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Short communication

The influence of chitosan on the microstructure and stability of a poly(D,L-lactide-co-glycolide)-based W/O emulsion to be processed by spray drying

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Introduction

Drug-loaded emulsions for spray drying should be optimised in terms of their rheological behaviour and stability under operating conditions (Guido, 2011; Tolstoguzov et al., 1974). We investigated the stability, microstructure and rheology of a PLGA/DCM-based W/O emulsion, an intermediate in the production of spray-dried drug-loaded microparticles. Two emulsions containing vancomycin hydrochloride (VAN) and PLGA (poly(D,L-lactide-co-glycolide)) with and without chitosan as a hydrophilic stabiliser were characterised using low-field nuclear magnetic resonance (LF NMR) to determine magnetic relaxation properties and droplet size. The rheological characterisation and theoretical interpretation of the obtained rheological data allowed the determination of velocity and shear rate/stress profiles within the feed path - aspects that are crucial for the industrial scale-up of the emulsion spray drying process.

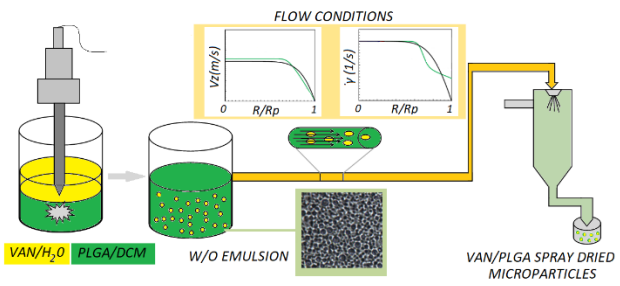

Fig. 1. Preparation of VAN/PLGA emulsion and spray drying

Materials and methods

Vancomycin hydrochloride was manufactured by Guangzhou Greensyn Pharma Co, Ltd (Guangzhou, China). Evonik (Darmstadt, Germany) was the supplier of poly(D,L-lactide-co-glycolide) (Resomer® RG 502 H, L/G ratio 50/50, acid terminated, Mw 7,000-17,000 Da, inherent viscosity 0.16-0.24 dl/g in chloroform at 25°C). Chitosan (from shrimp shells, low viscosity (20–200 mPas, c = 1 wt% in 1% acetic acid)) was purchased from Sigma-Aldrich (Steinheim, Germany). Dichloromethane was purchased from Merck (Darmstadt, Germany). Other materials were of analytical grade.

The dispersed aqueous phase (5 g) was prepared by dissolving vancomycin hydrochloride (625 mg) in purified water. To obtain the continuous organic phase (50 g), PLGA (2.5 g) was dissolved in dichloromethane. In the second emulsion, chitosan (50 mg) was dissolved in the aqueous phase with vancomycin hydrochloride. The emulsions were prepared by ultrasonication using Sonopuls HD 4200 with titanium flat tip TT213 (BANDELIN electronic GmbH & Co. KG, Berlin, Germany), 30 s at 100 % amplitude in a cold bath and stored in well-sealed glass vials at room temperature for 24 hours (Jurić Simčić et al., 2023).

LF NMR measurements (average spin–spin relaxation time of the hydrogens present in emulsions and dispersed phase droplet size distribution) were performed with a Bruker Minispec mq20 (0.47 T, Karlsruhe, Germany). HAAKE Mars III rheometer, equipped by a plate-plate

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(diameter 60 mm) measure device embedded inside a solvent trap was used for rheological characterization. Suitable mathematical models that can describe the experimental flow curves were fitted to the experimental data.

Results and discussion

The emulsions obtained were milky white and homogeneous. During the 24-hour period, the emulsions were monitored for signs of phase separation, which appeared as slight discolouration at the bottom of the vial. The physical segregation occurred through the formation of weak, reversible flocs that were easily broken by shaking, while the dispersed phase droplets retained their integrity. LF NMR measurements showed that the average spin–spin relaxation time and relaxation spectrum of the hydrogens present in freshly prepared and 24 h aged emulsions were very similar. In contrast, a completely different relaxation spectrum was determined for the non-reconstituted demixed emulsion, reflecting a completely different microstructure. However, for the emulsion containing chitosan, the number of relaxation times was the same and their values were very similar, indicating a higher structural reproducibility than for the emulsion without chitosan. Since chitosan is a hydrophilic polymer, it forms a network in the inner water droplets, which stabilises the system (McClements and Dickinson, 1996; Zhu et al., 2019). Considering the R-value (ratio between the LF NMR signal intensity with and without applying two opposite magnetic field gradients) and measuring the self-diffusion coefficient of the water molecules in the aqueous phase, the size distribution of the emulsion droplets was determined. The tested emulsions mainly contain droplets with a diameter of about 1 µm to 10 µm (Table 1), with the emulsion containing chitosan having a narrower droplet size distribution.

Table 1. Droplet size distribution results for freshly prepared emulsions

	D50 (volume) (µm)
VAN/PLGA	9.0 ± 0.90
VAN/CHITOSAN/PLGA	8.2 ± 0.04

Rheological characterisation showed that the two emulsions had the same non-Newtonian shear thinning behaviour. The zero shear viscosity was higher for the emulsion containing chitosan. The narrower droplet size distribution and the higher zero shear viscosity indicate a higher long-term stability, as the movement of the droplets is hindered.

Knowledge of the flow curves proved that laminar flow occurred in the tested tubing, shear rate and shear stress profiles of the flowing fluid and the velocity profile of the fluid were determined. This allowed us to structurally characterise the emulsions at rest and the flow conditions in the tested feed tubes of the spray dryer.

Conclusion

The use of chitosan as a stabiliser made it possible to obtain PLGA/DCM-based emulsions with a narrow droplet size distribution in the range 1-10 µm. Shaking was sufficient to restore the original emulsion structure and the emulsions exhibit high zero shear viscosity, which explains the increased long-term stability due to hindered droplet movement. LF NMR enabled the determination of the droplet size distribution and provided information on the magnetic relaxation properties (emulsion fingerprint), which proved to be a suitable tool for the structural comparison of different emulsions. The determination of flow curves, which is necessary to determine the flow conditions (shear rate/shear stress) to which the fluid is subjected when flowing in a tube, is essential for the scale-up of industrial processes. These conditions can strongly influence the emulsion structure and affect the properties of the final dry product. With this analysis, the shear rate/shear stress could be determined for each type of tube.

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