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Regenerated cellulose capsules for controlled drug delivery: Part III. Developing a fabrication method and evaluating extemporaneous utility for controlled-release

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ABSTRACT

In this article, we describe a method to utilize cellulose dissolved in dimethyl sulfoxide and paraformaldehyde solvent system to fabricate two-piece regenerated cellulose hard shell capsules for their potential use as an oral controlled drug delivery a priori vehicle. A systematic evaluation of solution rheology as well as resulting capsule mechanical, visual and thermal analysis was performed to develop a suitable method to repeatedly fabricate RC hard shell capsule halves. Because of the viscoelastic nature of the cellulose solution, a combination of dip-coating and casting method, herein referred to as dip-casting method, was developed. The dip-casting method was formalized by utilizing two-stage 2^2 full factorial design approach in order to determine a suitable approach to fabricate capsules with minimal variability. Thermal annealing is responsible for imparting shape rigidity of the capsules. Proof-of-concept analysis for the utility of these capsules in controlled drug delivery was performed by evaluating the release of KCl from them as well as from commercially available USP equivalent formulations. Release of KCl from cellulose capsules was comparable to extended release capsule formulation.

1. Introduction

Capsules are regarded as the oldest and among the most popular dosing platforms for oral drug delivery. Modern two-piece hard shell capsules are primarily manufactured from gelatin and hydroxylpropyl methylcellulose (HPMC). Their popularity stems from better patient compliance and the ease of commercial process scale-up (Podczeck and Jones, 2004). For controlled drug delivery from the capsules, the encapsulated formulation typically comprises multi-particulates or mini-tablets that are processed *a priori* using a suitable coating unit operation in order to apply a polymer-based rate-limiting film/membrane on them. The commonly utilized gelain and HMPC shells do not offer any resistance to drug release as they are water soluble under physiological conditions. Hence, even though the encapsulation approach provides an alternative pathway for better patient compliance of controlled-release dosage form, the cost-effectiveness of the commercial scale manufacturing process of such an encapsulated controlled release drug product is eclipsed by the increased complexity in the number of unit operations involved in obtaining a suitable core formulation that is encapsulated within these shells.

In order to reduce manufacturing costs of capsule-based controlled release drug products, it would be quintessential to utilize a capsule shell that would inherently control the release of the solute from the capsule core. Ideally, the encapsulating formulation would comprise a dry powder combination of the drug, filler, and/or suitable flow improving excipients, that are simply introduced into this capsule shell, using traditional encapsulating equipment. Several investigators have cited the need for such two-piece hard shell capsule as an extemporaneous platform for controlled drug delivery (Thombre et al., 2014; Waterman et al., 2011). This type of vehicle would be utilized as a universal platform for rapid screening and feasibility analysis of un-processed powders and/or blends during early phase trials of new drug candidates for controlled delivery, through the oral route (Thombre et al., 1999, 2014). To that end, several investigators have looked into the application of functional coatings on commercially available gelatin and HPMC capsules in order to achieve controlled or targeted drug delivery (Dvorackova et al., 2011; Fahmy et al., 2009; Meghal et al., 2011; Sobhita et al., 2014). However, due to moisture sensitivity of gelatin and HPMC films, the inability of these capsules to retain their physical integrity in conventional pharmaceutical coating unit operations limits their utility for development of such drug delivery systems (Curtis-Fisk et al., 2012; Mei et al., 2006). Moreover, gelatin is prone to chemical degradation and/or cross-linking if exposed to extreme environments, such as those created in conventional substrate coating pharmaceutical unit operations (Jain and Singh, 2012; Song et al., 2011). Recently, several reports were published describing controlled drug delivery from cellulose acetate and ethyl cellulose asymmetric capsules (Jain et al., 2014; Wang et al., 2005). Pore formers and plasticizers are

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typically incorporated in the capsule walls in order to initiate water flux through the polymeric-barriers and facilitate drug release. Literature reports have indicated aging effects of these polymers with conventional plasticizers and pore formers, which can potentially alter the release characteristics of the enclosed solute over the shelf life of the product (Bao et al., 2015; Muschert et al., 2009).

To overcome the physical and chemical stability limitations of the aforementioned platforms, the use of regenerated cellulose (RC), prepared by non-solvent mediated precipitation of cellulose/dimethyl sulfoxide-paraformaldehyde (cellulose/DMSO-PF) (also known as methylolcellulose (MC)) is proposed for the fabrication of two-piece hard shell capsule-based controlled drug delivery system (Kumar and Bhatt, 2015). The use of hard-shell RC capsules is proposed due to their unique capability of forming near-transparent, monolithic, smooth and water-insoluble membranes, when MC solution is precipitated on a substrate using a suitable non-solvent, and the resulting membrane is thermally annealed. When theses membranes are exposed to aqueous media, significant water uptake by them is observed due to the hygroscopic nature of cellulose. This water uptake disrupts the loosely held hydrogen bonded intra- and/or inter-polymer domains which leads swelling and self-formation of water filled cavities and pores through which the enclosed solute traverses across them in hydrated state (Bhatt and Kumar, 2015b). The inherent pore forming capability can be modulated by inclusion of short chain cellulose and native celluloses in the MC solution (cellulose degree of polymerization of approximately 250 and 900, respectively). During the precipitation process, the short chain celluloses tend to create smaller, fewer and tortuous pores as the shorter regenerated cellulose aggregates are able to form more ordered and hence stronger hydrogen bonded inter- and intra-polymer domains that cannot be broken by the intruding water (Bhatt and Kumar, 2015a). The utilization of chemically unmodified cellulose is also cost effective as it is a naturally occurring and abundantly available polymer.

This article aims to derive a suitable fabrication process for RC capsules by analyzing MC solution characteristics. The potential use of RC capsules as a controlled-release platform is also examined through *in-vitro* evaluation of drug release from them and its comparison to some commercially available USP, equivalent capsule and tablet type extended-release dosage forms.

2. Materials and methods

2.1. Materials

Cellulose in the form of cotton linter sheets was obtained from Southern Cellulose Products Inc. (Grade R270; Chattanooga, TN). Paraformaldehyde and dimethyl sulfoxide were obtained from Fischer Chemicals (Fair Lawn, NJ). Potassium chloride was purchased from Fisher Chemicals (Fair Lawn, NJ) and Arcos Organics (Geel, Belgium). Size 0 gelatin capsules were obtained from Capsugel® (Morristown, NJ) and stored at 25 °C prior in air tight containers prior to use. KCl reference standard was procured from Ricca Chemical Company (Arlington, TX).

2.2. Methods

2.2.1. Preparation of methylolcellulose (MC) solution

Methylolcellulose (MC) solutions containing 0.5%–5.5% w/w cellulose were prepared according to the method described in our previous work (Bhatt and Kumar, 2015a).

2.2.2. Solution rheology assessment

The rheology of the MC solutions was analyzed on a rotational plate rheometer (Haake Rheostress 6000, Thermo Scientific, Waltham, MA) equipped with a 20 mm diameter upper and lower parallel plate surfaces. The gap between the concentric plates was set to 0.5 mm. The sample of about 1–3 g was poured on the bottom plate and conditioned to 25 °C prior to initiating the study. The steady shear viscosity measurements were carried in the range of 0.01 to 1000 s^{-1}. Dynamic oscillatory measurements were carried out in the angular frequency range of 0.1–100 rad/s. The linear viscoelastic regime was determined by performing a strain sweep at a fixed frequency of 10 rad/s. The 5% strain was chosen for all dynamic measurements.

2.2.3. Fabrication of RC capsule halves

Mold pins utilized in fabricating RC capsules were machine carved from polytetrafluoroethylene (PTFE) blocks in the shape of a cylinder of 7.7 mm and 8 mm diameter and 20 mm length, with one edge carved to the shape of a dome and the other edge carved as a flat face. The MC solutions were contained in 20 mL glass scintillation vials and sealed with screw caps. They were degassed and conditioned to 25 °C in a water sonication bath (Bransonic Ultrasonic Cleaner, Model 5200, Bransonic Corporation, Danbury, CT) for 30 min, prior to initiating the dip-coating process. Mold pins were immersed in MC solution and then withdrawn through the opening of the scintillation vial at 1 cm/s. This velocity was chosen to ensure that the thickness of the draining MC solution on the mold pin surface was greater than the gap between the mold pin surface and the opening of the scintillation vial. The coated pins were then placed on electric motors (GKH model GT-21, G. K. Keller Corp, Floral Park, N.Y.) and spun at 75 rpm, at a 45° angle to the horizontal for a desired period of time. After the spinning step, the coated mold pins were immersed in a water bath (>5 L) for 24 h to ensure complete precipitation of cellulose. Water was replaced in the bath periodically. Following precipitation, the pins were placed in a thermostatic oven for 24 h at 105 °C for thermal annealing. The thermally treated capsule shells were then ejected and trimmed to the length of 18.5 mm using a surgical blade. The resulting shell's inner dimensions were equivalent to size 0 gelatin capsules. For application of multiple sequential coatings, once the mold pins were spun for desired time period, they were then immersed in acetone bath for 5 min, followed by air-drying for 10 min. After air-drying, the mold pins were re-immersed in MC solution and the process repeated until desired numbers of coatings were applied. After final application of MC solution, the mold pins were placed in a water bath (>5 L) for 24 h to ensure complete precipitation of cellulose, followed by thermal annealing as per the aforementioned procedure.

To evaluate the role of fabrication variables on obtaining capsules shells with desired wall thickness and minimal variability, two 2^2 full factorial design-of-experiments (DOE), with replicates and center points, were generated on an IBM compatible computer equipped with Minitab 17 software packaged (Minitab, Inc., State College, PA). In the first DOE, MC solution concentrations (X_1), between 2.20% and 4.40% w/w, and mold pin spinning time (X_2) between 5 and 25 min, were chosen as independent variable in a 2^2 full factorial DOE. The responses observed were average capsule wall thickness (Y_1) and the relative standard deviation (RSD) in thickness (Y_2), by measurement of twelve locations on three capsules. All other variables were held constant. The second DOE evaluated the responses Y_1 and Y_2 based on the number of sequential coatings of MC solution applied on the mold pin (from 1 to 7, X_3), and, cellulose concentration in solution 2.20% w/w and 4.40% w/w cellulose in MC, X_4). Thickness measurements were performed using a high precision micrometer (Fowler® 0–25 mm Xtra-value Digital counter, Fowler High Precision, Newton, MA). Center point terms were included in the DOE to evaluate the linearity of the predicted models. Statistical analysis and analysis of variance (ANOVA) was performed within this software package. Backward elimination of the terms in the linear models was performed and all statistically insignificant terms were eliminated using $\alpha = 0.05$, wherever the ANOVA determined the term's p-value >0.05.

To examine the role of thermal annealing, capsule shells were also freeze dried after final precipitation step in water. The wet shells were first flash frozen by placement in dry-ice, followed by vacuum drying for 24 h to remove frozen water (Labconco Freezone 4.5, Labconco