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Skin-friendly nanocrystals of miconazole nitrate – synergistic combination with chlorhexidine digluconate

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Miconazole nitrate (MN) is a well-known fungicide used against fungal skin infections. Due to the poor solubility of MN in water (1:3000, ethanol 96% 1:140) and the occurrence of skin irritations while using organic solvents or solubilized solutions, the aim was to develop a skin-friendly formulation based on an aqueous nanosuspension with a skin-friendly stabilizer.

Chlorhexidine digluconate is reported to improve the antifungal activity of MN due to synergistic effects [1]. Combination products on the market are e.g. the veterinary shampoo Malaseb® (1 ml Malaseb® shampoo contains 20 mg miconazole nitrate and 20 mg chlorhexidine digluconate). Thus chlorhexidine digluconate was added to the nanosuspension, however it destabilizes suspensions. Thus a screening needed to be performed to identify a physically stable nanosuspension composition. Finally, a potential superior anti-fungal performance had to be tested.

In contrast to e.g. veterinary shampoos, which are washed off after a certain (unpleasant) incubation time on the fur of dogs/cats, the nanosuspension can be applied and forms a long-lasting depot due to the adhesiveness of the nanocrystals. The fungicide effect was determined against S. cerevisiae in inhibition zone assays.

MN 2 % with the same content of chlorhexidine digluconate in various 0.3 % stabilizer solutions were milled by wet bead milling (PML-2, Bühler AG, Switzerland), using 0.2 mm yttria stabilized zirconium oxide beads at 2000 rpm and 5 °C. As skin-friendly stabilizer poloxamer 407 and Tween 80 (even accepted for i.v. injection!) were used. Optimal milling time depending on stabilizer was 30 minutes for poloxamer 407 and 35 minutes for Tween 80. Size analysis was performed by photon correlation spectroscopy (PCS, Zetasizer Nano ZS, Malvern Instruments, UK) and additionally by light microscopy to detect potential larger particles/aggregates outside the measurement range of PCS. Dermal hydrogel formulations with 1 % MN nanocrystal were prepared by magnetic stirring of a freshly produced MN nanosuspension mixed with 5 % hydroxypropyl cellulose (HPC) for >3 hours while remaining of crystal size was monitored. Inhibition zone assays of the formulations were performed for

48h at 30°C on universal yeast agar plates with 20 µl of formulation. All MN nanocrystal formulations were tested against commercial products (“Malaseb”, “KSK Miconazol Crème” and MN dissolved in DMSO) and also against a microsuspensions.

The surfactants poloxamer 407 and Tween 80 were both identified as suitable stabilizers. After 30 respectively 35 minutes of milling time nanocrystals were obtained. For Tween 80 the main nanocrystal PCS diameter was 237nm/254 nm at 0.20/0.25 PCS polydispersity index (PdI) without/with chlorhexidine gluconate. MN nanocrystal size stabilized with poloxamer 407 was 313/350 nm at 0.27/0.20 polydispersity index, respectively. All PCS results were in good agreement with light microscopy, no aggregations. Incorporation into the HPC gel did not change the size distribution, no aggregation was observed by light microscopy. After one month of storage, PCS results showed negligible particle growth of 10 to 40 nm for the suspensions itself. The stability of the nanocrystals was not affected in hydrogel formulations, very few particles > 1 µm were visible by light microscopy.

Determining the formulations antifungal activity by an inhibition zone assay with S. cerevisiae demonstrated the advantages of nanocrystals. Inhibition zone diameters for all nanocrystal gel formulations, with and even without (!) chlorhexidine gluconate, were higher than the inhibition zone diameters for the commercial products having equal active concentration. The positive effect of the nanocrystals became very obvious when comparing them to MN microsuspension. The inhibition test diameters were almost two times higher for nanocrystals. “Miconazol KSK Crème” (commercial product only with MN) was in the same range as the MN microsuspension.

In conclusion, a physically stable nanocrystal combination product, both as suspension and also as hydrogel formulation, were successfully developed. The inhibition zone assay showed the improved fungicide effects compared to microsuspensions and existing commercial formulations. The developed formulation is thus suitable for developing a superior market product.

References:

1. Codd J.E., Deasy P.B. International Journal of Pharmaceutics. 1998 (173); 3-11.