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Short communication

Azelaic acid nanosuspensions stabilized by chitosan and hydroxypropyl methylcellulose

Sandra Miočić[1], Kristina Ferderber[1], Marjana Dürrigl[1], Biserka Cetina-Čižmek[1], Jelena Filipović-Grčić[2]

[1]PLIVA Croatia Ltd. Prilaz baruna Filipovića 25, 10000 Zagreb, Croatia
[2]University of Zagreb, Faculty of Pharmacy and Biochemistry, Ante Kovačića 1, 10000 Zagreb, Croatia

Introduction

Nanocrystals (NCs) are a promising drug delivery system for topical application due to their high drug loading, greater surface area, apparent solubility and good skin adhesion (Malamatari et al., 2018; Pelikih et al., 2018). In particular, NCs with a size of 400–700 nm have been shown to preferentially accumulate in hair follicles, further increasing bioavailability (Gu et al., 2022).

However, the main obstacle in the development and production of NCs is their instability, especially in the form of liquid nanosuspensions (NS). Therefore, the choice of the optimal stabiliser that enables nanonisation and ensures the stability of the resulting nanosuspensions is the main challenge in their development (Li et al., 2021). In this study, the influence of stabilisers on the particle size and stability of nanosuspensions with azelaic acid (AZA) as the active ingredient was investigated.

Due to its antibacterial and keratolytic effects, AZA is used in numerous topical preparations for the treatment of acne and rosacea. The main limitations of its therapeutic use are low permeation and skin irritation (Sieber and Hegel, 2014). The formulation of azelaic acid in the form of nanocrystals is therefore a suitable strategy to overcome this problem, especially since the hair follicles are the target in acne. This approach is also justified by recent study results showing increased dermal bioavailability of NC AZA, embedded in a hydrogel (10%), compared to a commercial AZA cream containing 20% AZA (Tomić et al., 2021).

Nanocrystals are usually prepared by wet bead milling. For the final dosage form to be prepared with 10% AZA without the need for NC isolation by drying, the ground NS should have a higher AZA concentration (> 10%) and sufficient short-term stability.

Depending on the solids content of the nanosuspension, particle size and stabiliser system, viscosity can increase significantly as the milling process progresses (Singhal et al., 2020; Tomić et al., 2021). Furthermore, research has shown that hydrophobic molecules with very low solubility, high molecular weight and melting point are ideal candidates for the preparation of stable NS (Li et al., 2021), in contrast to AZA, which has relatively high solubility and low hydrophobicity in terms of nanonisation. These findings make the selection of the appropriate type and concentration of stabilisers for AZA NS even more challenging. Stabilisers with different stabilisation mechanisms (hydroxypropyl methylcellulose (HPMC) and chitosan) were tested independently and in combination at different pH values to evaluate their effect in the preparation of stable AZA nanosuspensions. HPMC is a high molecular weight nonionic polymeric stabiliser that stabilises by steric hindrance, while chitosan, a cationic polymeric stabiliser, acts by both electrostatic and steric stabilisation (Li et al., 2021). The stabilisers were selected depending on the physicochemical properties of AZA, especially its ionisation (pKa: 4.53 and 5.33) (National Library of Medicine).

Materials and methods

Azelaic acid (Dermaz 99) was purchased from BASF (Ludwigshafen, Germany). Chitosan (low viscosity, from shrimp shells), acetic acid and sodium hydroxide were purchased from Sigma Aldrich (St. Louis, USA). HPMC (Methocel E5 LV) was purchased from DuPont

*sandra.miocic@pliva.com

(Wilmington, USA). Redistilled water was used for all experiments. AZA (5-20%) was dispersed in an aqueous stabiliser solution using a magnetic stirrer (IKA, Staufen, Germany) and a Silverson LM5 homogeniser (Silverson Machines Inc., East Longmeadow, USA). The resulting suspension was ground on a Dyno-Mill Researchlab bead mill (Willy A. Bachofen AG, Muttenz, Switzerland). Yttrium-stabilised zirconium oxide beads (Silibeads® type ZY-P Pharma, Sigmund Linder GmBH, Warmensteinach, Germany) with a size of 0.1–0.2 mm were used. The particle size distribution of the NS was determined by dynamic light scattering (DLS) using the Zetasizer NaNO ZS (Malvern Instruments, Malvern, UK). The presence of particles larger than 1 µm was checked using a light microscope (Olympus BX51, Olympus, Japan). The short-term stability of the NS concentrates was evaluated after ten days at room temperature and 40 °C using DLS (particle size) and light microscopy.

Results and discussion

Based on the DLS and light microscopy results, NS target particle size was achieved with both HPMC (7.5% AZA, z-average = 685 nm, PDI = 0.219) and chitosan (5% AZA, z-average = 554 nm, PDI = 0.383). Further attempts to increase the AZA concentration in the formulation failed in the case of HPMC due to the sudden increase in viscosity and in the case of chitosan due to the appearance of foam, which in both cases led to clogging of the mill. However, with the combination of HPMC (1.2 - 3.0 %) and chitosan (0.1 - 0.3 %), these problems were solved and concentrated 20% AZA NSs with a z-average of 300-700 nm were successfully prepared in the pH range of 3.4 - 4.6. Most of the formulations showed good stability at room temperature. However, at 40°C, some crystal growth occurred in samples with a z-average of ~300 nm and a higher pH (4.6), most likely due to increased solubility of the nanocrystals triggering Ostwald ripening.

Conclusion

Concentrated (up to 20%), stable azelaic acid nanosuspensions with the desired particle size were successfully prepared by combining two stabilisers, the nonionic polymer HPMC and the cationic polymer chitosan.

Specific interactions between the stabilisers and the azelaic acid nanocrystals prevented excessive viscosity build-up and enabled the milling of 20% nanosuspensions. Further research is needed to better understand these interactions.

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