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Improved solubility properties oftopical azithromycin nanocrystalsfor prophylaxis of borreliosisinfection

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The worldwide rate of Lyme disease infection has been increasing in recent years [1]. Among several defenses against it, using antibiotics is the most effective and economical approach [2]. Usually oral antibiotics are administered to patients who have been bitten by ticks. However the systematical administration of antibiotics could lead to some side effects such as bacterial resistance. Thus topical formulation for prophylaxis of Lyme disease infection is in demand.

Dermal azithromycin formulations have already been demonstrated efficacy and safety in clinical phase 1 and 2 studies [1-3]. Drug concentrations required being up to 10% [3]. However, the application of raw drug powder [2] limits bioavailability in the skin due to slow dissolution velocity of µm-sized crystals. Therefore in this study, the solubility properties of azithromycin were investigated when formulated as nanocrystal suspension (nanosuspension). Nanocrystals possess not only a higher dissolution velocity than large crystals, but also a higher saturation solubility, thus creating a higher concentration gradient and increasing skin penetration.

Azithromycin nanocrystals with a size of 189 nm were produced by bead milling, stabilized in suspension with tocopheryl polyethylene glycol succinate (TPGS). The saturation solubility of the nanosuspension compared to raw powder was determined in water by shaking for 8 hours in vials; dissolution velocity was determined by measuring dissolved drug concentrations as a function of time. The drug concentrations were analyzed by HPLC. The nanosuspension had an about 2 times higher saturation solubility in water (227 µg/ml) compared to the raw drug powder.

To create an even higher concentration gradient with the nanocrystal formulation, nanocrystals were dispersed in a water-propylene glycol mixture (80:20, w/w). The saturation solubility of the nanocrystals increased to 2828 µg/ml. In addition, the dissolution velocity was much higher for the nanocrystals than for the raw drug powder. Compared to their respective saturation solubility, the nanocrystals dissolved to 99% within 20 minutes and the raw powder showed only 68% dissolution even after 2 hours.

In summary, fast dissolution and increased saturation solubility could be shown for the azithromycin nanosuspension. Based on nanocrystal theory - it is expected that the drug concentration of 10% [3] in the dermal formulation can be distinctly reduced due to the higher thermodynamic activity of the nanocrystals, at simultaneously higher drug concentration in the skin.

References:

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