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RESEARCH ARTICLE

Novel nano-cellulose excipient for generating non-Newtonian droplets for targeted nasal drug delivery

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ABSTRACT

Purpose: Thickening polymers have been used as excipients in nasal formulations to avoid nasal run-off (nasal drip) post-administration. However, increasing the viscosity of the formulation can have a negative impact on the quality of the aerosols generated. Therefore, the study aims to investigate the use of a novel smart nano-cellulose excipient to generate suitable droplets for nasal drug delivery that simultaneously has only marginally increased viscosity while still reducing nasal drips.

Methods: Nasal sprays containing nano-cellulose at different concentrations were investigated for the additive's potential as an excipient. The formulations were characterized for their rheological and aerosol properties. This was then compared to conventional nasal spray formulation containing the single-component hydroxyl-propyl methyl cellulose (HPMC) viscosity enhancing excipient.

Results: The HPMC-containing nasal formulations behave in a Newtonian manner while the nano-cellulose formulations have a yield stress and shear-thinning properties. At higher excipient concentrations and shear rates, the nano-cellulose solutions have significantly lower viscosities compared to the HPMC solution, resulting in improved droplet formation when actuated through conventional nasal spray.

Conclusions: Nano-cellulose materials could potentially be used as a suitable excipient for nasal drug delivery, producing consistent aerosol droplet size, and enhanced residence time within the nasal cavity with reduced run-offs compared to conventional polymer thickeners.

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Introduction

Upper respiratory tract disorders such as rhinosinusitis, chronic-rhinosinusitis, seasonal allergy, and nasal infection are commonly treated using topical nasal administration [1]. Furthermore, the nasal cavity offers a perfect portal for the delivery of molecules into the systemic circulation [2] or brain [3]. The delivery of drugs to the nasal cavity is generally via nasal spray pumps, that deliver *ca.* 100 µl of formulation. The fluid can be either an aqueous solution or suspension of drug, as droplets of *ca.* 20–50 µm in diameter, with the majority of particles being >10 µm to avoid lower respiratory tract exposure [4,5].

One of the challenges of nasal drug delivery is ensuring the required dose is given in a minimal volume to avoid run off (i.e. nasal drip). Nasal drip is encountered when the formulation runs out of the nasal passage through the nostrils or down the back of the throat to be swallowed [6]. This results in dosing inconsistency as well as unpleasant taste, gag reflex and ultimately, poor compliance. To overcome this issue, a common approach is to incorporate excipient 'thickening' polymers into the aqueous component of the spray to increase viscosity and reduce run-off time. These polymers include hydroxyl-propyl-methyl-cellulose (HPMC), polyethelene glycol (PEG) and proprietary blends of microcrystalline cellulose (MCC), and carboxymethylcellulose sodium (CMC) in Avicel RC-591 (FMC, Philadelphia, USA).

However, increasing viscosity can have negative impact on the quality of the generated aerosol, since it will become increasingly difficult to generate droplets of a small size as viscosity increases. Increased viscosity also does nothing to stop fluid flow, instead only slowing it, so run-off occurs even for higher viscosity fluids. Thus, there is a limit to the volume fraction of excipient that can be used. An alternative to increasing viscosity through the use of conventional thickening 'swellable' polymers is to use smart materials with more complex rheological behavior than simply increased viscosity. These materials have similar rheological properties to water during droplet generation but controllable viscosity and a tunable and defined yield stress before and after deposition. One approach to achieve this is to use highly elongated network polymers, that have significant yield stresses on standing but undergo extensive shear-thinning upon agitation. Furthermore, in principle, such systems are likely to require lower volume fractions of excipient to achieve the same viscosity than their swellable polymer counterparts.

This paper investigates the use of a novel nano-cellulose excipient to generate droplets for nasal drug delivery. The nano-cellulose was fabricated using commercial food-grade Nata de Coco cubes of cellulose produced by Wong Coco (Jakarta, Indonesia) using cultures of *Acetobacter xylinus* bacteria [7]. The nano-cellulose material has very high aspect ratios (refer to

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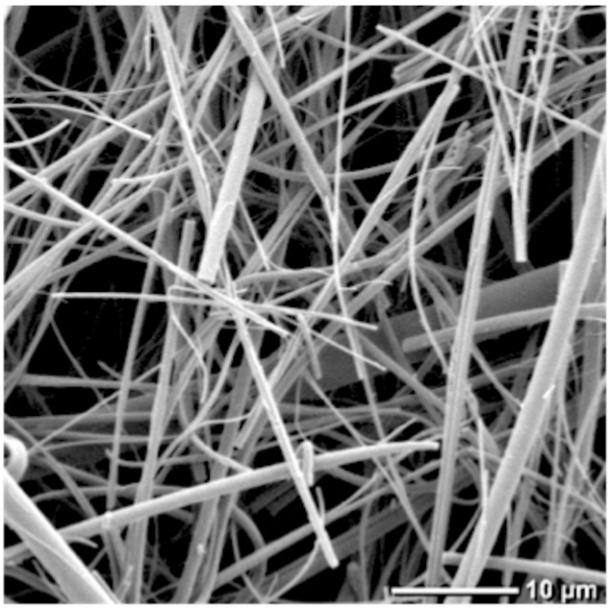

Figure 1. Scanning electron microscope image of nano-cellulose prepared by drying a 1% w/v solution on a TEM grid before imaging.

electron microscopy image in Figure 1) with thickness of around 50 nm and length of the order of 10 µm. Its fiber-like structure is likely to produce a complex network that imparts a small but useful yield stress when dispersed in water. Here, we study the rheological properties of this novel excipient and investigate its potential as an excipient for use in nasal sprays; comparing its aerosol properties to a conventional single-component hydroxylpropyl methylcellulose (HPMC) viscosity-enhancing excipient.

Materials and methods

Preparation of the smart nano-cellulose nasal formulation

Molecular dispersions (hereafter referred to as solutions) of HPMC (~26 kDa, 80–120 cP, 2% in H_2O, Sigma, Australia) and nano-cellulose were prepared in reverse osmosis purified water (Merck Millipore, Bayswater, VIC, Australia) in the following concentrations: 0.2%, 0.5%, 1.0% and 1.8% w/w. Nano-cellulose was prepared from bacterial cellulose cubes (Wong Coco, Indonesia). Cubes were first rinsed multiple times in deionized water to remove any non-cellulosic contaminants. Dispersions were then prepared using mechanical disruption in a laboratory blender (Sunbeam, Australia) followed by 5 min homogenization (T18 digital ULTRA-TURRAX homogenizer, IKA). The solids level of every feed stock was determined by gravimetric measurement and subsequent dilution with deionized water was then used to prepare different concentrations used in this study.

Scanning electron microscopy

The morphology of the nano-cellulose was analyzed by scanning electron microscope (JEOL-JCM 6000 NeoScope Benchtop SEM, Tokyo, Japan) at a number of magnifications, using 15 keV accelerating voltage. Prior to that, ~1 µl of the 1% w/w nano-cellulose suspension was added dropwise onto 200-mesh carbon coated Holey Copper grids and dried at room temperature. The sample was subsequently placed on adhesive black tabs, mounted onto aluminum stubs and gold coated with a sputter coater (BAL-TEC SCF 005, Tokyo, Japan).

Rheological characterization

The rheological characteristics of the nano-cellulose were evaluated using a stress-controlled rheometer (AR-1500 EX, TA instruments, New Castle, DE) with cone and plate geometry (cone diameter 6 mm, angle 2°). All measurements were performed at 25 °C and after a 30 s pre-shear and two min relaxation period. Elastic modulus, G', was obtained from a frequency sweep (from 10 to 500 s^{-1}) in the linear viscoelastic region at a constant stress of $\sigma = 0.01$ Pa. The yield stress was determined by fitting the flow curve to the Herschel–Bulkley model [8].

Run-off thickness film measurements

The run-off film thickness of each solution was evaluated by depositing 1 ml of either HPMC or nano-cellulose fluid onto a flat glass microscope slide which was then oriented to 45° from the horizontal. A Leica Wild M3C (Sydney, Australia) stereoscope connected to a Moticam 10MP (Causeway Bay, Hong Kong) camera was then used to record an image of the resulting film on the slide. Experimental film thickness was measured using image analysis via ImageJ software [9] and compared to theoretical calculations using:

$$h_i = \frac{\sigma_y}{\rho.g.cos\theta}$$

where h_i is the theoretical film thickness, ρ is the fluid density, g is gravitational acceleration, σ_y is the yield stress, and θ is the angle of the slope from the vertical [10].

Surface tension measurements

Droplet interfacial tension of the nano-cellulose at different concentrations was measured using a Kruss DSA100 pendant drop tensiometer. This was subsequently compared to surface tension measurements of water at room temperature.

Aerosol spray performance

For aerosol analysis, solutions were loaded into plastic nasal bottles and a VP7 nasal pump (100 µl, Aptar Pharma, Le Vaudreuil, France) with a spray nozzle (PRS 232NE + B63 NAT, Aptar) attached. Droplet size distribution of aerosols generated from the pump was measured using laser diffraction (Spraytec®, Malvern Instruments, UK). The pump was mounted at a measurement distance of 50 mm from the laser beam flow rate of 15 l/min pulled through the apparatus using a rotary vein pump (Becker Pumps, Sydney). Each formulation was tested seven times. Data were processed to produce a volume weighted particle size distribution and associated statistics.

Results and discussion

The viscosity of HPMC and nano-cellulose solutions as a function of shear rate is shown in Figure 2(A,B), respectively. In general, the viscosity for any given HPMC concentration remained constant as shear was increased from 10 to 500 s^{-1}. Such observations suggest that HPMC behaves in a Newtonian manner over this concentration and shear rate range. In addition, the viscosity increased linearly as a function of concentration. In comparison, the viscosity of the nano-cellulose solution was dependent on both the concentration and applied shear rate. At low shear rates (*ca.* 10 s^{-1}), for any given concentration, the viscosity of the nano-cellulose

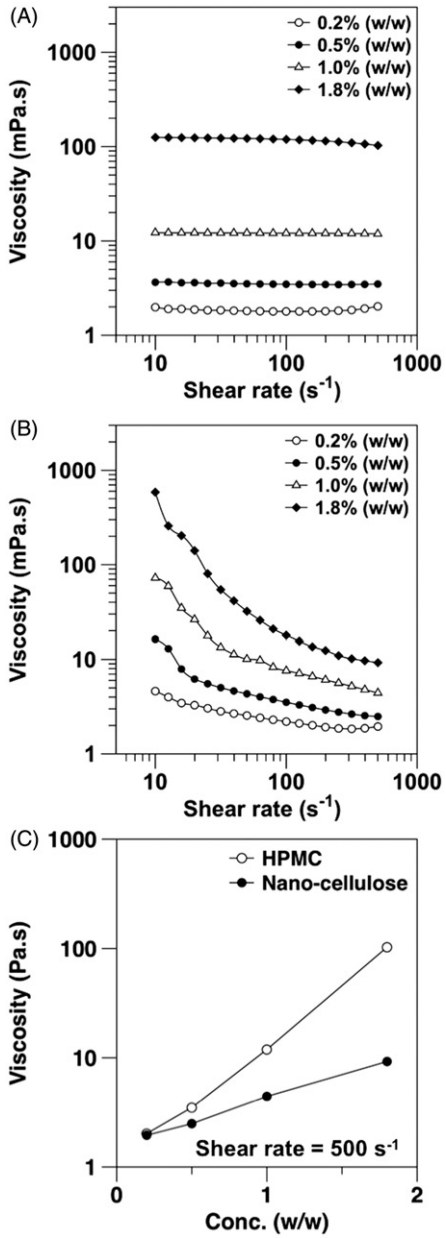

Figure 2. Viscosity of (A) HPMC and (B) SmartDrop solutions as a function of shear rate and concentration; (C) Viscosity as a function of excipient concentration at a fixed shear rate of 500 s^{-1}.

solution was approximately 10× that of HPMC at equivalent concentrations. However, as shear rate was increased, significant shear thinning was observed for all nano-cellulose solutions with the slopes indicating that all solutions would approach unity at high shear rates $\gg 500\,s^{-1}$. Since, the shear rate of conventional nasal spray pumps is estimated to be $\geq 10^5$ [11], it would be envisaged that the viscosity at these rates would approach 1 mPa s, essentially water. However, due to the shear rate limitation of rotational rheometry this measurement is not feasible. A direct comparison of the viscosity of the HPMC and nano-cellulose solutions at the higher shear rate of 500 s^{-1} suggests that nano-cellulose had significantly lower viscosities at higher concentrations (Figure 2(C)), which is likely to result in improved droplet formation when actuated through a conventional nasal spray. Analysis of the yield stress for nano-cellulose suggested that yield stress of the solution could be actively controlled by varying nano-cellulose concentration (Figure 3(A)). In general, a power law correlation was found

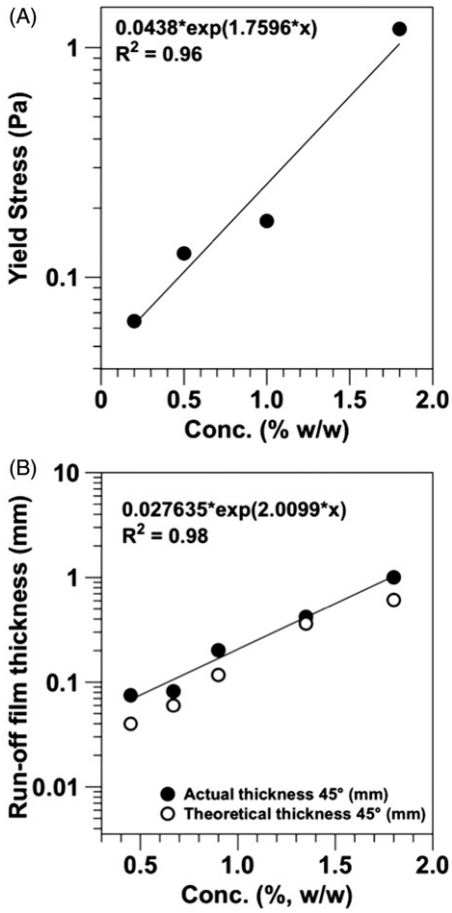

Figure 3. (A) yield stress of SmartDrop solutions as a function of concentration and (B) theoretical and actual run-off film thickness measurements of SmartDrop solutions.

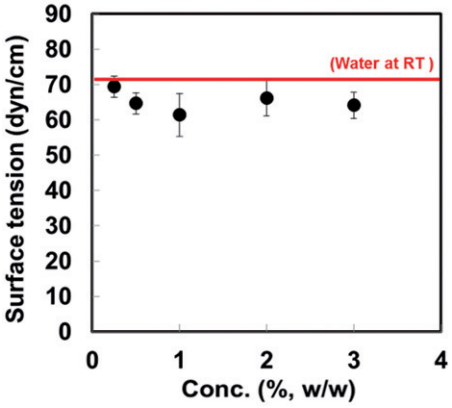

Figure 4. Surface tension of nano-cellulose solutions measured at room temperature by ring tensiometer.

between nano-cellulose concentration and yield stress. Nano-cellulose solutions exhibited a yield stress of 0.06, 0.12, 0.18, and 1.21 Pa for the solutions containing 0.2%, 0.5%, 1.0%, and 1.8% (w/w) excipient, respectively. In comparison, HPMC did not exhibit a yield stress. It is likely that the yield stress of the nano-cellulose is directly linked to the fiber aspect ratio and the strength of electrostatic interaction between contiguous fibers [12].

The run-off film thickness (Figure 3(B)) for nano-cellulose increased as a function of concentration and yield stress,

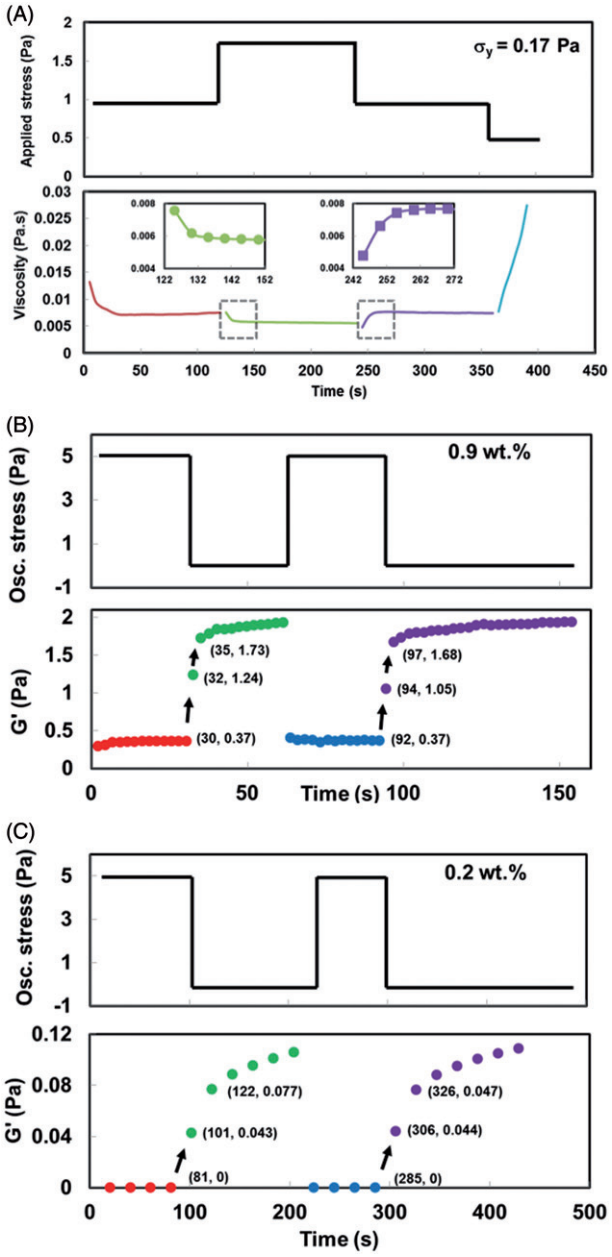

Figure 5. (A) The viscosity response time of 0.9% nano-cellulose solution is <5 s after sudden increase or decrease in applied stress, (B) Elasticity of 0.9% nano-cellulose solution regrows quickly, ~2 s, after a large oscillatory stress is suddenly reduced to zero in a stepwise oscillation measurement at a frequency of 1 Hz and (C) Elasticity of 0.2% nano-cellulose solution regrows quickly after a large oscillatory stress is suddenly reduced to zero in a stepwise oscillation measurement at a frequency of 1 Hz. The samples take ~10 s to reform fiber networks at lower nano-cellulose concentrations.

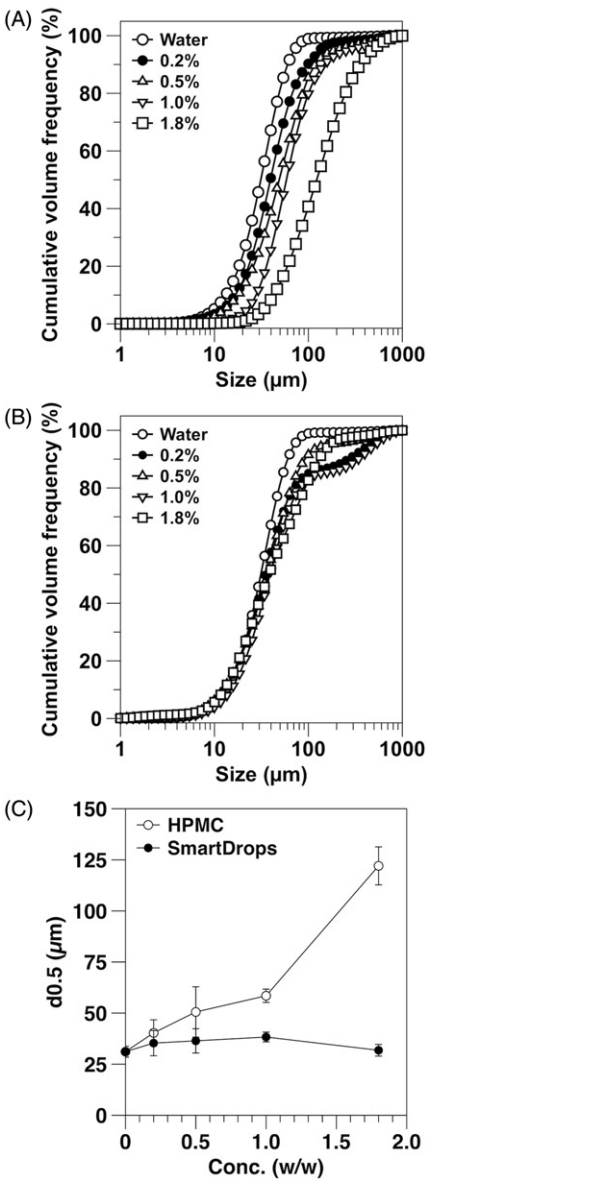

Figure 6. Volume weighted particle size distributions of (A) HPMC and (B) smart nano-cellulose solutions and (C) median particle diameter as a function of excipient concentration.

suggesting that this material could be used to generate thin films in the mucousa from ca. 0.1–1 mm with limited run-off. Interestingly, deviation was observed between the theoretical and experimental measurements with actual film thickness values being higher than theoretical values at lower nano-cellulose concentrations. It is likely that at such low concentrations, the surface tension component of the solutions interaction with the glass coverslip plays a role and some localized strengthening of the network occurs [13]. Furthermore, the surface tension (Figure 4) of the nano-cellulose solution was found to be only slightly lower compared to water at room temperature, indicating that the fibers have little effect on surface tension. Future studies will focus on more realistic surfaces and geometries. It needs to be noted however that the viscosity of the fluid is not the relevant property for enhancing coating thickness, as viscosity merely slows down flow. But rather, it is the fluid yield stress that is responsible for the observed coating benefits because the fluid does not flow at all when stresses are below the yield stress.

To demonstrate that the rheological network of nano-cellulose formulation will quickly reform after spraying to enhance retention in the nasal cavity, further rheological testing was performed. Step stress measurements are rheological tests that plot fluid viscosity or stress response as a function of time during sudden increase and decrease in applied stress. For flowing conditions, the response time of the viscosity of a 0.9% nano-cellulose sample is <5 s (Figure 5(A)). Another direct measure of microstructure recovery is via small-strain oscillatory tests of the dispersion fluid with the fluid response measured as a function of time. Figure 5(B,C) demonstrated that when the initial oscillatory stress of 5 Pa (30 times the yield stress value of 0.17 Pa) is suddenly reduced to

0.1 Pa, the elastic microstructure reforms rapidly after the stress is removed, taking ~2 s for 0.9% nano-cellulose solution (Figure 5(B)) and ~10 s for 0.2% nano-cellulose solution (Figure 5(C)). These viscosity responses indicate the rapid regrowth of fiber networks in the system when applied stress is suddenly reduced.

Volume weighted aerosol particle size distributions from HPMC and nano-cellulose solutions are shown in Figure 6(A,B), respectively. In general, HPMC modified the whole particle size distribution with increasing concentration resulting in an increase in median diameter. This is most likely due to increasing HPMC concentration causing a concurrent increase in liquid viscosity and thus reduction in droplet break-up at the actuator orifice. Specifically, the median diameter (Figure 6(C)) for the HPMC increased from 31.1 ± 3 μm to 122.0 ± 9.3 μm over the range of 0–1.8% w/w. The 0% w/w samples had a cone geometry that would result in maximal local deposition in the nasal cavity, however, as the concentration of HPMC was increased, the cone geometry became more confined and at high concentrations (i.e. 3% w/w, data not shown) failed completely since the liquid exiting the nozzle was in the form of a single jet. In comparison, the geometry of the nano-cellulose samples appeared to be similar and the median diameter for the nano-celluolose solutions was 31.1 ± 3 μm to 31.8 ± 2.9 μm over the range of 0–1.8% w/w (Figure 6(C)). Subsequently, it may be concluded that nano-cellulose may be a highly suitable excipient for formulating stable nasal sprays with consistent droplet size, enhanced residence time, with reduced run-off, after being deposited in the nasal cavity.

Conclusions

The use of nano-cellulose materials with very high aspect ratios may provide a means of producing stable aerosols that have enhanced rheological properties when compared to conventional HPMC 'swellable' polymer materials. The unique property of the nano-cellulose containing fluid is that it possesses a viscosity small enough to allow easy spray and droplet formation, while possessing a yield stress just large enough to enhance coating.

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Disclosure statement

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