Metronidazole Crystal Patterns formed during the Metamorphosis of Topical Carbopol Gels

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PURPOSE

This study was performed to investigate the identity of highly branched, swirling microstructures observed in the Reference Listed Drug (RLD) metronidazole gel, 0.75% product (MetroGel®) and in generic metronidazole gel, 0.75% products (Tolmar and Taro) following dose application, drying and metamorphosis. As part of this investigation, several formulation variables that had the potential to influence the appearance of these highly branched swirling microstructures were systematically evaluated.

METHODS

A small amount of each commercially available metronidazole gel, custom-made metronidazole solution, 0.75%, or custom-made metronidazole gel, 0.75% formulation was applied on a section of human cadaver skin and/or on glass slides, allowed to dry, and observed using light microscopy and/or by scanning electron microscopy (SEM). The SEM was performed by coating the dried sample with 62% silver adhesive 503 on a 12.7 mm sample stub (3.2 mm pin).

The custom-made Carbopol-based gels containing 0.75% metronidazole were also prepared with systematic formulation changes designed to elucidate the influence of aqueous vs. hydro-alcoholic solvent systems, pH, viscosity, and propylene glycol on the crystal structures formed during metamorphosis (drying) on a glass slide. In addition, two different 5-nitroimidazole active pharmaceutical ingredients (APIs), tinidazole and dimetridazole, that are similar in molecular structure to metronidazole, were formulated in solutions and gels, allowed to dry in a similar manner, and evaluated by microscopic analyses. Independently, X-Ray Diffraction (XRD) and Differential Scanning Colorimetry (DSC) studies were performed to characterize the unique crystalline microstructures that formed, and to assess whether there were differences in the polymorphic form of the material (metronidazole) that formed swirling microstructures under certain conditions, and linear microstructures under other conditions.

RESULTS

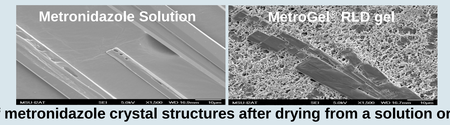

Fig. 1: SEM images of metronidazole crystal structures after drying from a solution or the RLD MetroGel®

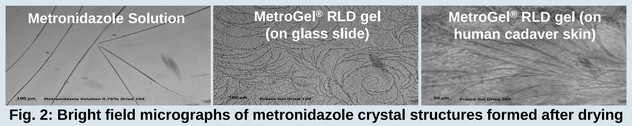

Fig. 2: Bright field micrographs of metronidazole crystal structures formed after drying from a solution, or from the RLD MetroGel® on either a glass slide or on human skin

Unique, highly branched swirling crystal microstructures of metronidazole were observed after the RLD MetroGel®, 0.75% products were applied and briefly allowed to dry on the surface of either the cadaver skin or the glass slide.

Impact of aqueous and hydro-alcoholic solvent systems: When metronidazole precipitated and crystallized from either an aqueous or hydro-alcoholic solution, elongated linear, unbranched crystal microstructures were observed, regardless of aqueous pH in the range of 3.5 to 12.4.

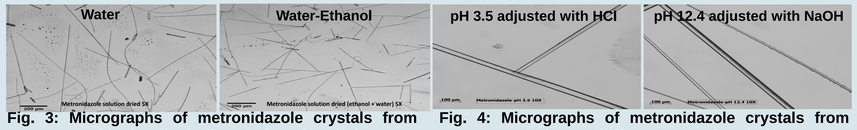

Fig. 3: Micrographs of metronidazole crystals from aqueous and hydro-alcoholic solution after drying

Fig. 4: Micrographs of metronidazole crystals from aqueous solutions at different pH's after drying

Impact of pH: The formation of crystal microstructures was specifically associated with the precipitation and crystallization of metronidazole from Carbopol-based gels, with neutral to alkaline pH values. Additionally, an increase in pH of a Carbopol-based metronidazole gel appeared to lead to more highly branched and more curved swirling crystal microstructures, regardless of the nature of the pH modifier.

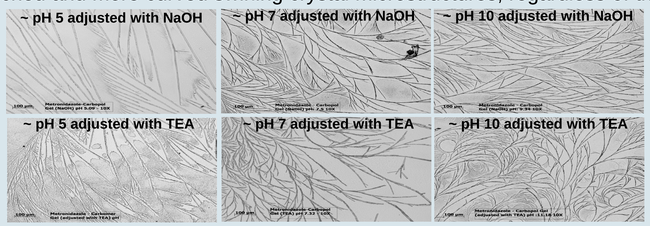

Fig. 5: Micrographs of metronidazole crystals from custom made Carbopol-based gels (Carbopol concentration-0.75%) after drying (Different bases, either sodium hydroxide (NaOH) or triethanolamine (TEA) was used to modify the pH, as indicated)

Impact of viscosity: An increase in the viscosity (with Carbopol content) of alkaline (pH 10) metronidazole gel formulations was associated with increased branching and curvature in the crystalline microstructures formed; this was not observed with gels at a lower pH (data not shown).

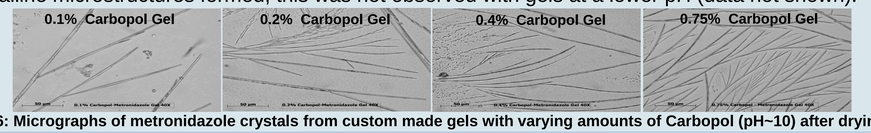

Fig. 6: Micrographs of metronidazole crystals from custom made gels with varying amounts of Carbopol (pH~10) after drying

Impact of propylene glycol (PG): PG was incorporated into the 0.75% Carbopol-based gels at pH 5 to understand the impact of excipients on the branching observed in marketed gels (pH ~5; Fig. 2) and custom made gel (pH~5). The addition of PG to the gel led to an increase in the branching density.

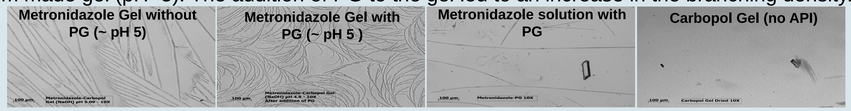

Fig. 7: Micrographs of metronidazole from custom made gels after drying with individual and combination of excipients

Impact of API: Studies with the other two 5-nitroimidazole APIs, tinidazole and dimetridazole, dried from solutions resulted in unbranched linear microstructures, whereas more branched and slightly more curved microstructures were formed when these APIs crystallized out from Carbopol-based gels.

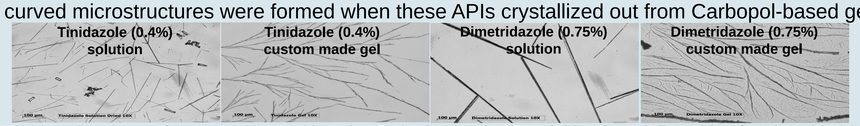

Fig. 8: Micrographs of crystal structures formed by other 5-nitroimidazole APIs, tinidazole and dimetridazole, when dried from a solution or a custom made Carbopol-based gel (Carbopol concentration 0.75%)

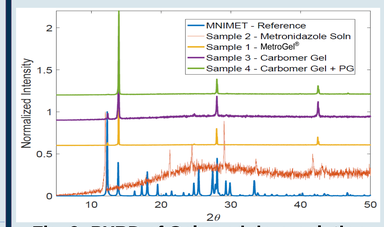

Fig. 9: PXRD of Gels and drug solution

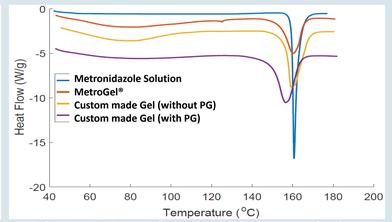

Fig. 10: DSC of Gels and drug solution

The XRD and DSC studies indicated that there was no change in the polymorphic form of metronidazole, despite the differences in branching and curvature observed for the metronidazole crystals under different conditions.

CONCLUSION

The highly branched, swirling microstructures observed in the RLD and generic metronidazole gel, 0.75% products following dose application, drying and metamorphosis were identified to be crystalline formations of metronidazole. The absence of these metronidazole microstructures with HPMC gels (data not shown) and the apparent requirement of a base for the formation of these crystal structures is consistent with a mechanism whereby the swirling crystal microstructures may arise from an interaction between a charged polyacrylic acid (Carbopol) and metronidazole. The increase in branching with an increase in pH may be attributed to an increased charge density of the polymer. The role of propylene glycol in intensifying the branching is not yet fully understood. Based upon the crystalline microstructures formed with the preparations of tinidazole and dimetridazole, it appears that the imidazole moiety of the compounds studied may be the chemical structure responsible for the formation of the branched crystalline microstructures under relevant conditions.

FUNDING ACKNOWLEDGEMENT & DISCLAIMER

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