Wissenschaftliche Posterausstellung: Poster 18

Surfactant optimization for dermal azithromycin nanocrystals

Sven Staufenbiel (1), Nan Jin (1), Cornelia M. Keck (1,2) and Rainer H. Müller (1)

1: Department of Pharmaceutics, Biopharmaceutics and NutriCosmetics, Freie Universität Berlin, Kelchstr.31, 12169 Berlin, Germany
2: Applied Pharmacy Division, University of Applied Sciences Kaiserslautern, Campus Pirmasens, Carl-Schurz-Str. 10-16, 66953 Pirmasens, Germany

Azithromycin dermal formulations have been reported recently possessing better clinical efficacy than other topical antibiotics in the prevention of Lyme Borreliosis infection [1, 2]. The formulation in clinical testing is an ethanolic solution due to the poor water solubility of the drug. However, in general dermal suspension formulations are often superior to solution formulations, especially when nanosuspensions are used. Therefore an aqueous azithromycin nanocrystal formu¬lation was developed. In addition, ethanol evaporates after application, leading to the uncontrolled precipitation of drug as large particles. Smaller sized nanocrystals are also superior because of the smaller size and related larger surface area leading to a higher dissolution velocity in the moisture environment of the skin.

A two-step pearl milling method for the preparation of azithromycin nanosuspension was applied investigating six different surfactants, respectively: Poloxamer 188, Poloxamer 407, coco glucoside (Plantacare® 810 UP), decyl glucoside (Plantacare® 2000 UP), polyoxyethylene-20 sorbitan monooleate (Tween 80) and tocopheryl polyethylene glycol succinate (TPGS). 10% drug was dispersed in 1% surfactant solution by Ultra-Turrax for 1 minute at 8000 rpm. Then the resulting suspension was wet milled with yttrium-stabilized zirconia milling beads (size 0.1mm) until the particle size could not be reduced further. The process was performed at 5 °C.

For all formulations, independent on the surfactant, nanocrystals with diameters around 300 nm (z-ave) and a narrow size distribution (photon correlation spectroscopy polydispersity index around 0.2) could be obtained in just 10 minutes milling time. The nanosuspensions themselves were stable for 3 months. The optimized nanosuspension stabilized with TPGS with a size of 189 nm, PI 0.194, was incorporated into a 5% hydroxypropylcellulose (Klucel GF®) gel. The gel had the final concentration of 5% azithromycin described as being suitable for dermal Lyme Borreliosis treatment [2] and is by now physically stable for one month (no nanocrystal aggregation).

In summary, TPGS was found to be the most suitable surfactant for producing azithromycin physically stable nanosuspension. Nanocrystals below 200 nm were produced in a short production time. Production with a pearl mill can easily be scaled up, and the nanocrystals were also physically stable in the final gel formulation.

References:
[1] Piesman, J., Hojgaard, A., Ullmann, A. J., Dolan, M.C., Antimicrob. Agents Chemother. 58 (1), 348-351, 2014
[2] Knauer, J., Krupka, I., Fueldner, C., Lehmann, J., Straubinger, R. K., J. Antimicrob. Chemother. 66 (12), 2814-2822, 2011