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Cellulose nanofibers as excipient for the delivery of poorly soluble drugs

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ABSTRACT

Poor aqueous solubility of drugs is becoming an increasingly pronounced challenge in the formulation and development of drug delivery systems. To overcome the limitations associated with these problematic drugs, formulation scientists are required to use enabling strategies which often demands the use of new excipients. Cellulose nanofibers (CNFs) is such an excipient and it has only recently been described in the pharmaceutical field. In this review, the use of CNF in drug formulation with a focus on poorly soluble drugs is featured. In particular, the aim is to describe and discuss the many unique properties of CNFs, which make CNFs attractive as excipients in pharmaceutical sciences. Furthermore, the use of CNF as stabilizers for crystalline drug nanoparticles, as a matrix former to obtain a long-lasting sustained drug release over several weeks and as a film former with immediate release properties for poorly soluble drug are reported. Finally, the preparation of pharmaceutical CNF foams together with poorly soluble drugs is highlighted; foams, which offer a sustained drug delivery system with positive buoyancy.

1. Introduction

The development of oral drug delivery systems to improve the efficacy of new drugs is plagued by their often very low aqueous solubility. Around 40% of marketed drugs and up to 70% of drug candidates in the pipeline of the pharmaceutical industry show poor aqueous solubility, consequently resulting in unsatisfactory treatment for the patient when given orally (Babu and Nangia, 2011; Eddershaw et al., 2000; Hauss, 2007). The problems associated with poor aqueous solubility can potentially be overcome by using enabling drug formulation approaches. The most frequently used strategies in the pharmaceutical industry are (i) particle size reduction (nano-sizing), (ii) the use of the amorphous form, and (iii) lipid based drug delivery systems. All of these approaches have led to products on the market. For example, the antinausea drug aprepitant as a nano-particulate formulation in Emend® (Hargreaves et al., 2011), the HIV drugs ritonavir and lopinavir as an amorphous formulation in the medicine Kaletra® (Vasconcelos et al., 2016), or the HIV drug saquinavir as a lipid based drug delivery system in Fortovase® (Porter et al., 2008). However, all of these approaches also come along with drawbacks.

Particle size reduction often does not lead to the desired dissolution increase because of limitations in size reduction (Merisko-Liversidge et al., 2003). Furthermore, because of the high surface energy, nanoparticles tend to agglomerate or aggregate and stabilizing excipients are needed to avoid the formation of bigger agglomerates or aggregates (Peltonen and Strachan, 2015). The main disadvantage of amorphous formulations is that they are physically unstable, and the solubility advantage is lost upon recrystallization (Hancock and Zograf, 1997). For this purpose, the amorphous form usually also requires the addition of stabilizing excipients such as polymers (Vasconcelos et al., 2016), mesoporous silica (Laitinen et al., 2013) or in form of smaller interacting molecules such as in co-amorphous formulations (Dengale et al., 2016). Lipid based drug delivery systems, on the other hand, frequently have chemical stability problems, scalability challenges and often only a low drug loading capacity (Muellertz et al., 2010; Porter et al., 2008).

The poor solubility of some drugs is often further complicated if the drugs have a narrow absorption window such as a site-specific absorption only in the stomach or the upper intestine. The transit time in these parts of the gastro intestinal tract are often variable and usually comparatively short, hence, adding to the low drug absorption and bioavailability despite the attempts of using enabling technologies. Drugs with a limited absorption window include for example levodopa (Hoffman et al., 2004), riboflavin (Hoffman et al., 2004; Klausner et al., 2002) and the poorly soluble drug furosemide (Chungi et al., 1979). In such special cases, a gastro-retentive drug delivery system, which has a prolonged residence time in the stomach, may enable an improvement in bioavailability when releasing the drug in a sustained matter to the absorption site.

The challenges associated with the formulation for a given (poorly soluble) drug usually depend on the specific requirements of the drug.

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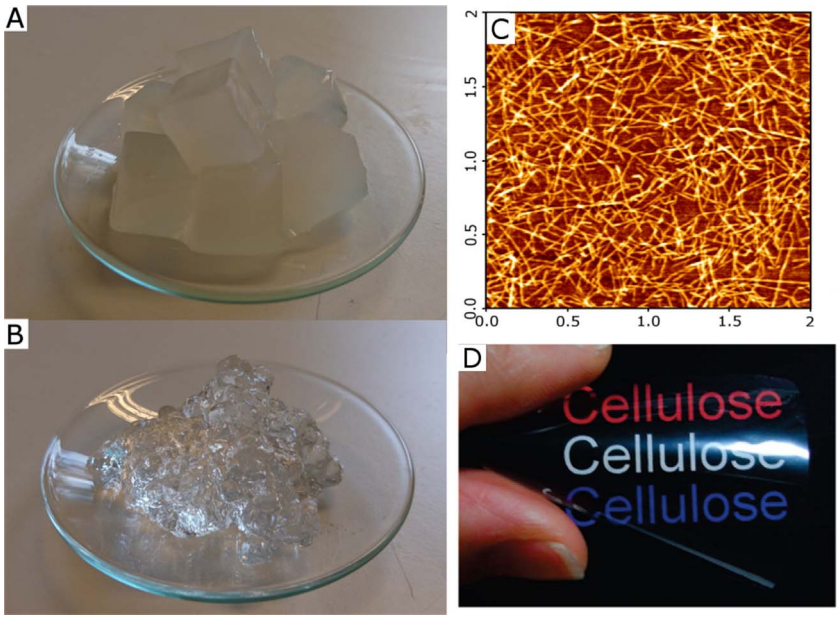

Fig. 1. (A) Commercially available cubes of nata-de-coco (marketed as coconut gel) made from bacterial cellulose. Nata-de-coco is a dessert that originates from the Philippines. In (B), a suspension of anionic cellulose nanofibers in water, the solid content is 0.9 wt%. The anionic CNF was prepared *via* a 2,2,6,6,-tetramethylpiperidine-1-oxyl radical (TEMPO)-mediated oxidation of pulp fibres from soft wood. (C) Atomic force microscopy image of TEMPO-CNF, adapted with permission from Ref. (Svagan et al., 2016b). (D) A transparent film made from TEMPO-CNF, reprinted with permission from (Fukuzumi et al., 2009). Copyright 2009 American Chemical Society.

In order to develop drug delivery systems with desirable properties, especially for problematic drugs, the use and development of new excipients (and formulation approaches) is often necessary. One promising excipient in this regard is cellulose nanofibers (CNFs). Interest in CNF as excipient in drug formulations has increased in the past few years, because of their unique rheological, barrier and physico-chemical properties which allow CNFs to stabilize oil/water and air/water interfaces, as well as their large surface area-to-volume that offer possibilities for positive molecular interactions with poorly-soluble drugs or stabilization of nanoparticles. Additionally, recent studies have demonstrated the possibility to, in a facile way, structure CNF based materials (particles, capsules, Pickering stabilized lipophilic droplets, films and foams) with tailored drug release properties. In this article the unique properties of CNF, and its use as excipient in drug formulations for poorly water soluble drugs, are reviewed.

2. Cellulose nanofibers (CNFs) – what is it?

There is a saying “a dear child has many names”, and this certainly holds true for cellulose nanofibers or cellulose nanofibrils, CNFs. CNFs have changed name several times since they were first reported in the early 1980′s (Turbak et al., 1983), and even today the nomenclature used in literature frequently leads to misunderstandings and ambiguities. Other names include microfibrillated cellulose (MFC), nanofibrillated cellulose (NFC), nanocellulose, and cellulose microfibrils, to mention a few. Indeed, a standardized nomenclature is urgently needed and, fortunately, such a nomenclature is presently under preparation by TAPPI (TAPPI, WI 3021). According to the definition by TAPPI, CNF is a type of cellulose nanofiber that contains both crystalline regions and amorphous regions, with dimensions of 5–30 nm in width and aspect ratio (=length/width) usually greater than 50 (). Cellulose nanofibers should not be confused with cellulose nanocrystals (Habibi et al., 2010) or microcrystalline cellulose (Thoorens et al., 2014).

Cellulose nanocrystals, CNC, are cellulose nanoparticles that consists of predominately pure crystalline cellulose, with dimensions of 3–10 nm in width and aspect ratio greater than 5 but usually less than 50 (). In other words, CNC are only the shorter crystalline segments that are found in CNF. Hence, CNC can be made from CNF by removing the amorphous parts that connect these crystalline segments in the CNF structure. However, CNC is typically produced by acid hydrolysis of pulp fibers, filter paper or other cellulosic materials (Habibi et al., 2010).

Microcrystalline cellulose, MCC, is an old and traditional excipient in pharmaceutical applications that was first commercialized under the brand name Avicel® in the early 1960′s (Thoorens et al., 2014). MCC is, amongst others, used in tablets as a binder enabling tablet production *via* direct compression. MCCs are obtained *via* hydrolysis of cellulose and the product is commonly prepared by spray drying the neutralized aqueous slurry of hydrolysed cellulose. The result is a dry powder of particles that are agglomerates of hydrolysed cellulose. The size of the MCC particles depends on processing conditions but is quite large, 50–200 μm, that is, several orders of magnitude larger compared to CNF.

Both MCC and CNC differ in properties compared to CNF, due to differences in aspect ratio (=length/width), size and structure. Differences are found in mechanical, barrier and rheological properties and these properties are described for CNF in the following sections.

2.1. Preparation of CNF

Cellulose nanofibers are produced from cellulosic materials derived from different botanical origin, *e.g.* wood, hemp, flax, cotton, algae or animals such as tunicate animals. In addition there is a certain type of bacteria, the most efficient and studied producer being *Acetobacter xylinum* (*Gluconacetobacter xylinum*), that are able to secrete nanoscale cellulose ribbons as an extracellular metabolite (Chawla et al., 2009). This so-called bacterial cellulose (BC), is devoid of hemicellulose, lignin and pectin, whereas CNF derived from other sources typically contains both hemicellulose and lignin. Bacterial cellulose is considered as a promising material for implants and scaffolds in tissue engineering, due to its biocompatibility, mechanical strength and chemical and morphological controllability (Petersen and Gatenholm, 2011). Bacterial cellulose is also a food-grade product and sold as the popular dessert “Nata-de-coco” in Asia. Nata-de-coco typically consists of cut cubes of BC emerged in some type of fruit juice or syrup. In Fig. 1a cubes of nata-de-coco are presented.

The isolation of cellulose nanofibers from the different cellulosic origins is performed using mechanical treatment, often in combination with some chemical or enzymatic pre-treatment prior to the disintegration step. The most common chemical pre-treatments are perhaps those that render the pulp fibers (pulp fibers are used when the botanical origin is wood) charged, *i.e.* anionic and cationic. This modification results in electrostatic repulsion between the fibers, which is also beneficial in the subsequent mechanical treatment step as it further