Powder Technology 217 (2012) 16–20

Contents lists available at SciVerse ScienceDirect

Powder Technology

journal homepage: www.elsevier.com/locate/powtec

Microcrystalline cellulose powder tableting via networked cellulose-based gel material

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ARTICLE INFO

Article history:
Received 21 May 2011
Received in revised form 26 September 2011
Accepted 1 October 2011
Available online 8 October 2011

Keywords:
Networked cellulose
Hydrolysis
Tablets
Slip-casting
Controlled release

ABSTRACT

Networked cellulosic (NC) gel material was prepared via 70% sulfuric acid dissolution and hydrolysis of microcrystalline cellulose (MCC) followed by regeneration in cold ethanol. The material was utilized as a multifunctional excipient for drug tablets production. Placebo tablets were prepared via slip-casting of simple formulas containing different concentrations of NC. The hardness of the prepared tablets was measured using tablet hardness tester and increased over a wide range and up to 420 N. It was noticed that the hardness is mainly dependent on NC material concentration in the formulation. Furthermore, high tablet hardness was observed using tablet friability tester. Paracetamol tablets of 30 mg label claim were prepared in a similar way. Despite their high hardness, the tablets showed a full drug release capability over time and up to 24 h. The release time was also influenced by the NC concentration. Content uniformity and mass variation testing of these tablets have confirmed the product homogeneity and proved the efficiency of slip-casting as a tablets production technique.

1. Introduction

Tablets are the most popular dosage forms because they can be easily produced and accurately dosed, easily administered by patients, and have good chemical and mechanical stability [1]. However, there are many challenges that face tablets production such as formulation optimization, limitations of batch processing, and the thermal sensitivity of active ingredients. Tablets are produced by the compression of active ingredients with some excipients. The compression requires high pressures that may increase the temperature of the formula. Degradation of active ingredients can be a consequence of such thermal stresses, which can affect the active content uniformity. Consequently, temperature-sensitive active ingredients are not producible in the tablet form but rather in the capsule form or as injection. On the other hand, capsules production is expensive compared to tablets production and the injections are not preferable to patients [2].

The relation between tablets fabrication, structure and drug release capabilities is strong. Tablets are required to be hard enough to tolerate the stresses to which they are exposed during packaging and transportation. Such requirement can affect the main purpose of tablet production, i.e. drug delivery. Tablets have to dissolve and release the drug substance consistently. The preparation of tablets with suitable hardness and dissolution characteristics and content uniformity requires careful optimization. For these reasons, one seeks tablet production techniques that avoid thermal stress and provide homogeneous hard tablets for drug delivery.

Work done by Pachulski et al. showed that casting of formulas of gel material of colloidal silica and binding agents with Paracetamol, without the need for any pressure, can be used to prepare tablets with good properties [3]. Szepes et al. prepared Theophylline tablets using freeze-casting of aqueous solutions of potato starch, citric acid, sacchrose and Theophylline. The tablets showed a rapid delivery of the Theophylline [4]. Also a work done by Witte et al. showed that the freeze-casting of aqueous solution of Ibuprofen produced immediate release tablets. The fast release was a result of the high porosity of the tablet body because of the unoccupied space left after the sublimation of the frozen water molecules [5]. Despite of the high quality of the dried product, freeze-drying is energy intensive and consequently an expensive technique [6]. It is also time intensive process that could need days to finish [7].

Pharmacists have been utilizing cellulose, mainly microcrystalline cellulose (MCC), in tablets formulation for a long period of time [8]. It is biocompatible, inexpensive and widely used as filler and binder in the excipient matrix [9]. Previous work done by the authors [10], demonstrated the production of networked cellulose (NC) in a gel form through sulfuric acid hydrolysis of microcrystalline cellulose (MCC) and regeneration in ethanol. The hydrolysis conditions for NC-production were optimized to produce NC material in a high yield. Fig. 1 shows the gel nature of the NC material. Accordingly,

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doi:10.1016/j.powtec.2011.10.002

the material showed a networked structure and behavior. The microstructure of the NC material was characterized using X-ray diffraction and transmission electron microscopy. The cellulose crystallinity changed from cellulose I to the more stable cellulose II upon regeneration. It is believed that cellulose II crystals work as connecting points of amorphous network of randomly distributed fibers. The new microstructure has different properties compared to the starting MCC material. In this work we focus on the preparation of networked cellulose (NC) gel material and its utilization in tablets fabrication via slip-casting. We are introducing a modified type of cellulose with properties that allowed the development of a new method of fabrication of tablets with a novel microstructure and release behavior.

2. Materials and methods

2.1. Materials

Microcrystalline cellulose (MCC) was provided by FMC BioPolymer (Avicel-PH 101). Sulfuric Acid, 95–97%, Reagent Grade, was purchased from Scharlau. Ethanol and Paracetamol (Acetaminophen) were purchased from Sigma–Aldrich.

2.2. NC material preparation

Details of the preparation of NC material have been published elsewhere [10]. Microcrystalline cellulose (MCC) powder was mixed with 70% (w/w) H_2SO_4 using Varian Dissolution System (VK7010) at 5 °C with 250 rpm agitation. The mixing ratio is 1 g cellulose for each 10 ml of H_2SO_4. After 30 min, a white material was precipitated by adding equivalent volume of cold ethanol (−17 °C) as anti-solvent. The product was collected and centrifuged at 4 °C three times for 10 min at 4700 rpm using Allegra™ 25R Centrifuge. The precipitate was collected again and dialyzed for three days until the pH is almost neutral. The resultant white suspension was weighed then sonicated using Hieschler Ultrasonic Processor UP400S for 30 min. After dialysis the yield was calculated by withdrawing a known amount of small sample and obtaining its oven-dried weight. The yield was calculated based on the solid product weight after hydrolysis and drying compared to the starting weight. The yield was 97.1%. NC suspensions, with different concentrations, were prepared either by drying or diluting to a given weight using water as solvent.

2.3. Placebo tablets preparation

Placebo tablets were prepared by mixing 75 g of each of the previously prepared NC suspensions with 15 g of MCC. The formulas were poured into a mold and left to air-dry for one day to produce circular-shaped tablets. The concentrations of the used NC-suspensions were 2.00%, 4.72%, 6.25%, 8.02%, 9.20%, and 11.66%.

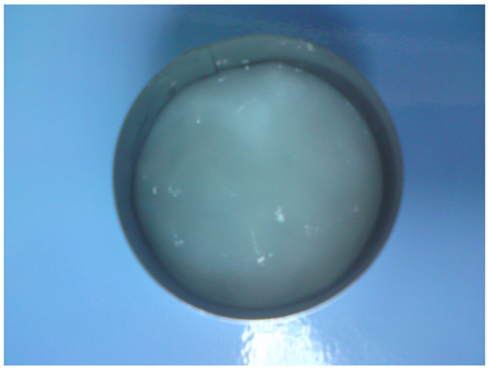

Fig. 1. The gel nature of the NC material upon regeneration.

2.4. Paracetamol tablets preparation

Paracetamol tablets were prepared by mixing 75 g of NC suspension with 12.6 g of MCC and 2.4 g of Paracetamol. The formulas were poured into a mold and left to air-dry for one day to produce circular-shaped tablets. The tablets were prepared in order to have a label claim of 30 mg Paracetamol. Five NC concentrations were used; 2%, 3%, 4%, 5%, and 6% in order to study the effect of NC concentration on the properties of the finished product.

2.5. Placebo and Paracetamol tablets testing

The hardness of the slip-casted tablets was measured using Dr. Schleunger®Pharmaton 8 M tablet hardness tester. The friability test was conducted using Erweka® TA220. For mass variation, twenty tablets were weighed individually. The relative standard deviation was calculated. All tests were conducted as per XXIV monograph in the United State Pharmacopeia (USP) for uncoated tablets.

To measure the content uniformity of the Paracetamol tablets, they were powdered then 30 mg equivalent weight of Paracetamol was transferred into a 250 mL volumetric flask. 200 mL of water was added to the flask and sonicated for 5 min then completed up to volume with water (sample stock solution). 10 mL of the stock solution was transferred into a 50 mL volumetric flask and completed up to volume by water. A portion of the solution was filtered using 0.2 μm PTFE filter. The absorbance of the filtrate was measured using Thermo Evolution300 UV spectrophotometer at 243 nm with a cell path of 10 mm. The Paracetamol content was measured against standard with the same final concentration (0.024 mg/mL). The test was repeated for 10 tablets. The average and relative standard deviation were calculated.

Paracetamol release was studied using Varian VK7010 Dissolution system connected to Cary50 UV spectrophotometer by fiber optics cords. The release was measured for six tablets, each in 900 mL of water at 37.0°C using paddle agitation of 50 rpm. The absorbance of the medium was directly measured from the vessel at different time intervals at 243 nm using cell path of 10 mm. The percentage Paracetamol release was measured against Paracetamol standard with a concentration of 0.033 mg/mL.

3. Results and discussion

3.1. MCC hydrolysis and structure modification

The gel form of networked cellulose has high porosity structure. This can provide enough space to be occupied by additives such as molecules of active ingredients (Fig. 2). At the same time, NC material has enhanced shrinkability and swelling as a result of the increase in the amorphous content. MCC particles were used to provide structural integrity and reduce shrinkability effects. The active ingredient and MCC particles are loaded inside a wet NC matrix; it is slip-casted and left to dry. Upon drying, the formula shrinks in volume and entraps both the active ingredient and the MCC particles. Fig. 2 shows a schematic of the mechanism by which NC encapsulates MCC and active ingredient particles. Both MCC and NC are of the same material, but with different structure. As a result, the bonding between the two is likely to occur because of hydrogen bonding and entanglement of the MCC within the network. Due to the preparation technique of NC material, where networked fibers are produced in an aqueous suspension, the NC is present in expanded form to cover large space that is filled with water. Mixing of MCC and active ingredients at this status allows excellent distribution of all components. Cellulose chains have intermolecular forces such as hydrogen bonding and