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Solid cellulose nanofiber based foams – Towards facile design of sustained drug delivery systems

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ABSTRACT

Control of drug action through formulation is a vital and very challenging topic within pharmaceutical sciences. Cellulose nanofibers (CNF) are an excipient candidate in pharmaceutical formulations that could be used to easily optimize drug delivery rates. CNF has interesting physico-chemical properties that, when combined with surfactants, can be used to create very stable air bubbles and dry foams. Utilizing this inherent property, it is possible to modify the release kinetics of the model drug riboflavin in a facile way. Wet foams were prepared using cationic CNF and a pharmaceutically acceptable surfactant (lauric acid sodium salt). The drug was suspended in the wet-stable foams followed by a drying step to obtain dry foams. Flexible cellular solid materials of different thicknesses, shapes and drug loadings (up to 50 wt%) could successfully be prepared. The drug was released from the solid foams in a diffusion-controlled, sustained manner due to the presence of intact air bubbles which imparted a tortuous diffusion path. The diffusion coefficient was assessed using Franz cells and shown to be more than one order of magnitude smaller for the cellular solids compared to the bubble-free films in the wet state. By changing the dimensions of dry foams while keeping drug load and total weight constant, the drug release kinetics could be modified, e.g. a rectangular box-shaped foam of 8 mm thickness released only 59% of the drug after 24 h whereas a thinner foam sample (0.6 mm) released 78% of its drug content within 8 h. In comparison, the drug release from films (0.009 mm, with the same total mass and an outer surface area comparable to the thinner foam) was much faster, amounting to 72% of the drug within 1 h. The entrapped air bubbles in the foam also induced positive buoyancy, which is interesting from the perspective of gastroretentive drug-delivery.

1. Introduction

Sustained drug delivery systems are designed to accommodate an extended therapeutic effect by releasing drug over a prolonged time period. The benefits, for drugs in need of sustained release, are improved pharmacokinetics as well as better patient compliance and safety, due to a predictable drug release profile and lower dosing regimen, e.g. a single daily dose instead of multiple. Sustained drug release is also important in the case of a drug with a short biological half-life as it improves the bioavailability of the drug. There are several approaches to achieve sustained release dosage forms, including dissolution, erosion and diffusion controlled strategies or a combination thereof, as well as osmotic release oral systems (OROS). The specific approach for a drug is selected based on factors such as its physico-chemical characteristics, absorption, metabolism, bioavailability, half-life and safety [1]. To obtain a sustained drug effect may be especially challenging when drugs 1) have a very limited or narrow absorption window or 2) are intended for local treatment in the stomach or upper intestine [2,3]. Because of the rapid passage time a conventional sustained release dosage form may not result in the desired effect [4]. Drugs that show a narrow and site specific absorption are for example furosemide [5], levodopa [4] and riboflavin [2,4]. On the other hand, treatment of helicobacter pylori and ulcer may be more effective with a local drug delivery in the stomach [6]. For this purpose, gastroretentive systems have been introduced as sustained release dosage forms [3]. This type of dosage forms remain in the stomach after administration and subsequently release the drug over a given time interval. To achieve gastric retention, different formulation approaches have been developed such as low density floating systems, high density systems, mucoadhesive and expanding dosage forms [4,7].

To achieve better drug delivery systems with desirable drug release profiles, the development of new materials is an unambiguous necessity. As such, cellulose nanofibers (CNF) is an interesting material, as CNF

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exhibits unique physico-chemical properties at different interfaces and has a large specific surface-area available for positive drug-CNF interaction. In addition, CNF has excellent mechanical properties that could be used to improve the mechanical stability of the dosage form. It has also been shown that CNF films have outstanding oxygen barrier properties at low relative humidities, due to strong nanofiber-nanofiber interactions and high crystallinity [8], and this property could be used to improve the oxidative stability of oxygen-sensitive drugs during storage. Nonetheless, its use as an excipient in pharmaceutical formulations has so far been reported only in a very limited number of publications. CNF has been used to prepare immediate release tablets [9], capsules [10,11] and particles [12] and it has also been used for controlled drug release in the form of films [13,14].

In a few recent studies, CNF was combined with non-edible surfactants and used to encapsulate air bubbles using the so-called Pickering method, which resulted in stable air bubbles [15–18]. In this very straight-forward processing way, wet-stable foams were attained that, upon drying, formed dry closed-cell foams (cellular solid materials). The reported dry foams were however only utilized in mechanical applications other than biomedical [16–18]. But such three-dimensional closed-cell structures are also interesting systems for extended release of drugs in pharmaceutical applications, because the presence of stable air-filled cells might create an extended diffusion path and this may alter the release characteristics. Note that air-pockets per se will not automatically give raise to prolonged release, for example if the pockets are interconnected (e.g. in aerogels) and quickly become filled with liquid, then they might increase drug release due to a larger surface area [19]. Unstable air bubbles might also become fused together when the material is exposed to liquid, as was recently shown for pellets with porous cores, and the bigger air bubble might cause mechanical stress and crack propagation in the in polymeric film coatings of the pellets, followed by increased drug release [20]. However, if air bubble stability can be achieved and if the processing step can be made simple and general, e.g. utilizing the Pickering method in the case of CNF, then this opens up a new and facile way for designing sustained drug delivery systems. The presence of closed cells in the foams is also expected to induce positive buoyancy for as long as the cells remain filled with air. For CNF based cellular solid materials, the loaded drug is also anticipated to be released in a modified manner when compared to a CNF film with the same drug load.

In the present contribution the aim is to demonstrate a general concept of preparing CNF based cellular solids using a pharmaceutically acceptable surfactant, i.e. lauric acid sodium salt (LA), as foaming excipient and to show how the drug release can be tailored. Such dry CNF foams have to our knowledge not been reported before. Furthermore, the aim is to provide a better understanding of the mechanism behind the stabilization of the air bubbles in the foam, as well as the drug release kinetics. Riboflavin was used as a water-soluble model drug since it is absorbed by active transport in the duodenum in the gastrointestinal tract and its biological half-life is about 66–84 min [21]. In other words, it is a good model for a compound that would benefit from extended release in the stomach, after oral administration, as this would improve the bioavailability and also enable a slower decrease in blood-plasma concentration compared to an intermediate-release dosage form such as a tablet [21].

2. Experimental section

2.1. Materials

Riboflavin was purchased from Unikem (Copenhagen, Denmark). Lauric acid sodium salt (LA) was obtained from Acros Organics (New Jersey, USA). Pepsin from porcine gastric mucosa (≥250 units mg^{-1} solid) was purchased from Sigma Aldrich (St. Louis, MO, USA). The materials were used as received. The enzymatic units for pepsin have been determined by the supplier on hemoglobin as substrate and one unit will cause a ΔA_{280} of 0.001 (light path 1 cm) per min at 37 °C and a pH of 2.0. "FaSSIF, FeSSIF & FaSSGF" powder was purchased from Biorelevant (London, UK). Commercial tablets Vitamin B_2 10 mg JenaPharm® (10 mg riboflavin, mibe GmbH, Brehna, Germany) was purchased from a local pharmacy. Bleached sulfite pulp (never-dried, 14 wt% hemicellulose, <1 wt% lignin) was a kind gift from Nordic Paper Seffle AB (Säffle, Sweden). The cationic CNF was prepared by reacting sulfite pulp with glycidyltrimethylammonium chloride (epoxypropyltrimethylammonium chloride) as previously described, with the modification that the reaction temperature was gradually increased from 40 to 50 °C during 1 h and then maintained at 50 °C for 1 h [22]. Also, the chemically modified pulp-fibers (solid content 1.3 wt% in Milli-Q water) were high-pressure homogenized three times, the details are given in a previous publication [22]. The amount of cationic groups was 0.13 mmol g^{-1} fiber, attained by conductometric titration [23]. Preliminary toxicology studies on cationic CNF have shown that it is not cytotoxic [24].

2.2. Preparation of foams and films

A 0.28 wt% cationic CNF suspension was prepared by diluting a stock suspension (1.3 wt% solid content) with Milli-Q water, followed by sonication (3 min, 90% amplitude, 1/2″ tip, 750W) using a Sonics Sonifier (Sonics and Materials Inc., Newton, CT, USA) and subsequently adjusted to pH ~9.7 with 1 M NaOH. Wet foams were prepared by adding 0.395 mL LA dissolved in EtOH (concentration 10 mg/mL EtOH, and with 60 μl of 1 M NaOH per mL EtOH) to 128 g of the above mentioned cationic CNF suspension under magnetic stirring followed by an ultrasonication step (80% amplitude, 1/2″ tip, 20s sonication, 10 pause, 750 W) for 2 min. Riboflavin was dispersed in Milli-Q water (solid content of 1 wt% or 6 wt% to prepare cellular solid materials containing 14 wt% or 50 wt% riboflavin, respectively) and added to the wet foam under magnetic stirring, see Scheme 1. The wet foam (22 g) was cast in Petri-dishes (diameter: 8.8 cm) and dried for 2–3 days at ambient conditions in the dark to obtain thin cellular solid materials. Dry foams were prepared in different thicknesses. The thin dry foams (ca. 0.6–0.8 mm) were prepared in one step, while the thick cellular solid materials (ca. 8 and 5 mm) were prepared by laminating several thin dry foams pieces using wet foam (ca 15 g) in between the thin foam pieces and drying in Petri-dishes (diameter: 8.8 cm) at ambient conditions in the dark, see illustration in Scheme 1. 206 g of suspension was used in total to create one thick foam sample (~8 mm thick) containing 14 wt% riboflavin. The thick CNF/LA foam without riboflavin (used in diffusivity experiments in SI) was prepared using a total of 97 g of suspension per sample. The final foams were stored in a desiccator with drying salt prior to usage.

CNF films containing 14 wt% riboflavin were prepared in a similar way to the foams, however, after the sonication step of the CNF/LA suspension, the generated wet foam was degassed to remove the air bubbles and the riboflavin dispersion was added under slow magnetic stirring. 22 g of the suspension was cast in Petri-dishes (diameter: 8.8 cm) and dried under ambient conditions in the dark and stored in a desiccator using a drying salt. A neat CNF film was prepared by casting and drying the neat CNF suspension (0.28 wt%). The CNF/LA films without riboflavin, used in the diffusivity experiments, were prepared by laminating two dry CNF/LA films (each prepared from 51 g of suspension) with degassed CNF/LA suspension. A total of 182 g degassed suspension was used in the preparation of one film (prepared in a Petri-dish, 8.8 cm in diameter).

The thickness of the thin cellular solid materials was analyzed with light microscopy (thickness measurements performed; $n > 20$) and the thickness of the riboflavin loaded film was obtained from Scanning electron microscopy images ($n > 60$). The wet and dry thickness of the CNF/LA film was measured ($n > 5$) with a Digimatic Indicator (Mitutoyo, USA). The thickness of the thicker foams was measured using a digital caliper.