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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, pH 1.2 and pH 6.8 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 pH 1.2, 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 pH 1.2 but with a more rapid release at pH 6.8. GDS may have wider application in reinforcing compacts with relatively low mechanical strength.

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 et al., 2016). 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, 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; Panomsuk et 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

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.

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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 et al., 2001; Nep and Conway, 2011a) and has been evaluated as a pharmaceutical excipient in oral formulations, as a binder or sustained release matrix (Nep and Conway, 2011b), as bioadhesive (Nep and Okafor, 2006; Nep and Conway, 2011c) or as a suspending agent (Nep and 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., 2016). 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 K4 M) 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., 2016).

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

The method of Nep et al. (2016) was adopted without modification. Briefly, the inner stem bark of *G. mollis* was dried and shredded. The material was then macerated in 0.1% sodium metabisulphite for 24 h. 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 h. 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 h. 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 h using a cellulose membrane with molecular weight cut-off at 12,500 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. (2016). 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. (2016).

2.3. Tablet formulation, compression, hardness and dimensions

The pure polymers (GGp, GDSp and HPMC K4 M) 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 pressure 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 K4 M 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

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