From lab-bench to large-scale production: low energy nanomilling bridges the gap[2]

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INTRODUCTION

In formulation development, the scale-up from a lab-bench production of small batches to a large-scale production due to a demand for bigger batches, e.g. for clinical trials or economic reasons, can often be challenging. Thus, the possibility to scale-up the manufacturing process is imperative for the success of a new formulation and should be evaluated during early stages of development. This applies to the production of nanocrystals (NC), which can be used to enhance the skin penetration properties of promising actives in the field of skin therapy, such as the flavonoid curcumin [1-3]. Curcumin is isolated from the rhizome of turmeric and acts as a selective inhibitor of the enzyme phosphorylase kinase. This leads to a positive effect on dermal wound healing after topic application with less inflammation and reduced scarring [2]. However, it shows an insufficient skin penetration, due to its poor aqueous solubility and low bioavailability [1]. Thus, the development of a suitable formulation for curcumin is crucial for its later use in therapy. After formulation development, low energy nanomilling with the NanoWitt-LAB 100 milling equipment enables an easy scale-up of the NC production in continuous operation. Therefore, it can be used as a suitable manufacturing process to determine the feasibility of a large-scale production.

AIM

The aim of this study was divided into two parts. The first part was the development of a curcumin NC formulation via a stabilizer screening to assess the most suitable surfactant for NC formulation production. The second part was the evaluation of the feasibility of the curcumin NC formulation for large-scale production.

MATERIALS AND METHODS

MATERIALS

Curcumin was used as a model drug and purchased from Receptura Apotheke (International compounding Pharmacy, Frankfurt a.M., Germany). The stabilizer screening was conducted with Plantacare® 818UP (PLC 818), Plantacare® 1200UP (PLC 1200) , Plantacare® 2000UP (PLC 2000), Poloxamer 188 (PLX 188), Poloxamer 407 (PLX 407) from BASF (Germany), Tween® 80 (VWR, Germany), d-α-tocopheryl polyethylene glycol 1000 succinate (TPGS) (Antares Health Products Inc, USA), Brij® L23 (Thermo Fisher GmbH, Germany) and Mirj™ S100 (Croda Personal Care, UK). Ultra-purified water was obtained from a PURELAB Flex 2 (ELGA LabWater, Veolia Water technologies Deutschland GmbH, Germany). Yttria stabilized zirconia beads (SiLibeads Type ZY-E, Sigmud Lindner GmbH, Switzerland) were used for the milling.

Stabilizer screening via small-scale bead milling

The stabilizer screening was conducted with formulations containing 5% (w/w) curcumin and 1% (w/w) surfactant and 94% (w/w) purified water. Nine different surfactants were used in the trial. The nanosuspensions were produced out of the bulk suspension via small-scale bead milling modified after [4]. The vials were placed on a multiple magnetic stirrer plate (Mixdrive15, 2mag AG, Germany) with external control unit and milled at 1,000 rpm for 24 h.

Large-scale production of curcumin NC

Based on the findings of the stabilizer screening, the selected curcumin NC formulation was manufactured under large-scale conditions with a state-of-the-art

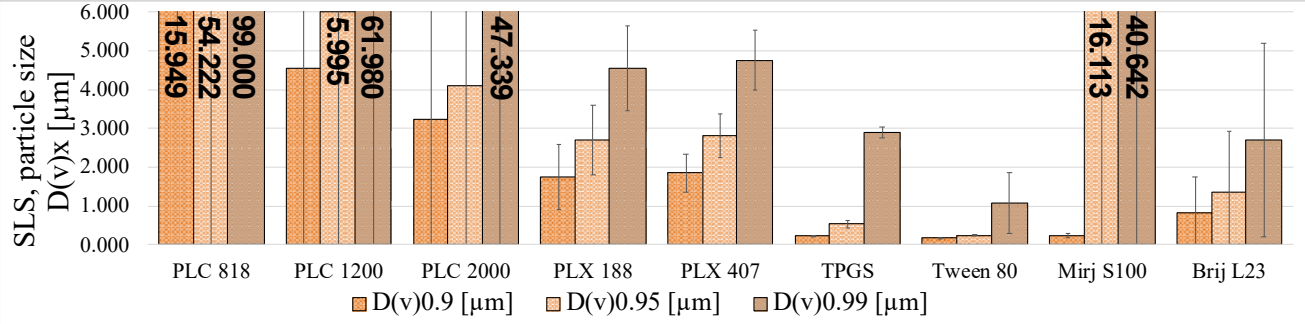

Figure 1: Results from SLS measurements of the curcumin nanocrystals stabilizer screening. TPGS is the stabilizer of choice.

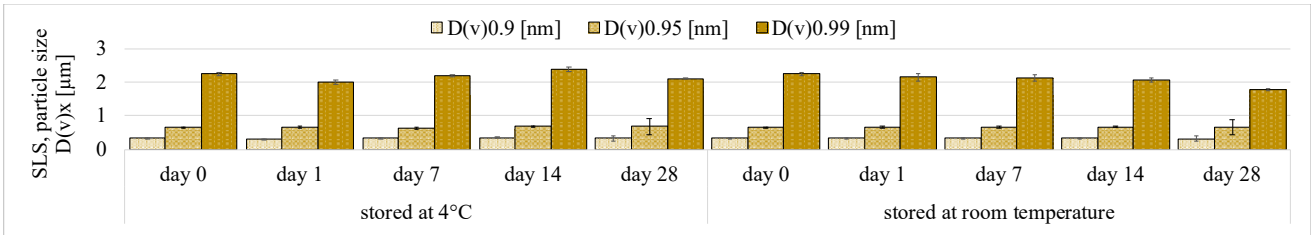

Figure 3: Stability of a TPGS stabilized curcumin nanosuspension. Samples were stored at 4°C and at room temperature.

NanoWitt-LAB 100 milling equipment (Frewitt fabrique de machines S.A, Fribourg, Switzerland) to evaluate the feasibility of a large-scale production of the curcumin NC. Milling was carried out in continuous mode configuration with a suspension circulation of 500 mL/min for 45 minutes. 4.7 m/s tip speed and a bead/suspension-ratio of 60/40 (V/V) were set. The utilized bead size was 0.3 - 0.4 mm. The batch size was 300 mL. Samples were stored at 4°C and at room temperature to evaluate the physical stability.

Characterization of NC

The hydrodynamic diameter (z-average) and the zeta potential (ZP) were measured by dynamic light scattering (DLS) using a Zetasizer Nano ZS (Malvern Panalytical GmbH, Germany). Static light scattering (SLS) was used to evaluate the volumetric particle size distribution with a Mastersizer 3000 (Malvern Panalytical GmbH, Germany). Data analysis was carried out by Mie-Theory. The real refractive index was set to 1.87 and an imaginary refractive index of 0.1 (blue light) and 0.01 (red light).

RESULTS AND DISCUSSION

Stabilizer screening via small-scale bead milling

TPGS and Tween® were suitable stabilizers for the curcumin nanosuspension (Fig. 1). Hence, TPGS was selected, due to its skin penetration enhancing ability [5], which is beneficial for the intended therapeutic use of the formulation.

Large-scale production and characterization of the NC

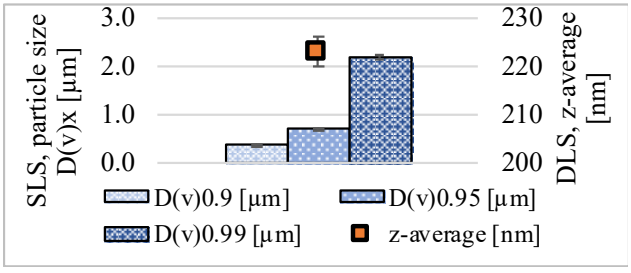

Figure 2: Results from SLS and DLS measurements of the TPGS stabilized nanosuspension.

Subsequently, the developed formulation was produced in large-scale via the NanoWitt-LAB 100 milling equipment. Sufficient nanonization was achieved after a short milling time of 45 min. Additionally, the low specific energy milling enabled an efficient diminution by keeping the product temperature below 18°C, preventing product degradation. The resulted particle size distribution is displayed in Figure 2. The manufactured nanosuspension showed a z-average of 230 nm. The D(v)0.99 value of approx. 2.2 µm indicated that some larger particles remained in the suspension. ZP in the original medium was -15 mV compared to -17 mV in conductivity water (50 µS/cm). The slight shift of the ZP predicts a strong attachment of the surfactant to the surface area, resulting in a sufficient stability of the suspension. Samples were stored at 4°C and at room temperature (Fig. 3). The TPGS NC formulation exhibited a sufficient stability over 28 days independent from storage conditions.

CONCLUSION

A curcumin NC formulation for topic application could be successfully developed via a stabilizer screening with small-scale bead milling. It was proven, that the developed formulation was also feasible for large-scale production with a NanoWitt-LAB 100 milling equipment, offering the possibility for an economic production. Sufficient nanonization was achieved after a short milling time, allowing a fast production of the curcumin NC. In conclusion, low energy nanomilling with the NanoWitt-LAB 100 milling equipment allowed the investigation of the feasibility of the nanosuspension for commercial production.

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