Hydro-alcoholic media effects on theophylline release from Sesamum polysaccharide gum matrices

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Hydro-alcoholic media effects on theophylline release from Sesamum polysaccharide gum matrices

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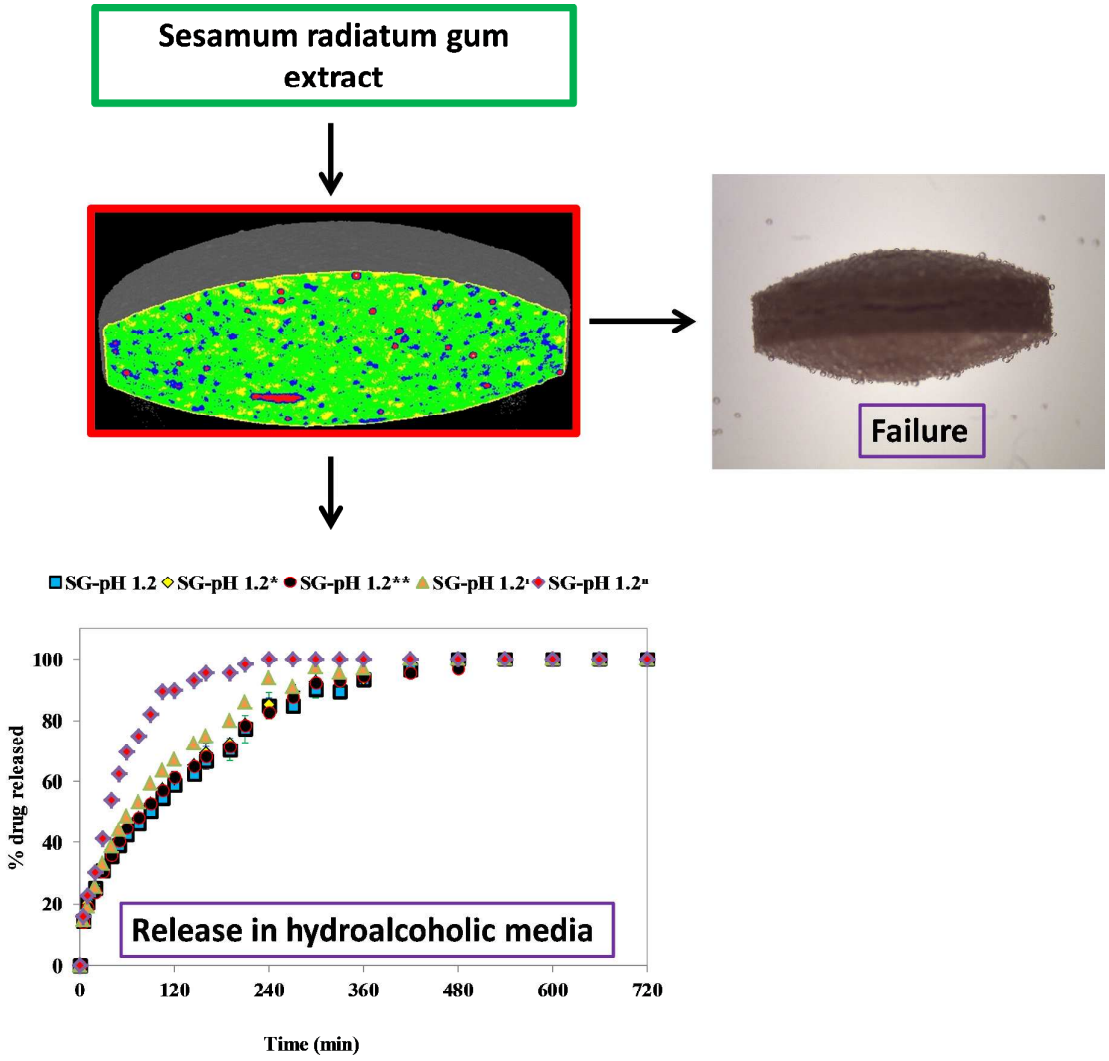
Novelty statement: *X-ray microtomography was used to show uniformity in the natural polymer compacts confirming mixing time used was adequate. However compacts showed failure in high concentrations of hydroalcoholic media.*

Graphical abstract



Abstract

Concomitant ingestion of alcohol and medications can greatly affect drug plasma concentrations as dose dumping or failure may occur as a result of the fact that formulation excipients may not always be resistant to alcohol. In this study, a natural polysaccharide (*Sesamum radiatum* gum) (SG) was extracted, characterised and used to formulate sustained release theophylline compacts to study the effect of varying alcohol concentrations (v/v) in dissolution media on drug release from these compacts. X-ray powder diffraction showed that the extracted gum was amorphous in nature with the powder having excellent compaction properties as observed with its compact being significantly harder than those prepared with pure **hydroxypropyl methyl cellulose (**HPMC**)** K4M. X-ray microtomography showed that the compacts produced were homogenous in nature, however, swelling studies showed failure of the compacts at the highest concentration of absolute ethanol used (40 %v/v). Dissolution studies showed similarity at all levels of alcohol tested (f_2 = 57-91) in simulated gastric (0.1N HCl, pH 1.2) and intestinal fluids (phosphate buffer, pH 6.8) for the HPMC compacts whereas dissimilarity only occurred for the SG compacts at the highest alcohol concentration in both media (f_2 = 35). The suitability of SG as a matrix former that can resist alcoholic effects therefore makes it suitable as an alternative polymer with wider applications for drug delivery.

K***eywords*****:** HPMC K4M, native sesamum gum, matrix tablets, theophylline, hydro-alcoholic, rheology

1. Introduction

Polysaccharides are hydrophilic materials, which hydrate and swell when in contact with water [1]. This makes them good candidates and when in contact with water they hydrate and swell. This property makes them good candidates in the formulation of solid oral dosage forms [1] and has increased the focus of scientific research into the use of these materials in the design of oral controlled release dosage forms [2–4]. The release of pharmaceutical actives from matrices of these materials is controlled by swelling and/or erosion of the matrices [2-4]. Drug formulations in the form of tablets or capsules can be made up of well over 30% polymers and a result changes in the material properties of these polymers under varying conditions in the gastrointestinal (GI) tract may have serious consequences of drug release from the matrices. This has made it important to evaluate the behaviour of polysaccharide matrices in harsh conditions that can be experienced in the GI tract. One of such conditions is the effect of alcohol intake on matrices in the gut. It has been reported that if a large volume of strong alcohol such as whisky/vodka is ingested in the fasted state or fed state there is a rather minor dilution or the dilution is dependent on the volume swallowed. Therefore if a medication is administered before, during and after alcohol consumption it may be exposed to varying concentrations of alcohol [5].

Alcohol-induced dose dumping is a major challenge in the pharmaceutical development of drugs especially those that have a narrow therapeutic index and controlled release formulations. This is due to the fact that these controlled release formulations generally contain higher drug doses than immediate release formulations since the drug content is intended to be released at a pre-programmed rate over a long period of time [6]. It is therefore important to be able to identify polymers or excipients that are alcohol-resistant in order to be able to include them in alcohol resistant pharmaceutical formulations. The oral administration of a dose dumping susceptible formulation with alcohol affects the release

regulating barriers of the formulation which could result in an overdose, escalation of pharmacological or side effects and in the worst case scenario death depending on the drug administered [7]. This is apart from the physiological effect of alcohol consumption which may prolong the gastric emptying rate and onset of drug absorption depending on the calorific content of the alcoholic beverage [8, 9]. A study carried out in 2016 in Great Britain reported that 58 % of adults consumed alcohol at least once in the week before they were interviewed. 27 % of the respondents "binge-drank" (consuming more than 8 or 6 units of alcohol for men and women respectively or 6 units) on their heaviest day of drinking [7]. This shows the increased likelihood of concomitant administration of medications with alcohol or presence of high concentrations of alcohol in the stomach when medications are consumed.

These investigations have become relevant in light of the withdrawal of Palladone® an extended-release once-a-day capsule of hydromorphone-HCl, from the market in 2005, after clinical testing showed subjects who took the product with alcohol had increased levels of the drug in their blood. The drug pellets were made from ethylcellulose, ammonia methacrylate copolymer type B and stearyl alcohol [10]. Informing patients not to consume alcohol whilst on medication is generally not considered an appropriate means of addressing a formulation interaction with alcohol especially patients on long-term medications; therefore it is imperative to study the effect of alcohol on formulations already in the market and to design formulations that are alcohol-resistant. Some authors have evaluated the effect of alcohol on the release of drugs such as aspirin, felodipine, glicazide, metformin hydrochloride and theophylline from matrix tablets [11] or pellets [6,12,13] and found the release rate increased and release kinetics changed with increasing alcohol content in the dissolution media [14–16]. Generally, if drug release is controlled by a polymer soluble in hydro-alcoholic solutions - similar to what is observed in the stomach after consumption of alcohol, drug release may

be rapid instead of being controlled for a significant length of time. This fast release can occur in drug reservoirs, which are surrounded by release-rate controlling polymeric films, as well as drug matrix systems, where the drug is incorporated within the polymeric matrix [17].The effect of alcohol on drug release from HPMC matrices have also been investigated and several authors have given contrasting results with one study stating that the presence of alcohol had moderate effects on *in vitro* drug release [15] while the other study demonstrated that there was a significant increase in aspirin release rate in the presence of high alcohol concentrations [14]. Therefore, it is becoming increasingly important to study the effect of alcohol of polymers, which are or have the potential to be used in pharmaceutical formulations.

Gum from the leaves of *Sesamum indicum* have been evaluated as a binder in paracetamol tablets [18] and as matrix former in tablet formulations [19]. In addition, the binding properties of gum [20] extracted from its closest specie - *Sesamum radiatum* and its matrices has been reported [21]. The structural properties of *Sesamum radiatum* gum (SG) has been elucidated and it showed that the gum from the leaves of this plant is a branched glucuronomannan [22]. Furthermore, SG demonstrated similar controlled release properties to HPMC in theophylline matrices. Therefore in this study, matrix tablets of SG containing theophylline as a model drug were evaluated to study the effect of alcohol on these matrix systems relative to HPMC. 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 [23-25]. Theophylline is a bronchodilator and is a partially water-soluble drug with its absorption being affected by food intake [26,27]. *In-vitro* drug release was investigated in hydro-alcoholic media solutions containing 5 – 40 % ethanol in acidic media (pH 1.2) or phosphate buffer (pH 6.8). The different alcohol concentrations represent the different alcoholic drinks usually

consumed with 5 % representative of beer, 20 % for mixed drinks and 40 % for hard liquor [28,29]. The effect of hydration and gel formation from their matrices in the hydro-alcoholic solutions were studied and rheological experiments were also conducted to ascertain the influence of the various hydro-alcoholic media on the gel layer produced from these polysaccharides.

2. Materials and Methods

2.1 Materials

Methocel (HPMC K4M) was a kind gift from Colorcon (UK). Lactose monohydrate (FlowLac® 100) was a kind gift from Meggle (Germany). Magnesium stearate obtained from Merck (Germany). Anhydrous theophylline was obtained from TCI Chemicals (Europe). Potassium chloride, hydrochloric acid, potassium phosphate monobasic sodium hydroxide, absolute ethanol were obtained from Fisher Scientific (UK). Absolute ethanol (Fisher Scientific, UK) was used to produce the hydro-alcoholic solutions in 5–40 % v/v with either 0.1N HCl (pH 1.2) or phosphate buffer (pH 6.8). Native SG was extracted in our laboratory as previously reported [22].

2.2 Extraction and characterisation of SG

2.2.1 Extraction of SG

To extract the mucilage, 1000 g of *Sesamum radiatum* leaves was macerated in 7.5 L of deionized water containing 0.1 %w/v sodium metabisulphite for 30 min at room temperature. The mucilage was filtered from the leaves using a muslin cloth and thereafter precipitated with 96 % ethanol. The precipitate was filtered and oven dried at 50 °C for 24 hours. The dried SG was size reduced to a particle size of < 200 µm using a sieve shaker and stored in

sealed plastic envelope before its use as a matrix former in the tablet formulations. All characterisations and release studies were conducted with the same batch of SG.

2.2.3 *Thermal Analysis*

Thermogravimetric analysis (TGA**)** measurements were carried out using a Mettler-Toledo TGA (Mettler-Toledo Ltd, UK) under nitrogen atmosphere at flow rate of 50 cm^3 min^{-1} with 20 ^oC min^{-1} heating rate in the temperature range of 25 - 900 ^oC using 70 µl Aluminium oxide crucibles. **Differential scanning calorimetry (**DSC**)** measurements were carried out using a Mettler-Toledo DSC (Mettler-Toledo Ltd, UK) under nitrogen atmosphere at flow rate of 50 cm^3 min^{-1} with 20 ^oC min^{-1} heating rate in the temperature range of 0 ^oC to 600 ^oC using 40 µl Aluminium pans.

2.2.4 *X-ray powder diffraction (XRPD)*

X-ray diffractometry was performed on a Bruker D2 Phaser (Bruker, UK) using a modified method reported by Laity et al. [30]. The samples were packed tightly in a circular aluminium cell and scanned in Bragg–Brentano geometry over a scattering angle range from 5 to 100°, in 0.02° steps at 1.5° min^{-1}. The sealed microfocus generator operated at at 40 kV and 30 mA.

2.3 *Rheological measurements*

Samples of SGp and HPMCp were each weighed and dispersed in different media - 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) to a final concentration of 2 % w/v. The samples were stored overnight under constant agitation at room temperature (~ 22 °C) to ensure full

hydration of polymer. Viscosity measurements of the samples were performed at 37 °C across shear rates ranging from 1 s^{-1} - 1000 s^{-1} for 5 min using a Bohlin Gemini rheometer fitted with a 55 mm cone and plate geometry with gap of 70 mm.

2.4 Drug saturated solubility

A saturated solution of theophylline was prepared by adding an excess of the drug to 10 ml samples of Media A-D (as described in section 2.3). This suspension was then shaken for 24 h at 37 ± 0.5 °C, centrifuged and filtered. The concentration of theophylline was determined spectrophotometrically at 270 nm.

2.5 Tablet formulation, compression, hardness and dimensions

Powder formulation blends (SGf and HPMCf) were prepared by mixing the appropriate amounts of ingredients as shown in Table 1 (insert Table 1 near here) for 10 min in a Turbula® (Type T2C, Switzerland) blender.

2.5.1 Bulk, tapped and true density of pure polymers and formulation blends

Bulk and tapped densities of the pure polymers (SGp and HPMCp) 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 then tapped until the volume of powder was constant. This represents the tapped volume of the 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.

2.5.2 Tablet compaction and porosity

Round convex tablets of pure polymers and powder blends with a diameter of 10.0 mm and a target weight of 250 mg were prepared using a single-punch tableting machine (Model MTCM-1, Globe Pharma US) compressed at 125.7 MPa. The compressed tablets were allowed to recover for 24 h, thereupon the tensile strength 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. Porosity was determined according to Equation 1.

$$Tablet\ porosity = \left[1 - \left[\frac{tablet\ weight\ /\ tablet\ volume}{true\ density\ of\ powder}\right]\right] X100 \qquad (1)\ [31]$$

2.6 X-ray microtomography (XμT) of compacted formulations

SG and HPMC compacts were examined by XμT, (Nikon XT H 225, Nikon Corp. Tokyo, Japan), using a tungsten target, with 90 kV accelerating voltage and 80 μA 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 [30].

2.7 In vitro release studies

Drug release was carried out using an automated USP dissolution apparatus II (paddle method) and the dissolution media was 900 mL 0.1 N HCl (pH 1.2) or phosphate buffer (pH 6.8) with ethanol concentrations of 0 to 40 (%v/v). The media was equilibrated to 37 ± 0.5 °C

with a paddle stirring speed of 100 rpm. Samples were withdrawn at selected time intervals and analysed by a UV spectrophotometry at 272 nm.

2.7.1 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 [32,33]. 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,* was also calculated [33].

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

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 dissolved at time *t.*

2.7.2 Similarity factor

Similarity between the drug release profiles was determined using similarity factor f_2 [34]

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

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 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 [31,35].

2.7.3 Kinetics of drug release

Drug release kinetics was analysed using Korsmeyer-Peppas equation as detailed in Siepmann & Peppas [36]. For cylinders, which were the shape of the tablet matrices made in the present study, n values of up to 0.45 suggest Fickian diffusion, and values above 0.89 suggest Case-II transport. A value between these two suggests anomalous transport occurring as reported in numerous studies [16,36–38].

2.8 Tablet swelling

Swelling dynamics were investigated using a digital camera (Leica ICC50HD) linked to image analysis software. A tablet compact was placed vertically in a small plastic Petri dish and 70 ml media was added at ambient temperature [16]. The petri dish was placed in a plane with a tungsten lamp light source, and the camera, equipped with macro lens was placed above to obtain images at intervals up to 120 min. The light beam direction was regulated to generate a high contrast image, with the tablet completely black in a bright background. Swelling was studied 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).

3. Results and Discussion

3.1 Characterization of SG

The diffraction pattern of SGp (Figure 1) (insert Figure 1 near here) showed it was completely amorphous in nature with the presence of the typical broad halo [39]. The thermal behaviour according to the primary thermograms and derivative thermograms show that heating at a rate of 10 ^{o}C min^{-1} from 25 ^{o}C to 600 ^{o}C under nitrogen atmosphere at flow rate of 50 cm^{3} min^{-1} resulted in two mass loss events for SG (Figure 2a) (insert Figure 2 near here). The minor weight loss of ~ 11.5% between 50 to 140 ^{o}C as observed in both the TGA and DSC traces (Figure 2b) is attributed to the loss of adsorbed and structural water, or due to desorption of moisture as hydrogen bound water to the polysaccharide structure [40,41]. The final weight loss of ~ 54.6% observed in the TGA trace has been attributed to the polysaccharide decomposition [42,43] which occurred between 251^{o}C and 302.3 ^{o}C and was also observed in the DSC trace. The thermal scission of carboxylate or carboxylic acid groups will result in evolution of CO_2 from the corresponding carbohydrate backbone and may be a probable mechanism for the thermal transitions observed [42].

3.2 Rheological measurements

All samples of both HPMC and SG in the media tested with or without ethanol exhibited shear thinning or pseudoplastic behaviour possibly due to the fact that the polymers form a viscous solution by polymer entanglement [44] (insert Figure 3 near here). The viscosity of HPMC was dependent on alcohol concentration as it slightly increased with increasing ethanol concentration. This could be due to the lower proportion of water and dielectric constant of the hydro-alcoholic mixture, which led to the formation of new bonds/structures between the polymer molecules and the solvating media [45]. This trend was not observed in SG, as the viscosity of SG reduced with increasing alcohol concentration. Overall, HPMC was relatively more viscous that SG in all the media tested.

3.3 Physical properties of formulation and formulation blends

Figure 4a shows that the hardness and porosities of the pure SG (SGp) and formulated SG (SGf) matrices to be higher than that of the pure (HPMCp) and formulated HPMC (HPMCf). (insert Figure 4 near here). This suggests that SGp is a highly compactible polymer as it formed the hardest compacts relative to HPMCp matrices [21,22]. In addition, there was a reduction in the porosity, and hardness of formulated compacts (SGf and HPMCf) relative to their pure polymers. This reduction was more significant for SG than was observed for HPMC (Figure 4a). There was a significant decrease in the true density for the formulated blend of SGf from its pure polymer (from 1.80 g/cm^3 to 1.59 g/cm^3). However there was an increase in the true density of HPMC formulated blends HPMCf (1.45 g/cm^3) relative to that of the pure polymer HPMCp (1.36 g/cm^3). Therefore, for SG as bulk and tapped densities increased on addition of the excipients, there were reductions in the true density, hardness, and porosity of the samples while for HPMC as the bulk, true and tapped densities increased there were reductions in the hardness and porosity of the samples on addition of the formulation excipients (Figure 4a and 4b). The X-ray microtomographic images (this technique is based on the differential absorbance of X-rays between materials of differing electron density [30] of compacted formulations of SG and HPMC were reconstructed are presented in Figure 5 (insert Figure 5 near here). The sagittal and diametric cross-sectional images from the formulation revealed differences in the distribution of the constituents of the formulations. Although difficult to determine the constituents of the HPMC mix due to the materials having similar densities, it was observed that the mixing time was adequate to produce a homogenous mix.

3.4 Performance of SG matrices under aqueous and hydro-alcoholic media

3.4.1. Acidic media

The influence of aqueous and hydro-alcoholic media on theophylline release from SG and HPMC matrices is depicted in Figure 6 (insert Figure 6 near here). The profiles show that none of the matrices exhibited any initial burst release normally attributed to the rapid dissolution of the drug from the surface prior to gel layer formation. Hydrophilic matrices form a gel layer on contact with the aqueous media as a result of polymer transition from the glass state to a more hydrated rubbery state [28,46]. The physical properties and composition of the gel layer controls the rate of entry of media into the matrices; drug diffusion rate and kinetics and matrix erosion [15,47]. The HPMC gel layer reduces the permeation of dissolution media into the slightly less porous polymer matrix (Figure 4), so drug release is sustained. The inclusion of varying amounts of alcohol up to 40% v/v in acidic media had no significant effect on theophylline release from the HPMC matrices as they all had similar release profiles (f_2 = 57-91, Table 2) (Insert Table 2 near here) using drug release from pH 1.2 containing no ethanol as the standard. The solubility of theophylline at pH 1.2 (13.12 ± 0.13 mg/mL) shows more than a 2-fold increase upon addition of 40%v/v absolute ethanol (28.18 ± 0.14 mg/mL). This implies that if the drug release was dependent by drug solubility in dissolution media, the release rate may be faster in the presence of alcohol [15]. However, this was not observed in the HPMC matrices studied and was in contrast to results by other researchers that observed that drug release from HPMC matrices was accelerated based on the proportion of the drug solubility in the medium [14]. This is in agreement to a previous study which observed that despite the increase in theophylline solubility at high alcohol levels, there was no significant effect on its release from tablets in acidic media containing up to 0-40% v/v alcohol [16]. Drug release from SG matrices showed similarity in acidic media containing up to 20%v/v alcohol but at 40%v/v, theophylline release was significantly faster (indicated by black arrow, Figure 6c) than at lower ethanol concentrations (f_2 = 32, Table 2).

As concentration of ethanol in dissolution media increased due to the slightly more porous matrix and a probably compromised gel layer, more dissolution media was able to penetrate /permeate into the compacts and this in addition to the higher solubility of theophylline in ethanol led to a faster drug release. This is similar to a previous study where aspirin release was accelerated in hydro-alcoholic media containing 40% v/v ethanol [14]. The presence of the high concentration of alcohol may have prevented the formation or led to the formation of a thinner gel layer or may have compromised the integrity of the matrix leading to the observed faster release at this concentration [47]. This is in agreement with the rheology results (Figure 3) where it was observed that there was a decrease in viscosity of SG with increasing alcohol content, which will therefore allow easier diffusion of media in and out of the matrices. This demonstrates that the increase in drug release is not only due to the drug properties but also due to the diminished retardant properties of the polymer in the presence of alcohol [48].

3.4.2 Alkaline media

Drug release profiles of HPMC obtained in pure phosphate buffer and its alcoholic mixtures tested showed similarity for all the samples with no significant differences in drug release in this media relative to the corresponding acidic mixtures (Figure 6b). SG matrices showed a similar trend to what was observed in acidic media with similarity up to 20% v/v ethanol but dissimilarity (f_2 = 35) at 40% v/v ethanol (indicated by red arrow in Figure 6d).

The T_{50}, T_{90}, DE, MDT and MDR values in hydro-alcoholic acidic /alkaline media containing 40% ethanol (Table 2) (insert Table 2 near here) for the SG matrices show significantly different values when compared to release in hydro-alcoholic acidic /alkaline media containing 0-20%v/v ethanol. Therefore, at high alcohol concentrations (40% v/v) there may be an increased risk of dose dumping in SG matrices depending on when gastric emptying

may be in the fed or fasted stomach. It is important to state that in the human body, formulations administered shortly before or after alcohol consumption are unlikely to be exposed to GI fluids containing 40% v/v alcohol for a long period of time because of the rapid absorption of alcohol that occurs in the tract [15,49].

3.4.3 Release kinetics

Majority of the matrices exhibited anomalous transport with the release exponent, n = 0.45 - 0.57 (Table 2) with a few exceptions. The presence of increasing concentration of alcohol in the dissolution media did not affect the drug release mechanism from both types of matrices. The exceptions had n values ranging between 0.43 and 0.44, values which even though demonstrated Fickian diffusion kinetics did not vary significantly from the others.

3.5 Swelling studies on SG matrices

The swelling profiles of the compacts were assessed in the various hydro-alcoholic media (Media A-D) and the images in Figure 7 show the impact of hydration on the SG and HPMC matrices in pure acidic media (insert Figure 7 near here). It was observed that the swelling of both HPMC and SG matrices is anisotropic as they both increased in the axial and radial dimensions over time however axial swelling was greater than the radial swelling similar to reports by other researchers [14,16,50]. This is due to the flattening of the particles in the axial direction during the direct compression of the compacts [51]. The images showed swelling to be greater for the HPMC compacts axially with radial swelling being quite similar (Figure 8) (insert Figure 8 near here) in acidic media. HPMC swelling is due to the relaxation of polymer chains and it was observed that the HPMC matric retained its integrity when placed in the hydro-alcoholic solutions. This is similar to the observation by other researchers who observed that a high alcohol concentration up to 40% had little effect on the textural behaviour of HPMC compacts [47]. In HPMC, there is the formation of a release rate

controlling gel layer, which may be accompanied by polymer erosion [23] and this occurs in hydro-alcoholic media (5-40%) [47] even though the initial swelling capacity at 40% was diminished. It was interesting to note that there was failure in SG matrices where the highest alcohol concentration was used. In the acidic media, this occurred at the 2 h time point (Figure 9a) (insert Figure 9 near here), whereas in the alkaline media, failure occurred from 10 min onwards (Figure 9b). This may be due to the presence of the inorganic ions present in the dissolution media which may have contributed to the "salting out" of the polymer eventually resulting in failure [52]. The failure of the SG compacts in this high alcoholic media (40%) could have also contributed to the faster drug release observed in these media with the media being able to access the core of the tablet, thereby increasing the surface area available for drug diffusion out of the compacts.

4. Conclusion

Sesamum gum polysaccharide was extracted, characterised and evaluated for its drug release properties in different hydro-alcoholic concentrations in acidic and buffer media. SG polymer exhibited excellent compression, compaction and drug release properties comparable to HPMC (K4M). SG retained its hydrated structural integrity and showed resistance to media containing up to 20%v/v ethanol, except at the extreme concentration of 40% v/v ethanol where dissimilarity in the drug release profile was observed. The performance of SG in this study suggests that it can be used as an alternative to HPMC in sustained release formulations providing wider applications in drug delivery for these natural polymers in the developing world.

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Declaration of interest

The authors report no declarations of interest

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excipients for drug delivery, the mechanical properties of pharmaceuticals and excipients and the development of chewing gum delivery systems.

Dr A.M. Smith *is a Reader in Biopolymer Materials. He graduated from Salford University (Biochemical Science) in 1997 before gaining his PhD from Cranfield University. Alan previously worked as a research fellow at the University of Birmingham (School of Dentistry) and Aston University (School of Pharmacy) developing 3D cell scaffolds and polysaccharide based drug delivery systems before joining the University of Huddersfield as a Senior lecturer in 2011. He was promoted to reader in 2016.*

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Table 1: Unit formula for matrix tablets by direct compression

Formulation code	**Theophylline** (mg)	**Native sesamum gum (SG)** (mg)	**HPMC K4M** (mg)	**Lactose** (mg)	**MgSt** (mg)
SG	125	75	-	47.5	2.5
HPMC (K4M)	125	-	75	47.5	2.5

Table 2. Drug dissolution parameters and mechanism of drug release from SG and HPMC tablet matrices in various hydroalcoholic media.

Formulation-media	T_{50} (min)	T_{90} (min)	DE (%)	MDT	MDR	Similarity factor (f2)	RSQ (r2)	Diffusional exponent (n)
SG-pH 1.2	89.0	300.0	82.50	34.04	0.19	-	0.998	0.44
SG-pH 1.2*	81.5	276.0	83.53	35.15	0.20	83.27	0.996	0.45
SG-pH 1.2**	81.5	285.0	82.93	34.28	0.20	85.02	0.995	0.48
SG-pH 1.2[†]	64.0	224.0	86.32	37.65	0.22	59.30	0.994	0.50
SG-pH 1.2[‡]	36.5	124.0	92.82	41.92	0.30	31.59	0.978	0.57
HPMC-pH 1.2	62.0	203.0	87.58	41.61	0.23	-	0.992	0.46
HPMC-pH 1.2*	74.0	220.0	86.83	42.72	0.23	74.00	0.991	0.49
HPMC-pH 1.2**	88.0	264.0	84.90	40.86	0.20	57.01	0.988	0.44
HPMC-pH 1.2[†]	88.0	253.0	84.56	40.41	0.20	56.87	0.988	0.46
HPMC-pH 1.2[‡]	61.0	241.0	86.90	40.17	0.23	91.27	0.991	0.51
SG-pH 6.8	103.0	250.0	83.41	37.75	0.18	-	0.980	0.43
SG-pH 6.8*	99.0	265.0	83.63	39.79	0.18	92.63	0.969	0.45
SG-pH 6.8**	114.0	284.0	80.88	36.42	0.15	71.60	0.958	0.44
SG-pH 6.8[†]	98.5	302.0	82.03	37.92	0.18	92.67	0.972	0.46
SG-pH 6.8[‡]	43.0	152.0	90.71	48.38	0.26	34.61	0.965	0.52
HPMC-pH 6.8	69.0	246.0	86.45	41.44	0.23	-	0.993	0.49
HPMC-pH 6.8*	89.5	244.0	82.82	43.38	0.21	60.44	0.986	0.50
HPMC-pH 6.8**	87.5	242.0	84.46	44.27	0.21	62.48	0.980	0.47
HPMC-pH 6.8[†]	83.0	297.0	82.20	38.67	0.20	66.31	0.984	0.48
HPMC-pH 6.8[‡]	60.0	236.0	86.37	43.41	0.24	81.89	0.989	0.51

Figure captions

Figure 1: XRPD of SGp

Note: SGp is the extracted native polysaccharide gum of sesamum.

Figure 2: Primary thermograms of the major decomposition stage and the derivative thermogram for SGp (a), DSC thermogram of SGp (b).

Figure 3: Viscosity *vs*. shear rate for (a) SG, (b) HPMC.

Note: * indicate media contains 40 % v/v absolute ethanol.

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

Note: SGp is pure sesamum gum, HPMCp is pure hydroxypropyl methylcellulose, SGf is the formulated* sesamum 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 SG (a) and HPMC (b) detailing the homogeneity of the formulation mix.

Figure 6: Effect of theophylline release from SG and HPMC (abbreviated to HP) matrices in pH 1.2 (a, c) and pH 6.8 (b, d).

Note: * is medium containing 5 % v/v absolute ethanol, ** is medium containing 10 % v/v absolute ethanol, ᵻ is medium containing 20 % v/v absolute ethanol and ᴴ is medium containing 40 % v/v absolute ethanol

Figure 7: Effect of time of the hydration of HPMC and SG matrices in pH 1.2 media only

Figure 8: Effect of hydro-alcoholic media on a) radial b) axial thicknesses of HPMC and SG tablet matrices (n = 3)

Figure 9: Cracks indicated by red arrows a) SG after 120 min hydration in 40 %v/v absolute ethanol solution in pH 1.2 b) SG after 10 min hydration in 40 %v/v absolute ethanol solution in pH 6.8)

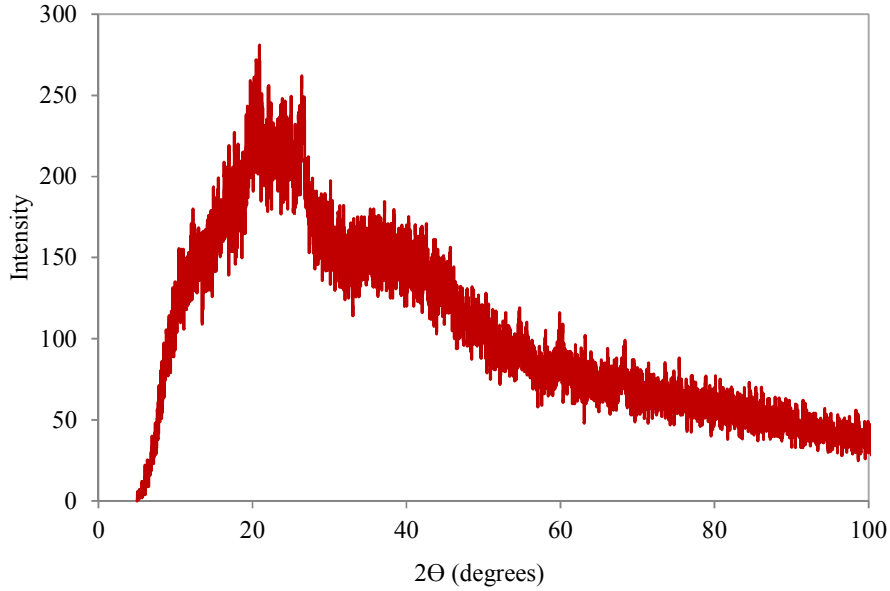


Figure 1

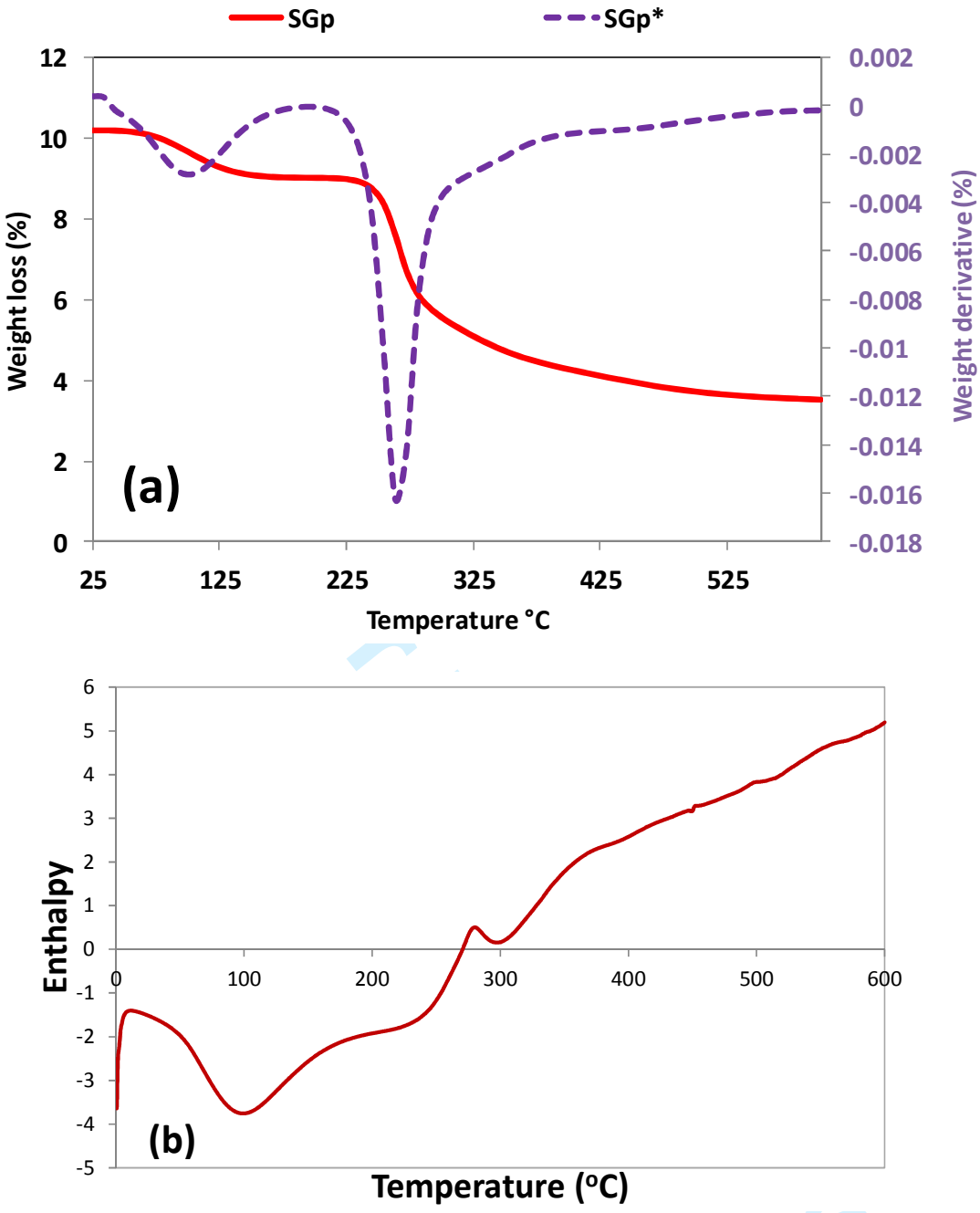
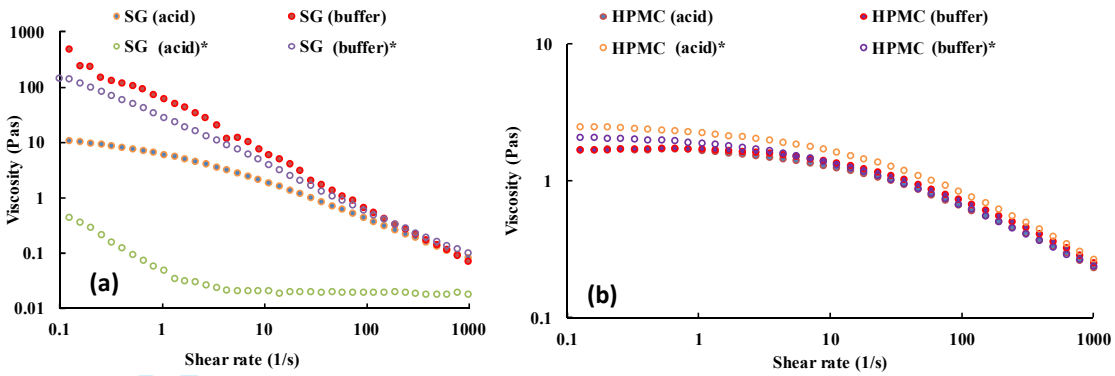

SGp
SGp*
Weight loss (%)
Weight derivative (%)
Temperature °C
(a)
Enthalpy
Temperature (°C)
(b)

Figure 2



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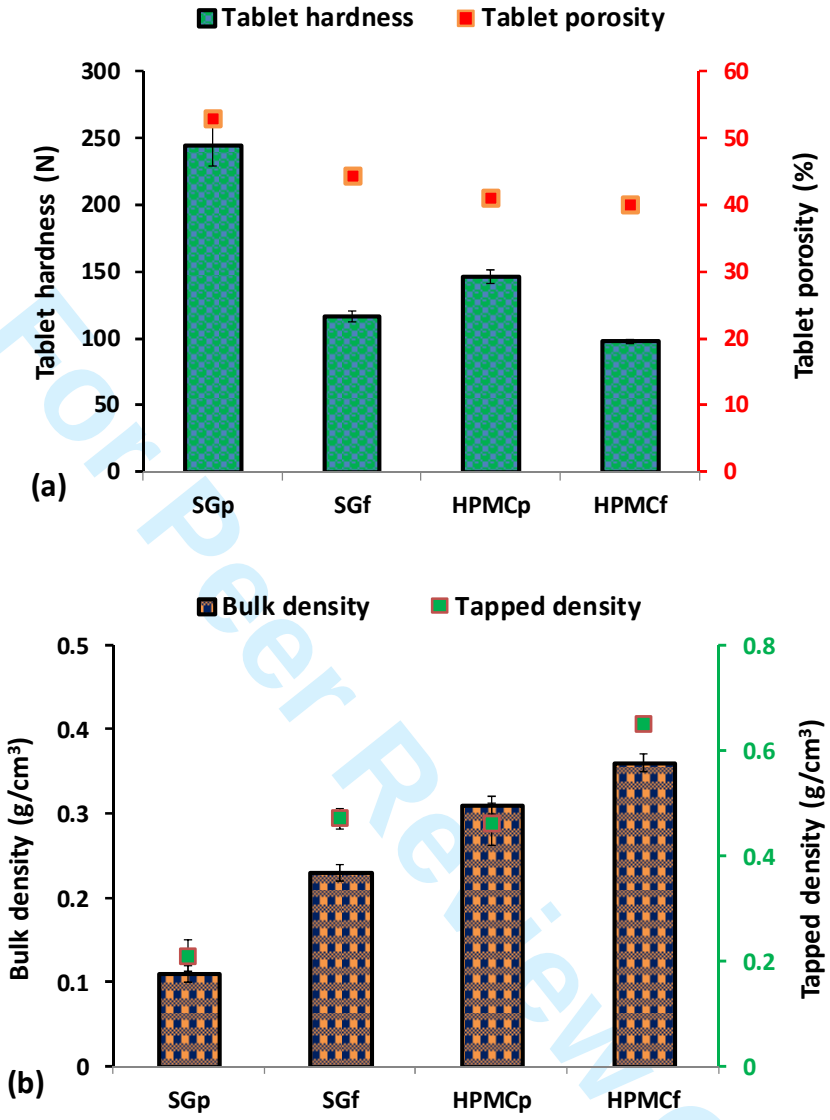

Figure 4

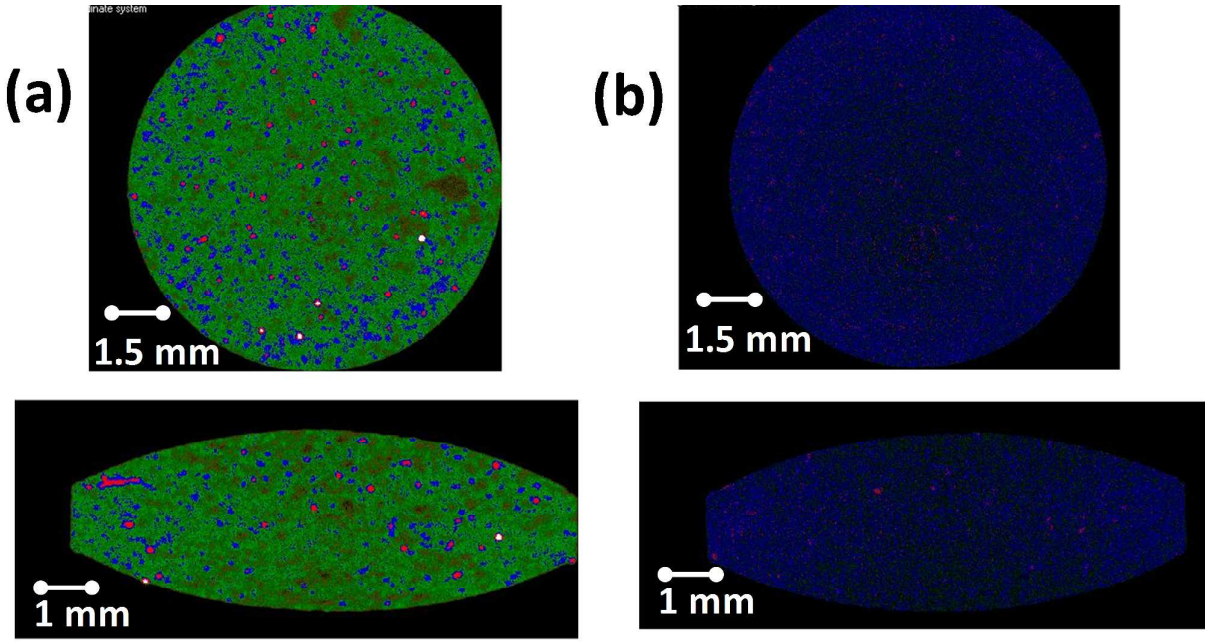

Figure 5

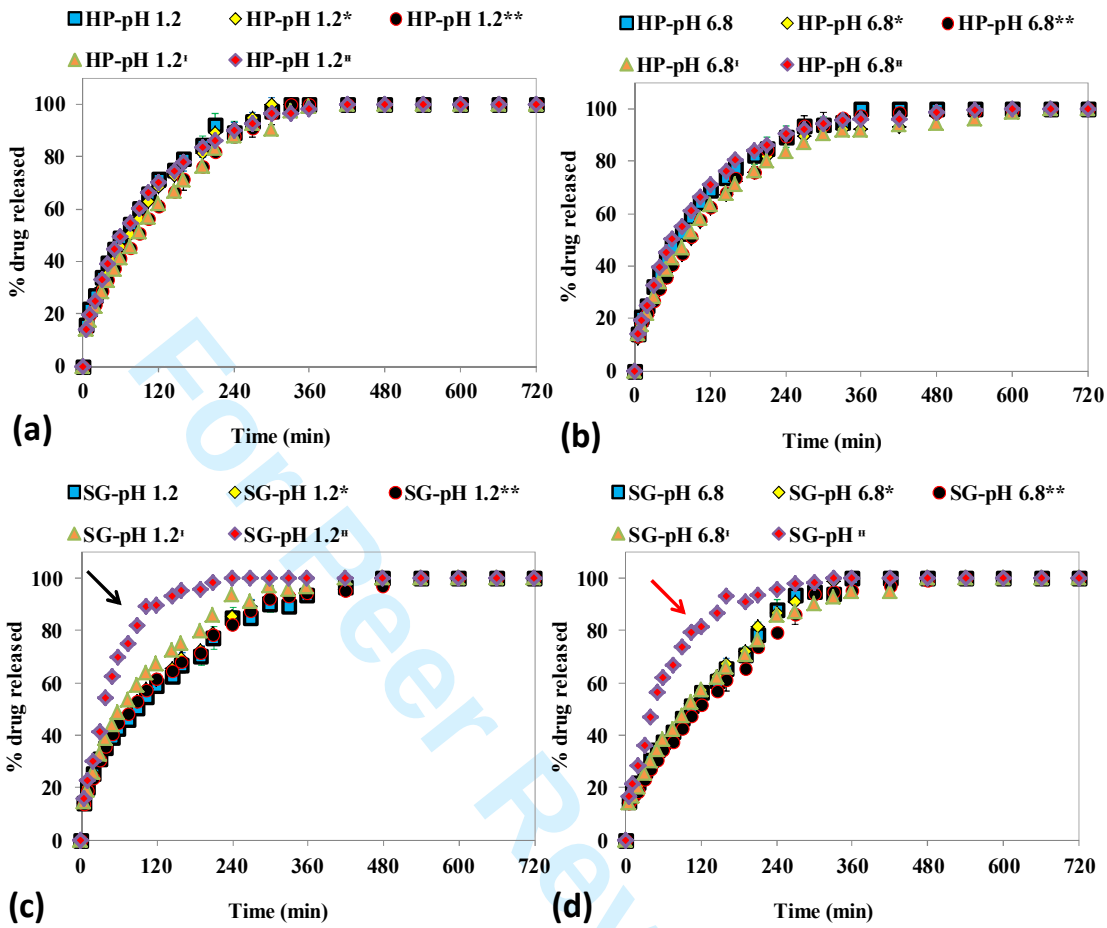

Figure 6

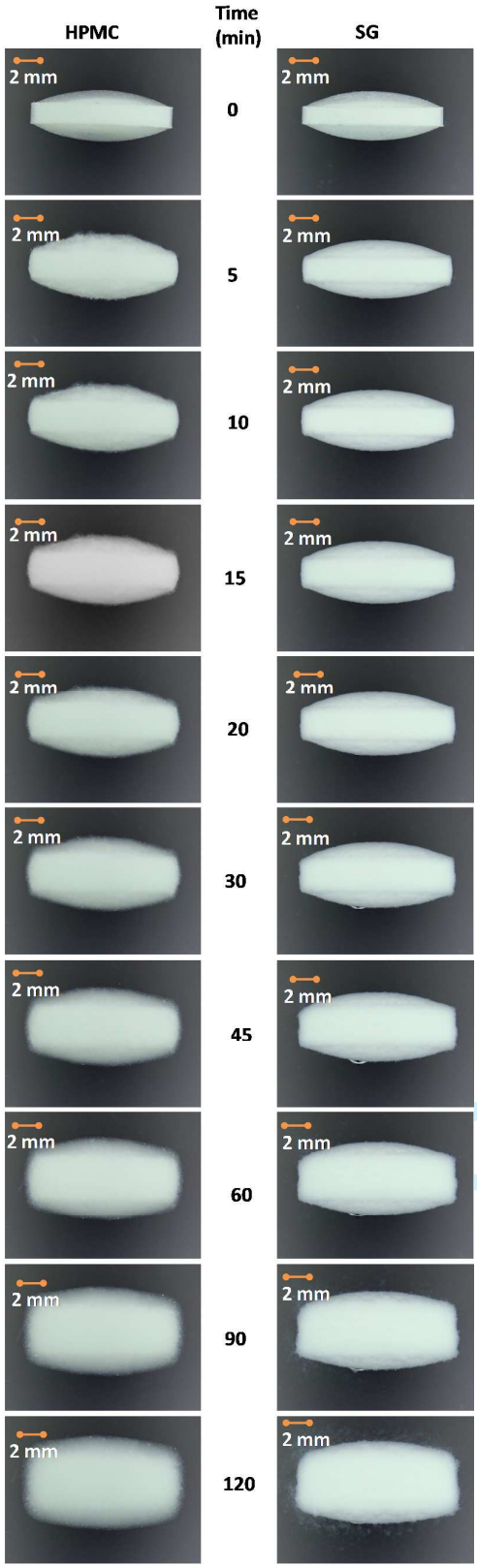

Figure 7

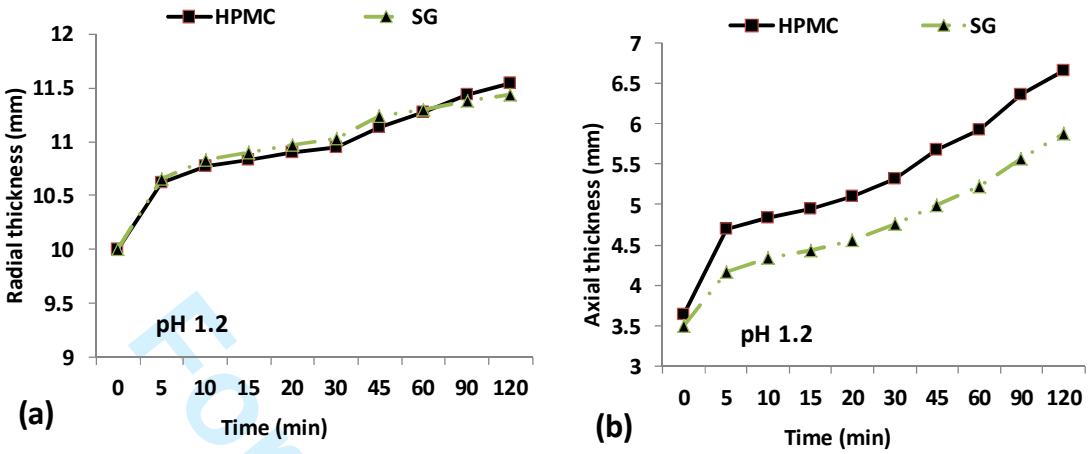

Figure 8

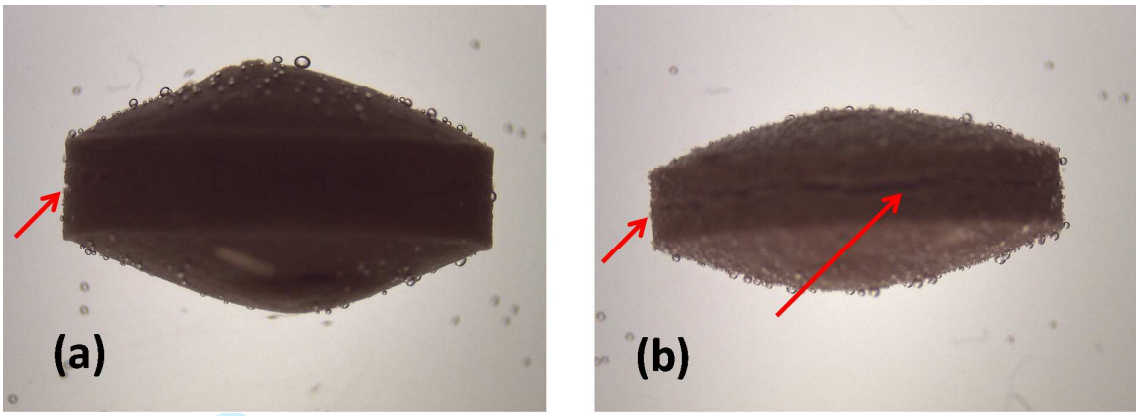

Figure 9