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Research Paper

Solid nanofoams based on cellulose nanofibers and indomethacin—the effect of processing parameters and drug content on material structure

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ABSTRACT

The unique colloidal properties of cellulose nanofibers (CNF), makes CNF a very interesting new excipient in pharmaceutical formulations, as CNF in combination with some poorly-soluble drugs can create nanofoams with closed cells. Previous nanofoams, created with the model drug indomethacin, demonstrated a prolonged release compared to films, owing to the tortuous diffusion path that the drug needs to take around the intact air-bubbles. However, the nanofoam was only obtained at a relatively low drug content of 21 wt% using fixed processing parameters. Herein, the effect of indomethacin content and processing parameters on the foaming properties was analysed. Results demonstrate that a certain amount of dissolved drug is needed to stabilize air-bubbles. At the same time, larger fractions of dissolved drug promote coarsening/collapse of the wet foam. The pendant drop/bubble profile tensiometry was used to verify the wet-foam stability at different pHs. The pH influenced the amount of solubilized drug and the processing-window was very narrow at high drug loadings. The results were compared to real foaming-experiments and solid state analysis of the final cellular solids. The parameters were assembled into a processing chart, highlighting the importance of the right combination of processing parameters (pH and time-point of pH adjustment) in order to successfully prepare cellular solid materials with up to 46 wt% drug loading.

1. Introduction

The growing number of drugs, and the importance to influence the release of drugs from their solid dosage forms, has stimulated the development of new excipients in order to improve drug delivery and compliance. Cellulose and its derivatives have a long tradition as excipients in pharmaceutical formulations, but cellulose in the form of cellulose nanofibers (CNF) is relatively unexplored and was only recently discovered as an excipient. CNF are derived from e.g. cellulosic pulp fibers, using mechanical disintegration combined with chemical modification. The dimensions of CNF is typically a couple of nm in width (wood) and several μm in length (Svagan et al., 2007). Individual nanofibers contain both hydrophobic and hydrophilic faces, giving raise to amphiphilic properties. Previous studies have shown that e.g. hydrophobic molecules adsorb to the hydrophobic surfaces of cellulose nanofibers (Mazeau and Wyszomirski, 2012) and that oil-in-water emulsions can be stabilized by neutral cellulose nanocrystals (crystalline segments of cellulose nanofibers) (Kalashnikova et al., 2012). Other interesting properties are high mechanical properties and excellent oxygen barrier properties of CNF films (Fukuzumi et al., 2009; Saito et al., 2013). A couple of studies have shown potentials with CNF in capsules preparation (Svagan et al., 2016a, 2014), in tablets (Kolakovic et al., 2011) and particles (Kolakovic et al., 2012a) and also as films for controlled drug release (Gao et al., 2014; Kolakovic et al., 2012b). Owing to the inherent physico-chemical properties of CNF, it was recently demonstrated that CNF, in combination with a surfactant, could be used to stabilize air-bubbles and also to prepare cellular solid materials suitable for pharmaceutical applications (Svagan et al., 2016b). In this study, the surfactant lauric acid sodium salt adsorbed to CNF, hereby altering the hydrophobicity of CNF, and hence, allowed to produce stable cellular solid materials. When adding the highly soluble model drug riboflavin to the wet-stable foam, drug loaded cellular solid materials with sustained drug release properties could be obtained. The authors suggested that surfactant based CNF cellular solid materials with sustained release properties can potentially be

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extended to many other drug molecules. In another study, a poorly-soluble model drug, indomethacin, was used as the foaming agent (Löbmann et al., 2017) to create a nanofoam. In this case, the model drug altered the hydrophobicity of the CNF and allowed for stabilization of air-bubbles. The release from these could be tailored from fast-release (collapsed foam in the form of a film, total release completed within ~10 min) to prolonged release (cellular solid material, 24 h). The prolonged release was due to the cellular foam structure of the dosage form. The air-bubbles changed the hierarchical structure of the material and as the drug could only diffuse through the cell walls and not through the stable air-bubbles, a prolonged release was obtained. In other words, drug-loaded CNF nanofoams have the ability to release drugs in a tailored way. Also, the change in release kinetics, i.e. fast or prolonged, was achieved quite easily, i.e. through casting and drying of a film/foam; making CNF based formulations attractive from a processing point of view. In addition to the controlled release, drug-loaded CNF-foams have other properties that could enhance the success of a medical therapy, for example, the ease of oral intake based on their flexibility and smooth surface. This property may be especially beneficial for the elderly or children whom often have problems swallowing tablets or other solid dosage forms (Bar-Shalom and Rose, 2014). Furthermore, personalized medicine, such as a specific drug amount depending on the body weight, adult or child or ethnicity, is getting more and more important in the future and therefore also individualized dosages may be feasible using CNF foams by simply cutting the foam in appropriate pieces with the desired dose. This is a big advantage in comparison to other controlled release oral delivery systems such as prolonged/sustained release coatings.

In a previous study on indomethacin/CNF nanofoams (Löbmann et al., 2017), the air-bubbles were assumed, but not experimentally proven, to be stabilized by a Pickering mechanism. First results showed that neither indomethacin itself nor CNF can stabilize air-bubbles, only their combination. However, the effect of processing parameters was poorly understood. For example, a cellular solid material was only attained with 21 wt% indomethacin and was not achieved in the presence of a higher drug-load (close to 50 wt%). The foaming properties of such a mixture should, however, be highly dependent on the molecular interaction between the indomethacin and CNF in order to stabilize air bubbles. The aim of the present study is to better understand how the parameters such as pH, drug content and processing order affect the foaming properties and the resulting cellular solid. Therefore, the parameters were systematically varied and discussed.

2. Materials and methods

2.1. Materials

Indomethacin (γ-form) was purchased from Fagron Group BV (Rotterdam, The Netherlands). Bleached sulfite pulp (never-dried, 14 wt% hemicellulose, <1 wt% lignin) from Nordic Paper Seffle AB, Sweden was used in the production of CNF with quaternary ammonium salt groups. The cationic CNF was prepared from glycidyltrimethylammonium chloride modified sulfite pulp as described previously (Svagan et al., 2016b). The CNF had a dimension of 3.9 ± 0.8 nm in width and several μm long, however, larger non-fibrillated aggregates could also be observed (Svagan et al., 2016b). The amount of cationic groups, 0.13 mmol of cationic groups per g fiber, was attained by conductometric titration (Hasani et al., 2008). Previous toxicology studies on cationic CNF have shown that it is not cytotoxic (Hua et al., 2014).

2.2. Preparation of CNF based foams, α-indomethacin and Na-amorphous indomethacin

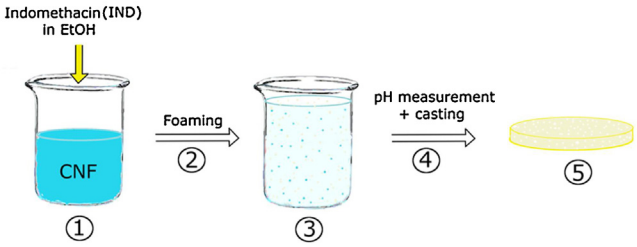
As a first step the main batch of cationic CNF 1.32 wt% was diluted with MilliQ-water to a resulting concentration of 0.28 wt%. To obtain a homogeneous suspension, the dilution was treated with ultra-sonication at an amplitude of 90% and a total run time of 180 s (Sonics, Vibracell). Indomethacin dissolved in Ethanol (EtOH) was added to 50 g of cationic CNF suspension, a total of 2.5 ml was added, using 47, 15, 7.5, or 1 mg of indomethacin per mL EtOH to prepare the cellular solid materials with 46, 21, 12 and 1.6 wt% (dry weight basis) indomethacin, respectively, see Scheme 1. The solution with 47 mg indomethacin per mL EtOH was prepared by heating (~40 °C) and simultaneously sonicating the solution in an ultra-sonication bath for ca. 5–10 min. The pH was adjusted using either 1 M HCl or 1 M NaOH solution and in one of two ways: 1) Pre-adjustment of pH: The pH of the 0.28 wt% CNF suspension was adjusted to different pH values (see Table 1 and Scheme 1) prior to drug addition and the foaming step using ultra-sonication described below or 2) Post-adjustment of pH: The pH was adjusted in the final wet foam (also containing drug) after the sonication step. To produce wet foams, the suspensions were ultra-sonicated for 1 min (Pulse-mode: 20 s pulse and 10 s pause, amplitude 80%). The foamed suspension was cooled down to room temperature afterwards and the pH was then measured. The pH was measured using a benchtop pH meter (sensION+ PH31 Advanced GLP, Hach, Loveland, CO, U.S.A) with an accuracy of 0.002 in pH. All pH measurements were performed at room temperature (approx. 22 °C). The wet foam (20–23 g) was cast into Petri-dishes (8.8 cm in diameter) and dried at ambient conditions (room temperature) in the dark (drying time 2-3 days). Prior to use, the cellular solid materials were stored over silica gel in a desiccator under dry conditions and protected from light. The thickness of films ($n \geq 7$) was assessed using a Digimatic Indicator (Mitutoyo, USA).

The α-polymorph of indomethacin was obtained by adding indomethacin dissolved in EtOH to water (pH 4.5, adjusted with 0.1 M HCl). The precipitate was filtered, dried at 37 °C overnight and then in vacuum oven at RT (1 day).

Amorphous sodium indomethacin was prepared by mixing an indomethacin solution in EtOH (50 mg mL^{-1}) with 1 M NaOH (at a 1:1 molar ratio of NaOH:Indomethacin) at RT. The amorphous sodium indomethacin was dried at ambient conditions (room temperature) for two days in a darkened fume hood.

2.3. Fourier transform infrared spectroscopy (FTIR)

Spectra were obtained using an ABB MB3000 (ABB, Zürich, Switzerland) in the total reflectance mode (using an attenuated total reflectance accessory). Measurements were performed of dry



Scheme 1. Schematic illustration of the different preparation steps. The pH is adjusted in either step 1 (pre-adjustment of pH) or step 3 (post-adjustment of pH).