe Pharma, US). The compressed tablets were allowed to recover for

24 h, thereupon the breaking force of the tablets was determined using a PharmaTest (Germany) hardness tester. The thickness and diameter of the matrix tablets were measured using a digital calliper. Compacts containing only the polymer were also prepared and tested using the same procedure described above.

### **2.3.2 X-ray microtomography (X $\mu$ T) of compacted formulations**

The compacted formulation were examined by X $\mu$ T, (Nikon XT H 225, Nikon Corp. Tokyo, Japan), using a tungsten target, with 90 kV accelerating voltage and 80  $\mu$ A gun current. A double-sided adhesive tape was used in mounting the formulated compact on to a sample stage after which a set of 1583 projections was collected. The set of projection images was reconstructed using CT-Pro, and then examined using VG Studio 2.1 software (Laity et al., 2015).

## **2.4 *In vitro* release studies**

An automated USP dissolution apparatus II (paddle method) (Pharma Test DT 70) was used to monitor the dissolution profiles of theophylline from the tablet matrices. The dissolution medium was 900 mL 0.1 N HCl (pH 1.2) or phosphate buffer (pH 6.8) equilibrated to  $37 \pm 0.5$  °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 concentrations of theophylline in the samples determined by UV spectrophotometry at 270 nm. For the determination of the effect of alcohol on drug release, drug release was monitored as above, however the media used for this testing comprised either 0.1 N HCl (pH 1.2) or phosphate buffer (pH 6.8) containing 0 – 40% (v/v) ethanol.

### 2.4.1 Dissolution parameters (dissolution efficiency (DE) and mean dissolution time (MDT))

The mean dissolution time (MDT) (**Equation 2**), 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., 2014, 2013; Khan, 1975; Mu et al., 2003). Also calculated was the dissolution efficiency (DE) (**Equation 3**), 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  $\Delta M_j$  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  $t$ .

### 2.4.2 Similarity factor

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

$$f_2 = 50 \log \left\{ \left[ 1 + \frac{1}{n} \sum_{t=1}^n w_t (R_t - T_t)^2 \right]^{-0.5} \times 100 \right\} \quad (4)$$

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  $t$ .

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

#### **2.4.3 Kinetics of drug release**

The kinetics of drug release were analysed using Korsmeyer-Peppas equation (Siepmann and Peppas, 2001a). For cylinders, which were the shape of the tablet matrices made in this 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 as reported in numerous studies (Asare-Addo et al., 2013; Ritger and Peppas, 1987; Siahi-Shadbad et al., 2011; Siepmann and Peppas, 2001b).

#### **2.4.4 Drug solubility**

A saturated solution of theophylline was prepared by adding an excess of the drug to 10 ml of the relevant media. This suspension was then shaken for 24 h at  $37 \pm 0.5$  °C, centrifuged and filtered. The concentration of theophylline was determined spectrophotometrically at 270 nm at ambient temperature, using a known concentration of theophylline in **Media A (0.1N HCl (pH 1.2) with 0 % ethanol); Media B (0.1N HCl (pH 1.2) with 40 % ethanol); Media C (phosphate buffer (pH 6.8) with 0 % ethanol) and Media D (phosphate buffer (pH 6.8) with 40 % ethanol) as the standard.**

### **2.5 Tablet swelling**

Swelling studies were conducted as detailed in Asare-Addo et al., (2013) (Asare-Addo et al., 2013). Briefly, swelling dynamics were investigated using a digital camera (Leica ICC50HD) linked to image analysis software. A tablet compact was placed vertically in a plastic Petri dish, and 70 mL of medium (0.1 N HCl (pH 1.2) or phosphate buffer (pH 6.8)) was added at ambient temperature. The petri dish was placed in a plane with a light source (tungsten lamp), and the camera, equipped with macro lens, was placed above. The light beam direction was regulated to generate a high contrast image, with the tablet completely black in a bright background. The same procedure was followed to investigate swelling in hydroalcoholic media of 0.1 M HCl (pH 1.2) or phosphate buffer (pH 6.8) containing 40 % absolute ethanol v/v. Images were obtained at regular intervals up to 120 min.

### **3. Results and Discussion**

#### **3.1 Characterisation of GGp and GDSp**

The successful extraction process of the GG and GDS yielded polysaccharides that were completely amorphous in nature, with the presence of the broad halo as observed in Figure 1 (Charlesby, 1953; Murthy and Reidinger, 1996).

The primary and derivative thermograms for GGp and GDSp are presented in Figure 2a and b. Table 2 gives the details of thermal behaviour according to the primary thermograms and derivative thermograms for the samples.

The thermal behaviour and stability data according to the primary thermograms and derivative thermograms showed two mass loss events for both samples. The early minor weight loss (9.6 -10.6 %) in samples in the range of 44.1-144.5 °C is attributed to the loss of adsorbed and structural water of biopolymers, or due to desorption of moisture as hydrogen bound water to the polysaccharide structure (Bothara and Singh, 2012; Iqbal et al., 2011;



Kittur et al., 2002; Peng and Wu, 2010; Popescu et al., 2011; Vendruscolo et al., 2009; Yang et al., 2007; Zohuriaan and Shokrolahi, 2004). The second weight loss event may be attributed to the polysaccharide decomposition (Varma et al., 1997; Zohuriaan and Shokrolahi, 2004). Both samples showed one-stage decomposition behaviour characterized by the initial decomposition temperature (IDT) at about 259 °C and final decomposition temperature (FDT) in the range 317-345°C. This stage resulted in a weight loss of 46.7 % (GGp) and 62.36 % (GDSp). Decomposition of materials at high temperature has been attributed to dehydration, depolymerization and pyrolysis which result in the formation of H<sub>2</sub>O, CO, and CH<sub>4</sub> (Zohuriaan and Shokrolahi, 2004). The char yield at 600 °C was from 24-29 %. A decrease in the amount of combustible gases and heat released from the thermal degradation process may be accountable for high char yields.

### 3.2 Rheological measurements

Figure 3 highlights the differences in the rheological behaviour of GG, GDS and HPMC in acidic media (pH 1.2) and phosphate buffer media (pH 6.8) with or without ethanol (40% v/v). This result showed that all the samples exhibited a shear thinning behaviour regardless of the type of polymer. This is due to the fact that the polymers form a viscous solution by polymer entanglement (Clark and Ross-Murphy, 2009). Figure 3 c highlighted that the viscosity of the HPMC increased with increased ethanol content while a reverse was observed with the Grewia polysaccharides. This effect might be due to the reduced volume of water in the hydroalcoholic mixture and dielectric constant of the hydroalcoholic solutions, leading to the formation of new bonds/structures between the polymer molecules and the solvating media (Jones et al., 2002). **Viscosity data from Roberts et al. 2007 has also shown stronger gels to form as a result of increased ethanol content in the media. Cloud point results from the same group showed that the interactions of the polymer solvated**

by the ethanol were far greater than the interactions of the polymer with water due to hydrogen bonding and van der Waal forces between the ethanol and polymer (Roberts et al., 2007). The rheological properties of these polysaccharides can impact on the kinetics and mechanism of drug release from these matrices as has been previously reported (Asare-Addo et al., 2013; Roberts et al., 2007). Nep et al. 2016 showed that there were no major structural differences between the GG and GDS polymer using FTIR analysis. The subtle changes in their viscosity could thus be attributed to the removal of starch and sugar content of the polysaccharides. They also reported the polymers rheological properties to be influenced by changes in pH which is expected as it is anionic in nature (Nep et al., 2016).

### 3.3 Physical properties of formulation blends and tablets

The true densities of the polysaccharides GGp and GDSp were the same ( $1.59 \text{ g/cm}^3$ ). The true densities for the formulated blends GGf and GDSf were also the same ( $1.53 \text{ g/cm}^3$ ) showing a slight decrease in true density upon blending with other formulation ingredients. However, there was an increase in the true density of HPMC formulated blends HPM Cf ( $1.45 \text{ g/cm}^3$ ) relative to that of the pure polymer HPM Cp ( $1.36 \text{ g/cm}^3$ ). The bulk density of the pure polymers increased upon blending with the other formulation ingredients as in **Figure 4**. All the formulated compacts also experienced a reduction in porosity as compared to their pure compacts. The results from Figure 4b suggest that GDSp is a highly compactible polymer as it formed the hardest compacts compared with GGp or HPM Cp matrices (Nep et al., 2015). The reconstructed X-ray microtomographic images of compacted formulations of GG, GDS and HPMC are presented in Figure 5. This technique is based on the differential absorbance of X-rays between materials of differing electron density (Baruchel et al., 2000; Laity et al., 2015; Stock, 1999). The sagittal and diametric cross-sectional images from the formulation

revealed differences in the distribution of the constituents of the formulations. It was observed that the GG polymer was congregated more towards the middle of the compact (indicated by red arrow). However, the GDS and **HPMC** compact showed an even distribution of all the constituents, indicating the mixing time was adequate to produce a homogenous mix. **This suggests that the removal of starch from the GG polysaccharide improved the mixing process of GDS and may make it potentially more resistant to damage. The mixing time of the native gum should therefore be potentially increased whenever it is used to ensure adequate uniformity. The use of solvents and process techniques in modifying pharmaceutical materials can have an effect on their electrostatic properties (Adebisi et al., 2016a, 2016b; Asare-Addo et al., 2015; Supuk et al., 2013). Asare-Addo et al. 2013a, 2016 showed HPMC to be effective in dissipating API charge. They showed an ordered mixture between HPMC and theophylline to occur which resulted in a homogenous and stable system. The destarching process may have changed the electrostatic property of the polysaccharide gum, causing an ordered mixture to occur and thereby improving content uniformity.** The differences between the GG and GDS thus suggest that the destarching process impacts on formulation mix. **The even distribution of the GDS and HPMC compacts suggest that as they come into contact with the dissolution media and water ingresses through the compacts, an even gel layer is formed thereby controlling drug release.**

### **3.4 Aqueous and hydroalcoholic media effect on drug release**

Figure 6 shows the influence of aqueous and hydroalcoholic media on theophylline release from GG, GDS and HPMC matrices. The profiles show that none of the matrices exhibited any initial burst release attributed to the rapid dissolution of the drug from the surface prior to gel layer formation. It was interesting to note that inclusion of 40 % v/v absolute ethanol for all the individual matrices studied at pH 1.2 (using drug release from pH 1.2 as the standard)

rendered all the release profiles similar ( $f_2 = 57-91$ , Table 3). Theophylline's solubility at pH 1.2 ( $13.12 \pm 0.13$  mg/mL) increases **to more than** 2-fold on addition of 40% v/v absolute ethanol ( $28.18 \pm 0.14$  mg/mL) implying that drug release, if controlled by solubility, should be faster in the presence of alcohol. Similar results have been reported for felodipine and gliclazide by Levina and co-workers (Levina et al., 2007). Asare-Addo et al (2013) also found that despite the increase in theophylline solubility in elevated alcohol levels, it had no significant effect on its drug release from tablets containing polyols at pH 1.2 (0-40 % v/v absolute ethanol concentrations) (Asare-Addo et al., 2013).

Drug release profiles in pH 6.8 and the various hydroalcoholic media tested were similar from HPMC and GDS matrices. GG matrices also showed similarity up to 20 % v/v absolute ethanolic concentration but dissimilarity ( $f_2 = 43$ ) occurred at 40 % v/v absolute ethanolic concentration (indicated by black arrow in Figure 6b). Destarching GG gum did not seem to have an effect on the  $T_{50}$ , DE, MDT and MDR values in pH 1.2 media and its varying alcoholic concentrations (Table 3). At pH 6.8 and its varying concentration of alcoholic concentrations however,  $T_{50}$  values for GDS were generally reduced (61-85 min) as compared with the GG (52-103 min) with the MDR also being generally higher for GDS compared to GG matrices. With regards to the kinetics of drug release, with the exceptions of drug release from GDS matrices from pH 1.2 ( $n = 0.44$ ), HPMC matrices in pH 1.2 (20 % v/v absolute ethanol concentration) ( $n = 0.44$ ) and GG matrices in pH 6.8 (20 % v/v absolute ethanol concentration) ( $n = 0.44$ ) where Fickian diffusion was occurring, all the studied matrices exhibited anomalous transport drug release kinetics ( $n = 0.45 - 0.57$ ).

GG and GDS are anionic polysaccharides (Nep et al., 2016) with HPMC being a non-ionic polymer (Asare-Addo et al., 2016; Streubel et al., 2000) meaning release from HPMC occurs due to pH independent swelling and erosion of its matrices when drug solubility is pH

independent. However, for GG and GDS pH dependent swelling and erosion of their matrices may be expected. Nep et al. (2016) reported the percentage content of uronic acids in GG (58 % w/w) and GDS (64 % w/w) and also the percentage degree of acetyl esterification in GG (34 %) and GDS (49 %) (Nep et al., 2016). The differences in the degree of acetyl esterification could account for the difference in the release profiles for GG and GDS as it has been reported that the degree of acetyl esterification of pectins can modify drug release (Sungthongjeen et al., 2004). The performance of GG and GDS with HPMC as a standard reference in both acidic and alkaline media and their varying absolute ethanolic concentrations is compared in Figure 7. Drug release from GG and GDS was similar to HPMC ( $f_2 = 78 - 94$ ) regardless of the concentration of ethanol used at pH 1.2. This suggests that GG and GDS is resilient to such media and has a potential for use as matrices that can resist such harsh conditions as can be experienced in the stomach. Release behaviour was also similar at pH 6.8, with the exception of GDS (highlighted by black arrow in Figure 7d) in pH 6.8 (5 % v/v absolute ethanol) ( $f_2 = 47$ ). GDS has been reported to release drug quicker in pH 6.8 than the native GG and HPMC (Nep et al., 2015).

### 3.5 Tablet hydration/swelling

The impact of hydration on HPMC, GG and GDS matrices in acidic media is shown in Figure 8. These images were also generated in pH 1.2 medium containing 5 % v/v absolute ethanol and pH 1.2 medium containing 40 % v/v absolute ethanol. The same experiments were also conducted at pH 6.8. Image analysis showed that HPMC, GG and GDS matrices increased in both the axial and radial dimensions over time with axial swelling being greater than the radial swelling (Asare-Addo et al., 2013; Colombo et al., 1990; Mitchell et al., 1990; Rajabi-Siahboomi et al., 1994; Roberts et al., 2007). An example of the effect of hydroalcoholic media on the radial and axial length of HPMC, GG and GDS matrices is

depicted in Figure 9. **Swelling was greater for HPMC, both radially (initially before changing to GDS by the 120 min time point) and axially in the absence of alcohol at pH 1.2. In pH 6.8, GG and GDS had similar radial and axial length swelling which were relatively higher than the HPMC compact. The extent of swelling at pH 1.2 and 6.8 (5 % v/v absolute ethanol solution) both radially and axially was ranked GG > GDS > HPMC in pH 1.2 (Figure 10a).** The GG and GDS matrices however split apart in less than 5 min when alcohol was increased to 40 % v/v at pH 1.2. This behaviour was also observed for GG matrices at pH 6.8 (40 % v/v absolute ethanol) (Figure 11). The GDS matrices however withstood these high alcoholic conditions **(Figure 10b).**

The effect of dissolution medium composition on swelling and erosion of HPMC polymers have been studied and results show that the rate of uptake of the dissolution medium decreases linearly with increasing ionic strength (Kavanagh and Corrigan, 2004). This decrease is attributed to the “salting out” of the polymer by inorganic ions present in the dissolution media. It has also been reported that as the ionic strength of dissolution medium increases, the polymer loses its water of hydration due to competition between the ions for water of hydration (Alderman, 1984). **In media containing 40% ethanol, the possible formation of a less porous/stronger gel may have increased the diffusion pathway thereby decreasing gel erosion as seen by Roberts et al. 2007. The high content of starch (11.8 %) in GG may have contributed to its failure as starch can act as a disintegrating agent (Nep et al., 2016).** GDS tablet matrices behaved in a similar way to HPMC in the varying pH 6.8 conditions.

#### **4. Conclusion**

The performance of different grades of Grewia polysaccharide was evaluated for its drug release properties in different hydroalcoholic media. X-ray microtomography showed

obvious differences in the degree of homogeneity of the different compacts prepared using different grades of the Grewia polysaccharides. Compacts prepared with the native gum was not homogenous leading to the compacts breaking up on contact with the dissolution media in the swelling studies. The starch free Grewia polysaccharide had superior compression and compaction properties to that of the native Grewia gum and HPMC (K4M) and made homogeneous compacts. This suggests that the removal of starch improved the mixing process and the polysaccharides became more resistant to damage. In addition, this also suggests that the mixing time of the native gum should potentially be increased whenever it is used. The different grades of the polysaccharides exhibited resilience in different hydroalcoholic media mimicking the stomach and small intestines with no significant differences in their release profiles relative to HPMC under similar conditions. Therefore, they can be used as an alternative to HPMC providing wider applications in drug delivery for these natural polymers in the developing world.

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Table 1: Unit formula for matrix tablets by direct compression

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

Table 2: Thermogravimetric parameters derived from primary thermograms in Figure 2

	<b>GGp</b>	<b>GDSp</b>
Weight loss due to moisture (%)	10.64±0.11	9.67±0.41
Weight loss due to decomposition (%)	46.67±0.51	62.18±5.26
DTG maxima (°C)	295.59±0.04	285.85±0.37
Char yield (%)	29.11±0.99	24.42±1.89
Initial decomposition temperature - IDT (°C)	259.45±0.81	259.72±0.73
Final decomposition temperature- FDT (°C)	345.97±0.58	317.09±1.22

Table 3: Drug dissolution parameters and mechanism of drug release from HPMC, Grewia gum and destarched Grewia gum tablet matrices in various hydroalcoholic media.

Formulation-media	T <sub>50</sub> (min)	DE (%)	MDT (min)	MDR (%min <sup>-1</sup> )	Similarity factor ( $f_2$ )	RSQ ( $r^2$ )	Diffusional exponent ( $n$ )
GG-pH 1.2	66.5	86.91	38.67	0.22	-	0.990	0.45
GG-pH 1.2*	72.0	85.87	40.19	0.22	76.49	0.975	0.49
GG-pH 1.2**	77.5	84.60	40.70	0.22	69.45	0.981	0.50
GG-pH 1.2 <sup>†</sup>	79.5	84.55	40.52	0.21	71.97	0.991	0.50
GG-pH 1.2 <sup>‡</sup>	60.0	87.31	43.71	0.23	84.32	0.990	0.49
GDS-pH 1.2	70.0	87.27	45.23	0.22	-	0.988	0.44
GDS-pH 1.2*	78.0	86.28	44.61	0.22	76.95	0.981	0.47
GDS-pH 1.2**	81.0	84.81	40.28	0.21	69.99	0.980	0.49
GDS-pH 1.2 <sup>†</sup>	81.0	85.07	39.56	0.21	69.55	0.991	0.50
GDS-pH 1.2 <sup>‡</sup>	62.0	87.16	39.66	0.22	82.75	0.974	0.49
HPMC-pH 1.2	62.0	87.58	41.61	0.23	-	0.992	0.46
HPMC-pH 1.2*	74.0	86.83	42.72	0.23	74.00	0.991	0.49
HPMC-pH 1.2**	88.0	84.90	40.86	0.20	57.01	0.988	0.44
HPMC-pH 1.2 <sup>†</sup>	88.0	84.56	40.41	0.20	56.87	0.988	0.46
HPMC-pH 1.2 <sup>‡</sup>	61.0	86.90	40.17	0.23	91.27	0.991	0.51
GG-pH 6.8	96.0	80.52	35.45	0.18	-	0.986	0.46
GG-pH 6.8*	103.0	81.62	37.62	0.18	83.40	0.982	0.49
GG-pH 6.8**	101.5	79.22	36.44	0.17	88.71	0.964	0.44
GG-pH 6.8 <sup>†</sup>	98.0	78.92	35.47	0.18	93.74	0.983	0.45
GG-pH 6.8 <sup>‡</sup>	52.5	86.57	38.92	0.25	43.35	0.989	0.57
GDS-pH 6.8	61.0	89.90	58.71	0.27	-	0.980	0.54
GDS-pH 6.8*	66.5	89.45	54.12	0.24	73.36	0.918	0.51
GDS-pH 6.8**	73.5	88.86	50.88	0.23	59.97	0.914	0.48
GDS-pH 6.8 <sup>†</sup>	85.0	86.60	51.70	0.22	70.41	0.947	0.51
GDS-pH 6.8 <sup>‡</sup>	74.5	85.07	34.87	0.21	79.62	0.954	0.47
HPMC-pH 6.8	69.0	86.45	41.44	0.23	-	0.993	0.49
HPMC-pH 6.8*	89.5	82.82	43.38	0.21	60.44	0.986	0.50
HPMC-pH 6.8**	87.5	84.46	44.27	0.21	62.48	0.980	0.47
HPMC-pH 6.8 <sup>†</sup>	83.0	82.20	38.67	0.20	66.31	0.984	0.48
HPMC-pH 6.8 <sup>‡</sup>	60.0	86.37	43.41	0.24	81.89	0.989	0.51

Note: \* is medium containing 5 % v/v absolute ethanol, \*\* is medium containing 10 % v/v absolute ethanol, <sup>†</sup> is medium containing 20 % v/v absolute ethanol and <sup>‡</sup> is medium containing 40 % v/v absolute ethanol

Figure 1: PXRD pattern measured for GGp (a) and GDSp (b) indicating its low intensity and amorphous nature.

Note: GGp is pure grewia gum alone (native polysaccharide) and GDSp is the destarched grewia gum

Figure 2: Primary thermograms of the major decomposition stage of GGp and GDSp with their representative (a) derivative thermogram and (b) enlarged derivative thermogram for GDSp

Note: GGp is pure grewia gum alone (native polysaccharide) and GDS is destarched grewia gum

Figure 3: Viscosity vs. shear rate for (a) GG, (b) DSGG and (c) HPMC. Diamond symbols represent samples dispersed in buffer media, while circle symbols represent samples dispersed in acidic media.

Note: Filled or open symbols correspond to media without ethanol and media with 40 %v/v ethanolic content respectively.

Figure 4: Bulk and tapped densities of pure and formulated blends (a), tablet matrix properties of porosity and hardness for pure polymers and formulated blends.

Note: GGp is pure grewia gum, GDS is pure destarched grewia gum, HPMCP is pure hydroxypropyl methyl cellulose, GGf is the formulated\* grewia gum, GDS is the formulated\* destarched grewia gum and HPMCF is the formulated\* hydroxypropyl methyl cellulose. \*Formulated according to table 1. “Pure” in this context means the polysaccharide alone with no API or additives.

Figure 5: X-ray micro-tomographic sagittal and diametric images of compacted formulations of GG (a), GDS (b) and HPMC (c) detailing the homogeneity of the formulation mix.

**Colour code from density histogram: For figure 5a, green colour is GG polymer, blue colour is theophylline and red colour is lactose. For figure 5b, green colour is GDS polymer, red colour is theophylline and blue colour is lactose. For figure 5c, blue colour is HPMC, red colour is theophylline and green colour is lactose.**

Figure 6: Effect of theophylline release from GG, GDS and HP hydrophilic matrices in pH 1.2 (a, c, e) and pH 6.8 (b, d, f).

Note: \* is medium containing 5 % v/v absolute ethanol, \*\* is medium containing 10 % v/v absolute ethanol, <sup>†</sup> is medium containing 20 % v/v absolute ethanol and <sup>‡</sup> is medium containing 40 % v/v absolute ethanol

Figure 7: A comparison of the effect media on the performance of theophylline release from GG, GDS and HP hydrophilic matrices in (a, c, e, g, i) pH 1.2 and (b, d, f, h, j) pH 6.8.

Note: \* is medium containing 5 % v/v absolute ethanol, \*\* is medium containing 10 % v/v absolute ethanol, <sup>†</sup> is medium containing 20 % v/v absolute ethanol and <sup>‡</sup> is medium containing 40 % v/v absolute ethanol

Figure 8: The effect of time of the hydration of HPMC, GG and GDS matrices in pH 1.2 media only

Figure 9: Effect of **pH 1.2** media on a) radial b) axial thicknesses of HPMC, GG and GDS tablet matrices ( $n = 3$ ).



**Figure 10: The effect of time of the hydration of HPMC, GG and GDS matrices in pH 1.2 media containing 5 %v/v absolute ethanol (a), the effect on hydration time on GDS matrices in pH 6.8 containing 5 %v/v absolute ethanol and 40 %v/v absolute ethanol (b)**

Figure 11: GG exhibiting cracks (cracks indicated by red arrows) after 2 min (a) and 6 min (b) hydration in pH 6.8 (40 % v/v absolute ethanol solution).

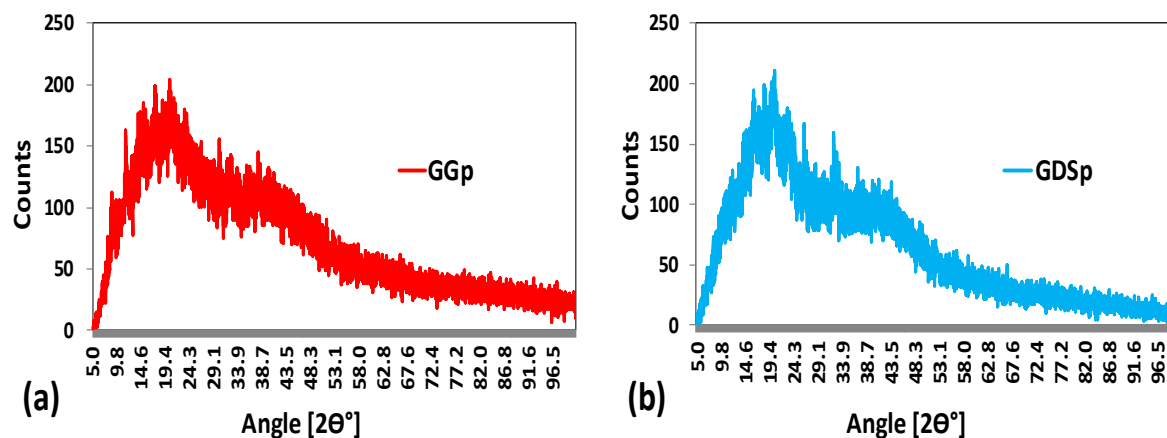


Figure 1

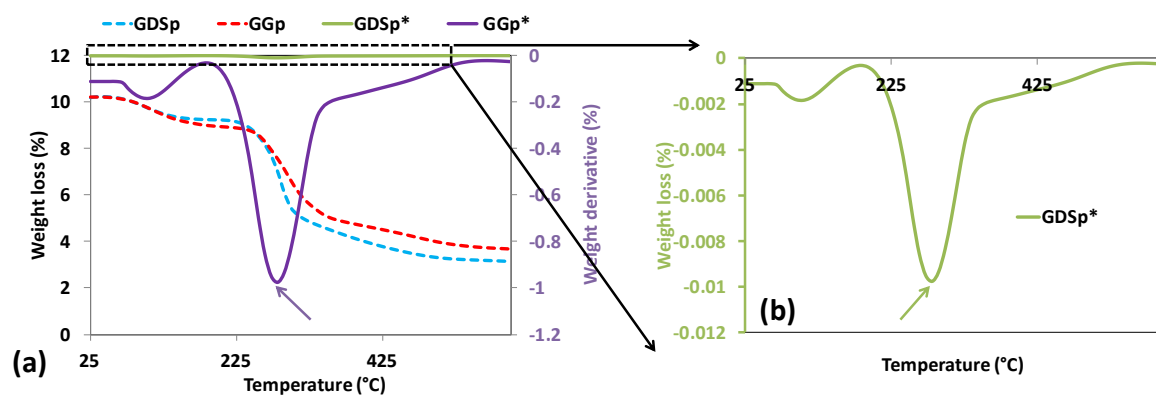


Figure 2

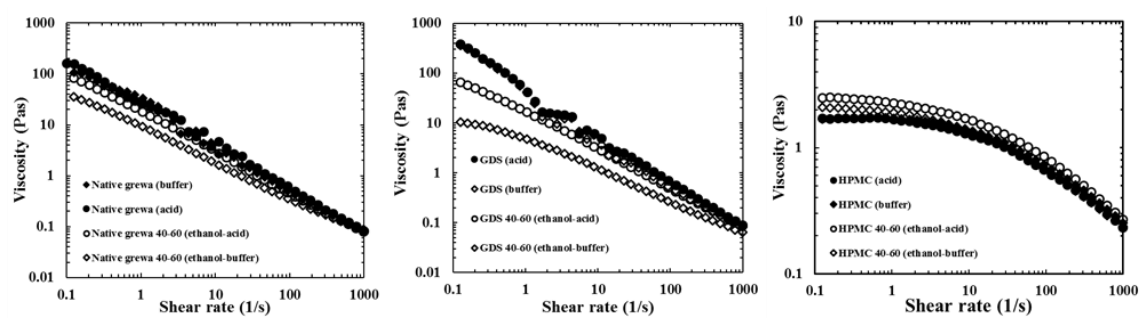


Figure 3

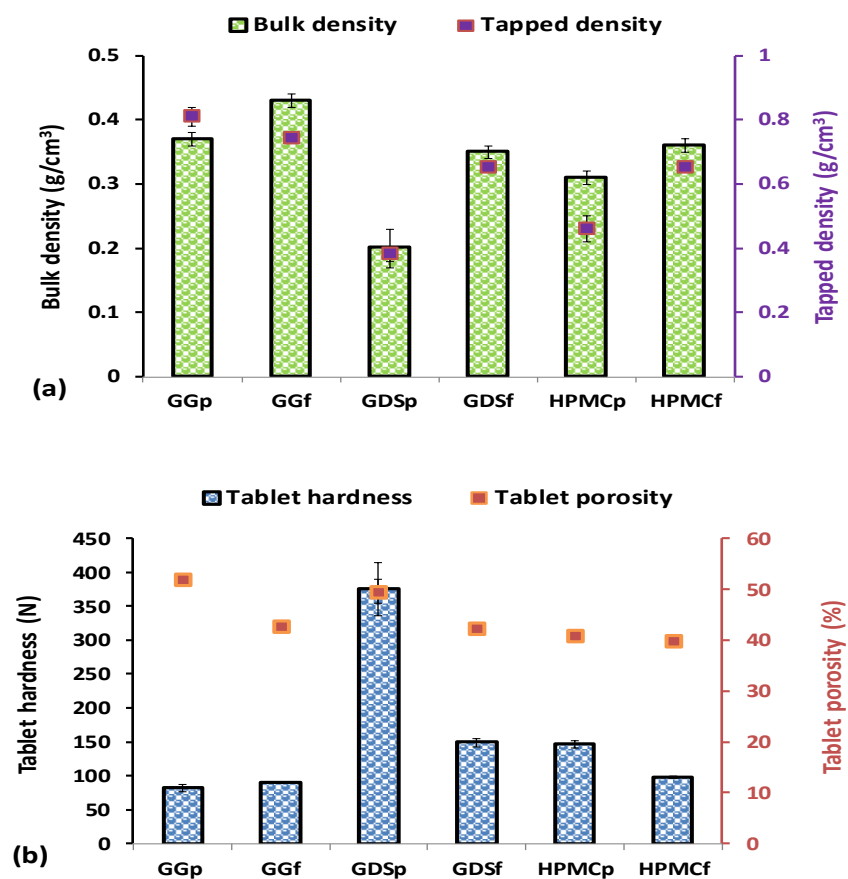


Figure 4

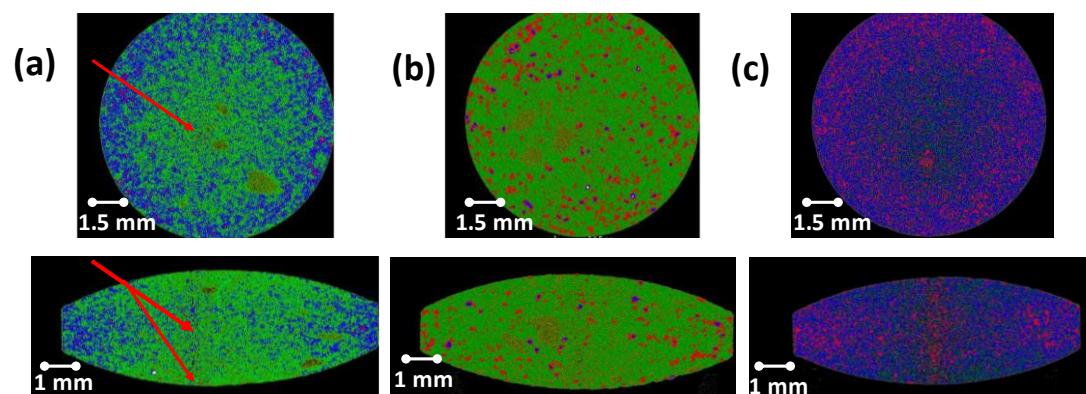


Figure 5

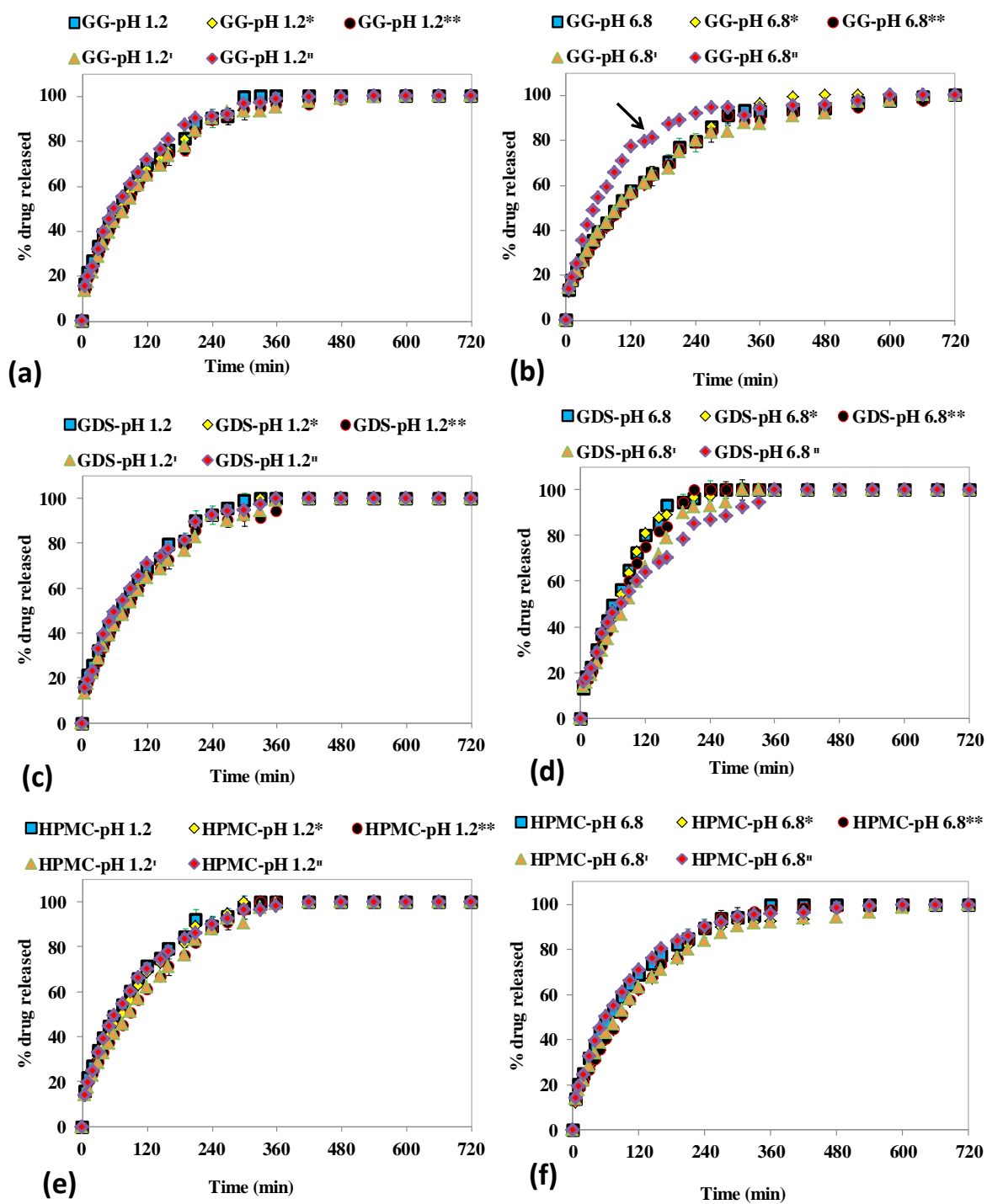


Figure 6

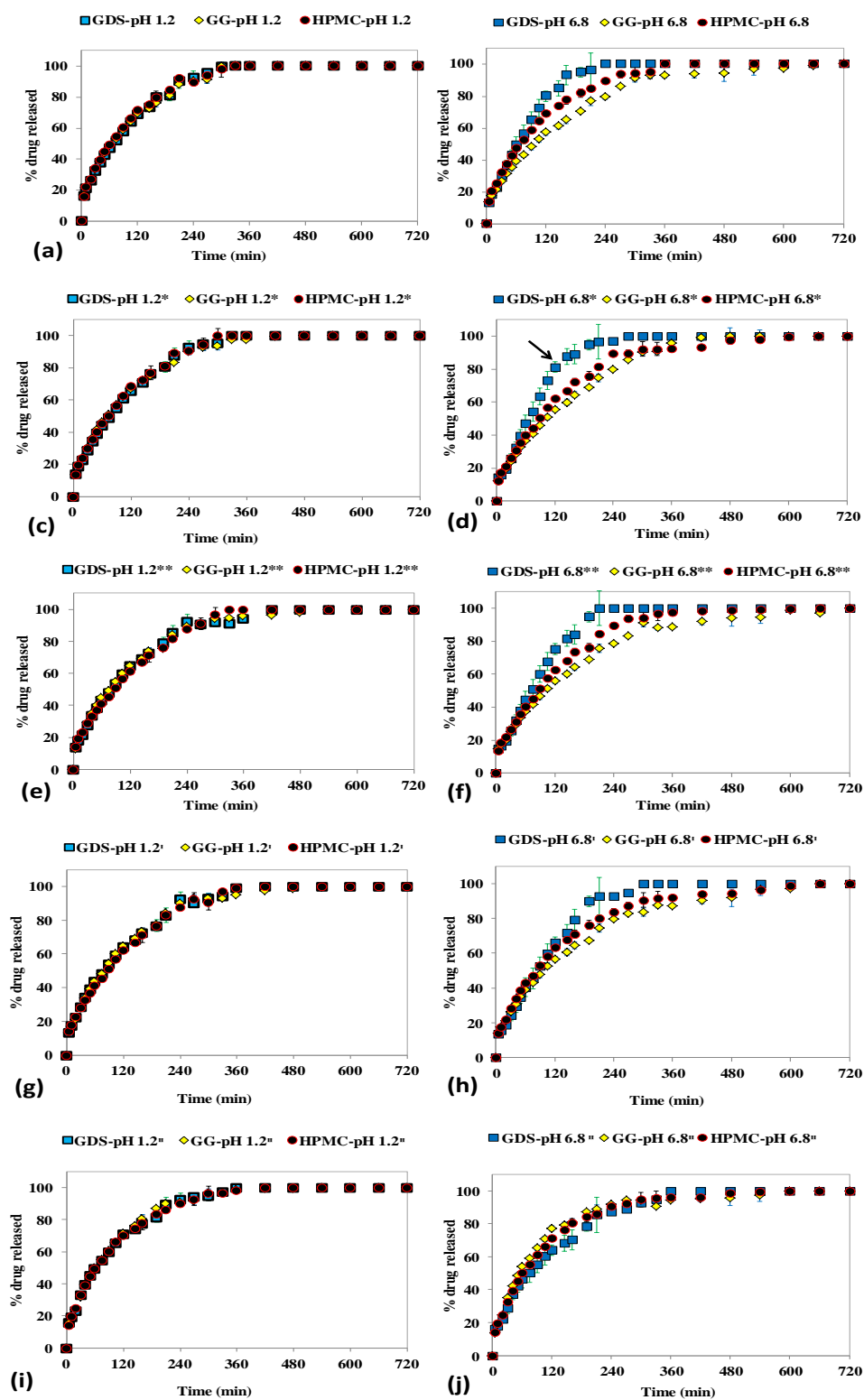


Figure 7



Figure 8



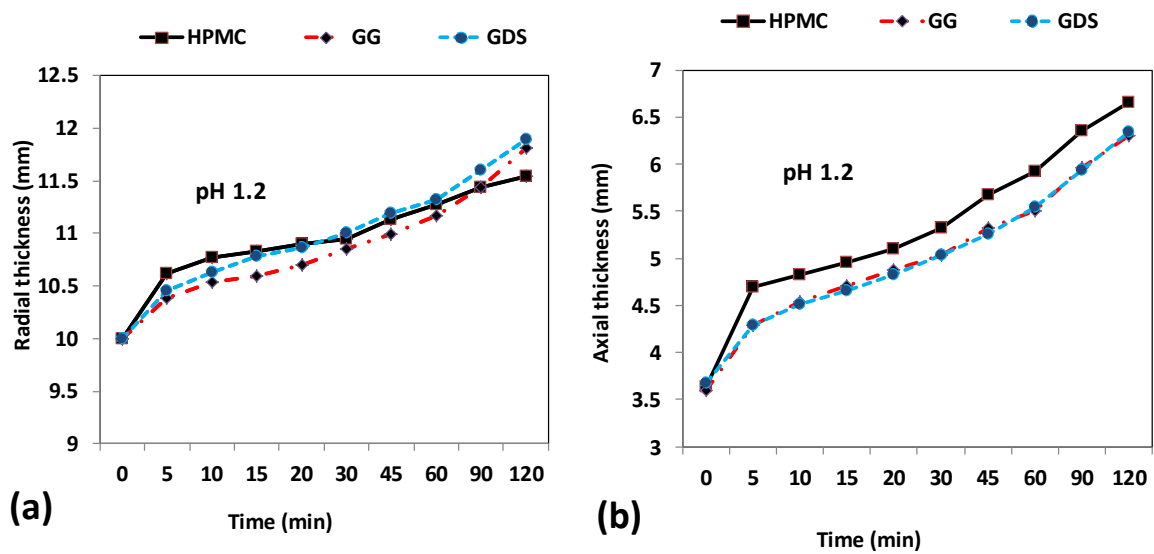


Figure 9

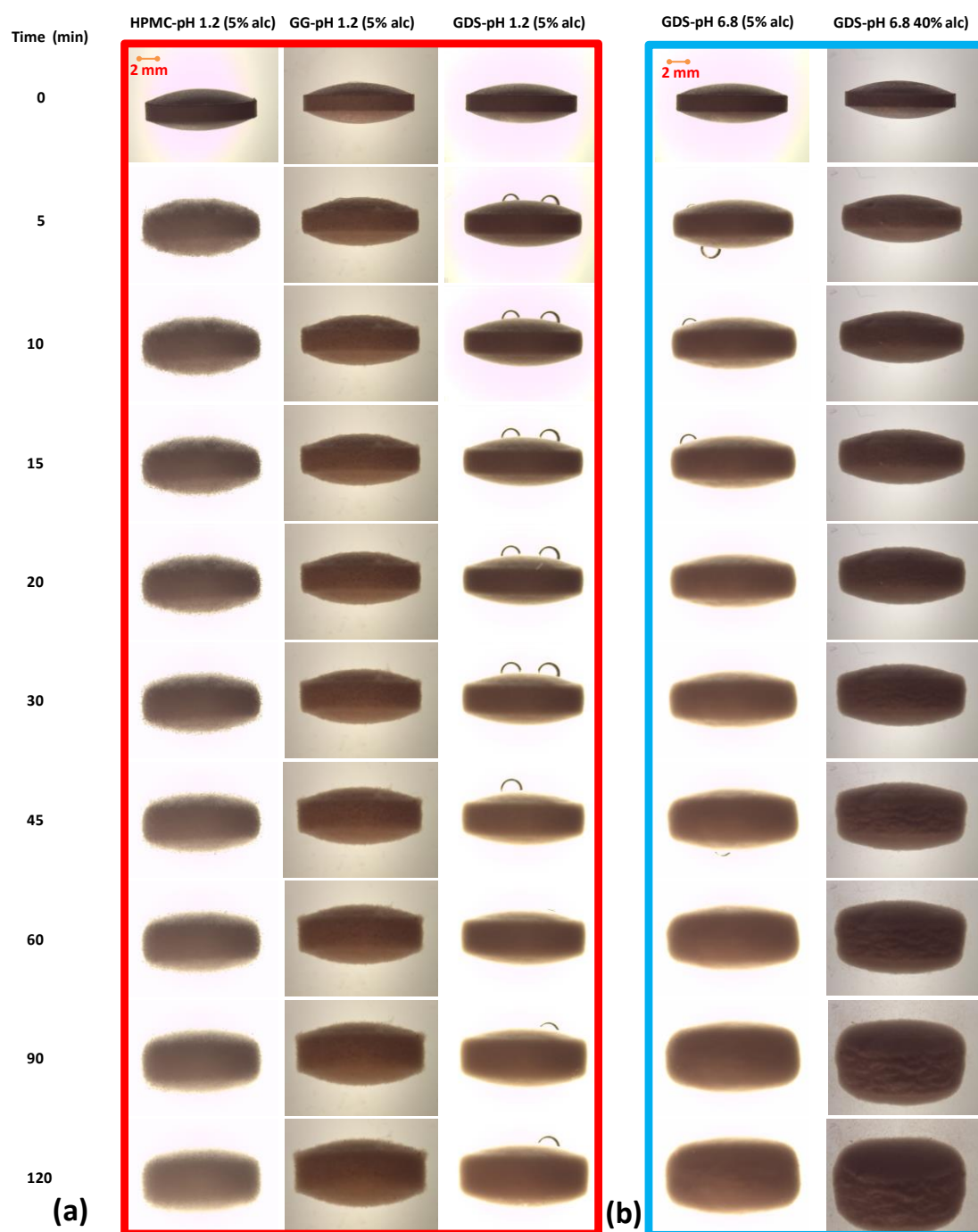


Figure 10

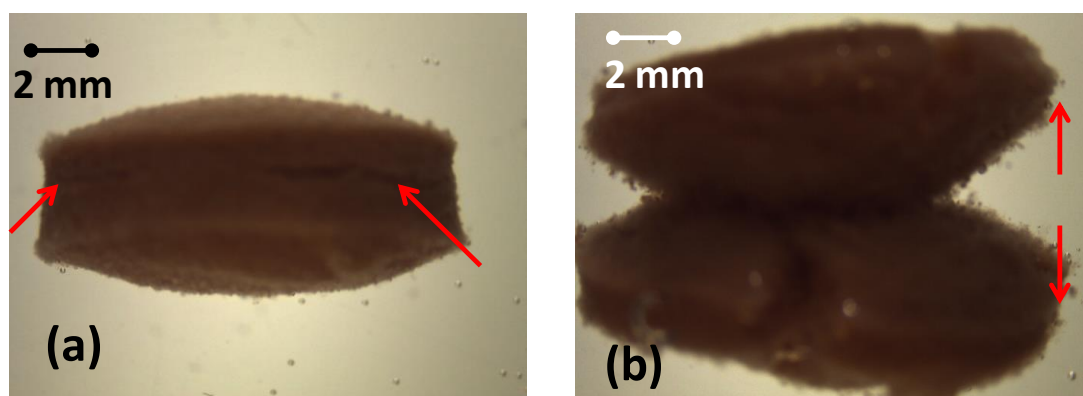


Figure 11