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Research Paper

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

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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 K4 M (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.

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; Sujja-areevath 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 and Asare-Addo, 2014; Nokhodchi et al., 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

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

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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 (Akdowa 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®, 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., 2013a,b). 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., 2013a,b, 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., 2013a,b; 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 μm, d_{50} of 78.67 μm, d_{90} of 141.63 μm and d_{99} of 171.10 μm 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 h 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 redispersion 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 h. 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 h. 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 h using a cellulose membrane with molecular weight cut-off at 12500 Da. The material was then precipitated using 2 vol of 95% ethanol followed by a solvent exchange using 1 vol 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 $cm^3\ min^{-1}$ with 10 °C min^{-1} heating rate in the temperature range of 25 °C to 600 °C using 70 μL 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.,