Metronidazole crystal patterns formed during the metamorphosis of topical carbopol gels.

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ABSTRACT

Metronidazole topical formulations such as gels, creams, and lotions are used in the treatment of bacterial vaginosis and inflammation lesions of rosacea. Metronidazole precipitating from a Carbopol-based gel resulted in the formation of unique, highly branched, curvilinear microstructures. In contrast, metronidazole precipitated as linear, acicular crystals from drug solutions. The reason for the change in crystal habit was investigated by preparing different custom-made solutions and gels. Custom-made solutions were prepared using different solvent systems. Custom-made gels were prepared using different concentration of pH modifier, carbopol and other excipients. Characterization studies were carried out on the recrystallized metronidazole using bright-field microscopy, polarized microscopy, scanning electron microscopy (SEM), Differential Scanning Calorimetry (DSC), Fourier transform infrared spectroscopy (FTIR), and Powder X-Ray Diffractometry (PXRD). The results indicated that the change in crystal habit was likely due to the interactions between the nitro-imidazole moiety of metronidazole and the polymer without a change in the polymorphic form.

KEY WORDS: Metronidazole, carbopol gel, crystal habit, 5-nitroimidazole, drug-polymer interaction

INTRODUCTION

The recrystallization of a drug from its vehicle can result in changes in its polymorphic form, thereby leading to changes in the physical properties such as solubility, melting point, and others depending upon the solvent used, temperature, pressure, container, and so on (1). The solvent and method of crystallization are some of the factors known to influence the crystal habit due to the interactions between the solvent and the facets of growing drug crystals (2).

Topical semisolid products undergo metamorphosis after application onto the skin leading to changes in their composition and microstructure, which influence the performance of the drug product. These changes are due to the shear the formulation experiences during the application and evaporation of the volatile solvents from the product (3). Evaporation of the solvents may result in the precipitation of the drug from the vehicle causing crystal dissolution-dependent delivery of the drug at the site of action (4).

Metronidazole gel, 0.75% used for topical treatment of inflammatory lesions of rosacea, consists of dissolved drug in a Carbopol-based hydrogel (5). This study investigated the formation of unique, highly branched, curvilinear microstructures observed on glass slides as well as human cadaver skin following metamorphosis, which contrasted with the long needle-like crystals that

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formed when metronidazole precipitated from water. Martino *et. al.,* studied the influence of changes in solvent polarity on the resulting metronidazole crystal habit. It was inferred that solvents having a higher polarity index led to formation of acicular or needle-shaped crystals, while those solvents with a low polarity index led to formation of isodimensional crystals (6).

The change in crystal arrangement of metronidazole on precipitation from the gel is driven by the formulation composition and/or structural features of the molecule. In this study, several formulation variables such as pH, solvent system, polymers, the concentration of Carbopol gel, addition of propylene glycol, and active pharmaceutical ingredients (API) with a 5-nitroimidazole structure were systematically evaluated for their effects on crystallization. Custom-made solutions and gels were prepared and subjected to metamorphosis. The precipitated drug was studied using different characterization techniques like using bright-field microscopy, polarized microscopy, scanning electron microscopy (SEM), Differential Scanning Calorimetry (DSC), Fourier transform infrared spectroscopy (FTIR), and Powder X-Ray Diffractometry (PXRD).

MATERIALS AND METHODS

Materials

Metronidazole was purchased from Acros Organics (Geel, Belgium), hydroxypropyl methylcellulose (HPMC) from the Dow Chemical Company (Michigan, USA), sodium hydroxide from Ward's Science, triethylamine from Sigma Aldrich, and hydrochloric acid from VWR International, LLC, Ontario, Canada. Carbopol 940 was gifted by Lubrizol Advanced Materials Inc., (Ohio, USA). Metronidazole gels USP, 0.75% manufactured by Prasco Laboratories (Ohio, USA), Taro Pharmaceutical Industries Ltd. (Haifa Bay, Israel), and Tolmar Inc. (Colorado, USA) were procured from Health Center (University of Mississippi), (Mississippi, USA). Human cadaver skin was procured from the New York Firefighters Skin Bank.

Methods

Preparation of metronidazole solutions

Metronidazole solutions (0.75% w/w) were prepared by dissolving metronidazole in purified water using a vortex mixer to form a clear transparent solution. The pH of the solutions was adjusted using either hydrochloric acid or sodium hydroxide to make the solutions acidic or basic (as needed). A hydroalcoholic solution of metronidazole (0.75% w/w) was also prepared by dissolving metronidazole in a mixture of purified water and ethanol (50% v/v).

Preparation of custom-made metronidazole/Carbopol gels

Metronidazole gel (0.75% w/w) was prepared by adding of Carbopol (0.75% w/w unless otherwise specified) into the metronidazole solution and mixed using a stirrer to form a homogeneous gel. The gel was either left as such or modified using pH modifiers (sodium hydroxide and triethylamine) as specified to form a clear and smooth gel.

Preparation of custom-made metronidazole gels using other polymers

Metronidazole gels were also prepared by the addition of 0.75% w/w HPMC in metronidazole solution and the pH was adjusted to 7 using sodium hydroxide.

Preparation of custom-made metronidazole/Carbopol gels of different pH using different pH modifiers

To observe the impact of pH on the crystal habit, metronidazole-Carbopol gels (0.75 %w/w) were prepared as previously detailed and the pH was modified using either sodium hydroxide or triethylamine. Three different gels having a pH of 5, 7, and 10 were prepared by using each of the pH modifiers.

Preparation of custom-made metronidazole/Carbopol gels of different viscosities

Custom-made metronidazole gels (0.75% w/w) of different Carbopol concentrations were prepared as previously mentioned using different concentrations of Carbopol (0.1%, 0.2%, 0.4%, and 0.75%) to

study the effect of viscosity on the crystal habit of the metronidazole formed after drying of the metronidazole/Carbopol gel.

Preparation of custom-made metronidazole/Carbopol gel with propylene glycol

Carbopol gels neutralized using sodium hydroxide to pH 5 were prepared with and without propylene glycol (1.0% w/w) to observe the impact of propylene glycol on the crystal habit of metronidazole.

Preparation of Carbopol gels with other 5-nitroimidazole compounds

To study whether the 5-nitroimidazole moiety in metronidazole was responsible for the observed crystal growth patterns, Carbopol gels were also prepared using tinidazole (0.4% w/v) and dimetridazole (0.75% w/v) solutions. Tinidazole and dimetridazole also have the 5-nitroimidazole moiety in their chemical structure. The solutions with these compounds were prepared using the same procedure as the metronidazole solution.

Characterization

Light microscopy, scanning electron microscopy and polarized light microscopy

A small amount of each commercially available metronidazole gel, metronidazole solution, and custom-made metronidazole gels was applied on glass slides. They were dried briefly at room temperature, followed by observation using brightfield light microscopy (Zeiss Axio Imager.A2) and polarized microscope (Olympus BX-51 optical microscope with dual polarizing filters). Similarly, the marketed metronidazole gel and solution were applied on a 12.7 mm sample stub (3.2 mm pin). The dried sample was coated with 62% silver adhesive, and observed using a scanning electron microscope at 5.0 kV (JEOL JSM-6500F).

Fourier transform infrared spectroscopy

Metronidazole, custom-made metronidazole gel with sodium hydroxide and propylene glycol, and its control formulations were dried and subjected to FTIR studies using an Agilent Cary 660 FTIR Spectrometer (Agilent Technologies, Santa Clara, CA, USA) to investigate the interaction between drug and other ingredients of the formulation. The spectra were collected over the range of 600–4000 cm^{-1} with 16 scans and a resolution of 4 cm^{-1}. The spectra were normalized after the baseline correction of the entire spectrum.

Differential Scanning Calorimetry (DSC) and Powder X-ray diffraction (XRD).

DSC (Q100 DSC, TA Instruments, New Castle, DE) and powder XRD (X'Pert Pro MPD system, PANalytical B.V., Almelo, the Netherlands) were performed on the dried samples of metronidazole solution, marketed metronidazole gel, (0.75%) product and custom-made metronidazole gels (with and without propylene glycol) to assess whether the change in crystal habit was driven by a change in the polymorphic form. For DSC experiments, ~5 mg samples were sealed in an aluminum sample pan. Heat flow with respect to temperature was compared with an empty aluminum reference pan as samples were heated at 20°C/min under a 50 mL/min dry nitrogen purge to a final temperature of 180°C. Data were interpreted relative to an enthalpy calibration using an indium standard and a 3-point temperature calibration using o-terphenyl, indium, and tin. The PXRD samples were analyzed in transmission mode, using CuKα radiation (λ=1.5406 Å), an elliptical mirror, and an X'CeleratorTM detector, and respective operating voltage and amperage of 45 kV and 40 mA. Diffraction data were collected at an angular step size of 0.017° 2θ (61.37 s/step) over a range of 2–60° 2θ. Reference diffraction patterns were obtained from the Cambridge Structural Database (CSD, Cambridge, UK) (7), while visualization of planes was done using the Mercury platform available from the CCDC (Mercury 2022.1 Windows, Cambridge, UK) (8).

RESULTS AND DISCUSSION

Light microscopy

Unique, highly branched, curvilinear microstructures were observed after the marketed metronidazole gel, 0.75% products were applied and briefly allowed to dry on the surface of either the cadaver skin or the glass

Table 1 Crystal habit of marketed gel and solution

GEL	METRONIDAZOLE CONC. (%w/w)	CARBOPOL	pH MODIFIER	pH	CRYSTAL HABIT
Marketed metronidazole gel	0.75%	Present (Quantity unknown)	Present (Quantity unknown)	5.2 ± 0.0	Curvilinear crystals
Metronidazole Solution	0.75%	Absent	Absent	-	Straight elongated crystals
Custom-made Gel	0.75%	0.75%	Absent	3.51	No precipitation

slide. In contrast, when metronidazole precipitated and crystallized from an aqueous solution, elongated linear crystals were observed, without any branching. A control formulation comprised of metronidazole and Carbopol was also prepared and observed after drying. Crystals were not observed in the control formulation, which might be due to the higher solubility of the drug in the Carbopol base (Table 1, Figure 1).

Impact of hydro-alcoholic solvent system and pH on the crystal structure of metronidazole precipitated from solution

When precipitated from a hydro-alcoholic solvent system or the acidic or alkaline solutions, the crystals of metronidazole were needle-like, similar to the crystals precipitated from aqueous metronidazole solution without any pH modifications (Table 2, Figure 2).

Crystal structure of metronidazole precipitated from HPMC

Crystals were not observed in the micrographs of custom-made metronidazole gels made from HPMC, with and without a pH modifier, even allowing for prolonged drying times. This may be due to differences in interaction between metronidazole with the HPMC relative to that in Carbopol gels (Figure 3).

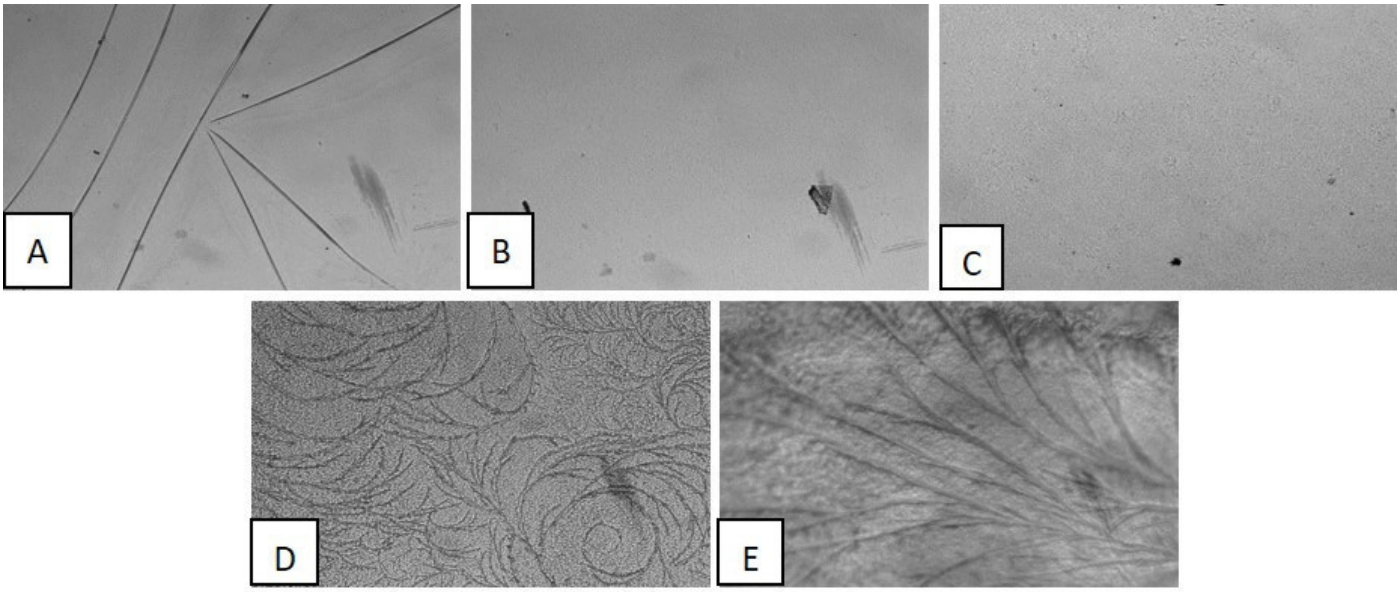

Figure 1 Bright field micrographs after drying of (A) metronidazole solution, (B) residue after drying of Carbopol gel without metronidazole, (C) residue after drying Metronidazole/Carbopol gel, (D) MetroGel® on a glass slide, and (E) MetroGel® on a human skin. Metronidazole crystals that formed after drying (A) differed in habit from those observed after drying (D), and (E).

Table 2 The effect of the solvent on metronidazole crystal habit

METRONIDAZOLE CONC. (%w/w)	TYPE OF SOLVENT	CRYSTAL HABIT
0.75%	Aqueous	Linear
0.75%	Hydro-alcoholic	Linear
0.75%	Aqueous (acidic)	Linear
0.75%	Aqueous (basic)	Linear

Effect of pH on the crystal structure formed during metamorphosis

Metronidazole crystals were not observed after samples of the metronidazole-Carbopol gel were dried without addition of alkaline agent (pH = 3.51). This contrasted observation of the metronidazole-Carbopol gels alkalized to pH >4, from which curvilinear metronidazole crystals grew after drying. The solubility of metronidazole varies minimally over this pH range (9), suggesting that the Carbopol inhibits crystallization of the metronidazole differently at the pH values studied. The results also illustrated that an increase in the pH of a Carbopol-based metronidazole gel led to increasingly branched curvilinear crystal microstructures, regardless of the nature of the pH modifier (Table 3, Figure 4).

The influence of viscosity (polymer concentration) on crystal structure formed during metamorphosis

It was observed that when the viscosity of alkaline (pH 10) metronidazole gel formulations was increased (with increasing Carbopol content), the crystalline microstructures that formed had increased branching and curvature (Table 4, Figure 5).

The influence of propylene glycol on crystal structure formed during metamorphosis

It was observed that the habit of the crystals formed from dried custom-based metronidazole gels adjusted to pH 5 was different from the crystal habit of the marketed gel (pH 5). To understand the differences in crystal habits of these gels, the impact of adding propylene glycol to the formulations was studied, with

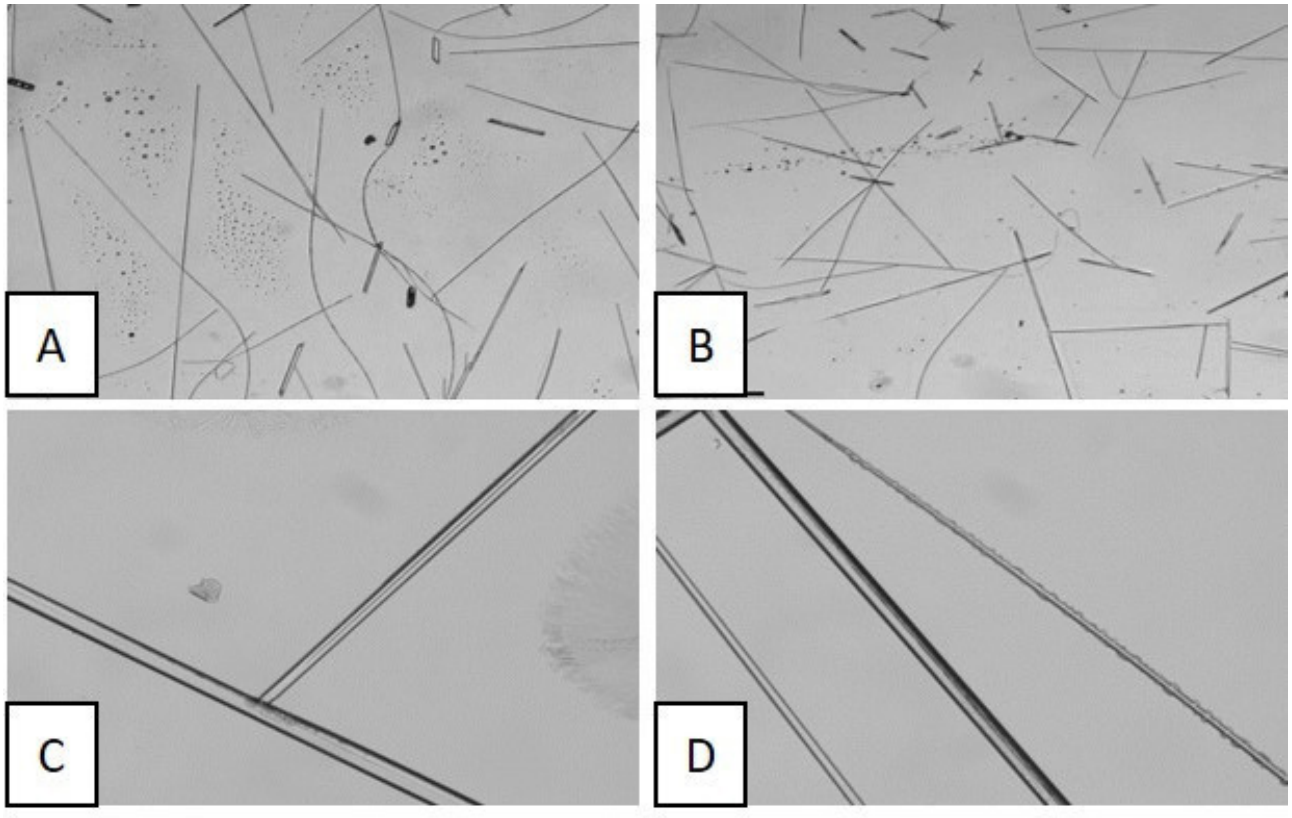

Figure 2 Bright field micrographs of metronidazole crystals formed after drying from (A) aqueous solution (B) hydro-alcoholic solution (C) aqueous solution at acidic pH (D) aqueous solution at alkaline pH.

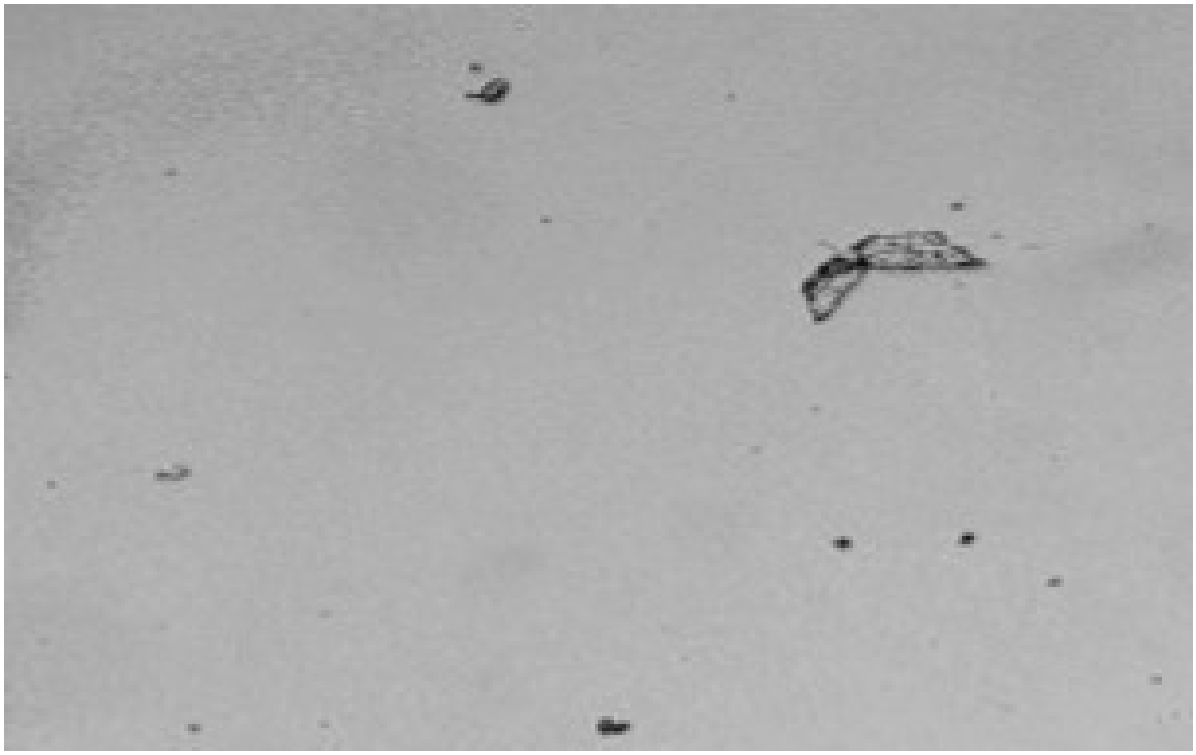

Figure 3 Bright field micrographs of residue formed after drying of custom made HPMC gel.

Table 3 The effect of the gel pH on metronidazole crystal habit

GEL	METRONIDAZOLE CONC. (%W/W)	CARBOPOL CONC. (%W/W)	PH MODIFIER	PH	CRYSTAL HABIT
Custom-made	0.75%	0.75%	NaOH	5.1	Less branched and curvilinear
			NaOH	7.5	Moderately branched and curvilinear
			NaOH	9.3	Highly branched and curvilinear
			Triethylamine	4.3	Less branched and curvilinear
			Triethylamine	7.3	Moderately branched and curvilinear
			Triethylamine	11.2	Highly branched and curvilinear

Table 4
the effect of the gel viscosity or polymer concentration on metronidazole crystal habit

GEL	METRONIDAZOLE CONC. (%w/w)	pH MODIFIER	pH	CARBOPOL CONC. (%w/w)	CRYSTAL HABIT
Custom-made	0.75%	NaOH	~ 10	0.10	Linear
				0.20	Less branched and curvilinear
				0.40	Moderately branched and curvilinear
				0.75	Highly branched and curvilinear

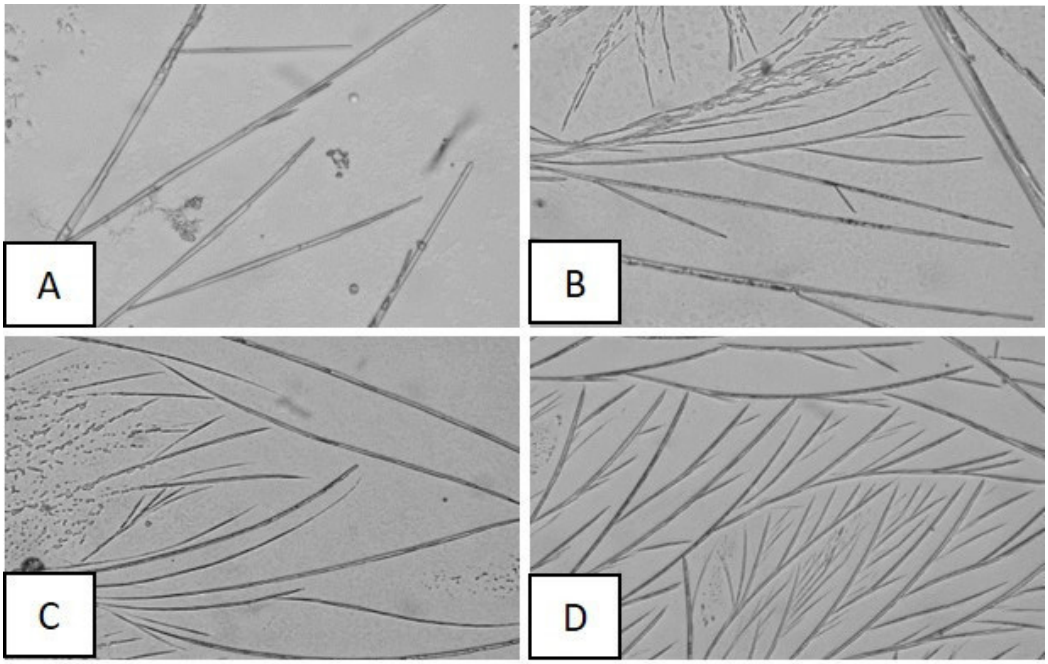

Figure 5 Bright field micrographs of metronidazole crystal structures formed after drying from Carbopol-based metronidazole gels with different polymer concentrations at pH 10 (A) 0.1% Carbopol (B) 0.2% Carbopol (C) 0.4% Carbopol (D) 0.75% Carbopol.

respect to the crystal habit of metronidazole precipitate. Figure 6A shows the formation of branched crystals in the presence of Carbopol, while Figure 6B shows that the branch density of the curvilinear crystals increased when metronidazole was grown from gels containing propylene glycol. Overall, fewer needle-like crystals grew from the metronidazole solution that included propylene glycol (Figure 6C), with no branching observed.

Responsible heterocyclic ring for peculiar metronidazole crystal structure formed during metamorphosis

Studies with tinidazole and dimetridazole, both of which have the same 5-nitroimidazole moiety as metronidazole, resulted in unbranched needle-like crystals when grown by drying aqueous solutions. In contrast, when these APIs were recrystallized from Carbopol-based gels (Figure 7), the crystals that formed were branched and slightly curved. This reinforced that branching of tinidazole, dimetridazole, and metronidazole was likely the result of interaction between the drug and the Carbopol, potentially, with faces expressing the 5-nitroimidazole group.

Scanning Electron microscopy

The results of the scanning electron micrographs are similar to the observations made using light microscopy. The crystals precipitated from the solutions were

Table 5 The effect of the propylene glycol on the metronidazole crystal habit

GEL	METRONIDAZOLE CONC. (%w/w)	CARBOMER CONC.	PH MODIFIER	PH	PROPYLENE GLYCOL	BRANCHING
Custom-made Gel	0.75%	0.75%	NaOH	5.09	Absent	Less branched and curvilinear
Custom-made Gel				4.9	Present	Highly branched and curvilinear
Solution				-	Present	Linear

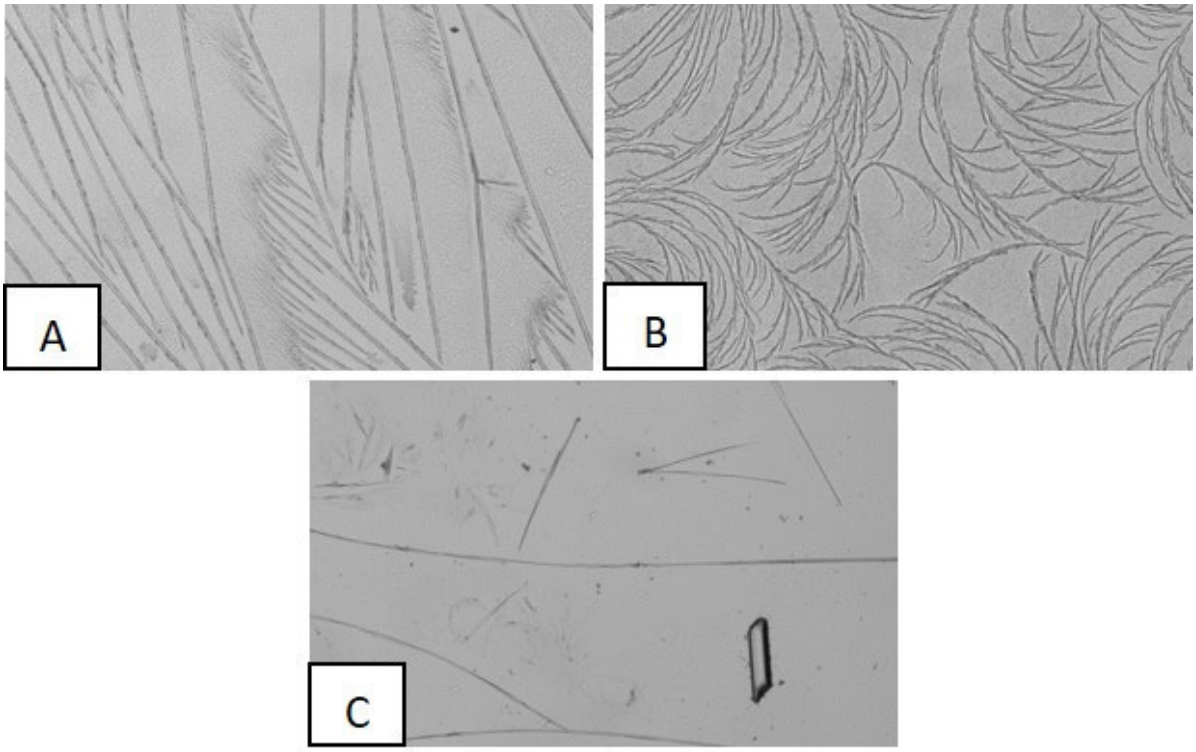

Figure 6 Bright field micrographs of metronidazole glycol crystal structures formed after drying gels (A) from Carbopol based metronidazole gels without propylene glycol and (B) from Carbopol based metronidazole gels with propylene glycol (C) from metronidazole solution with propylene.

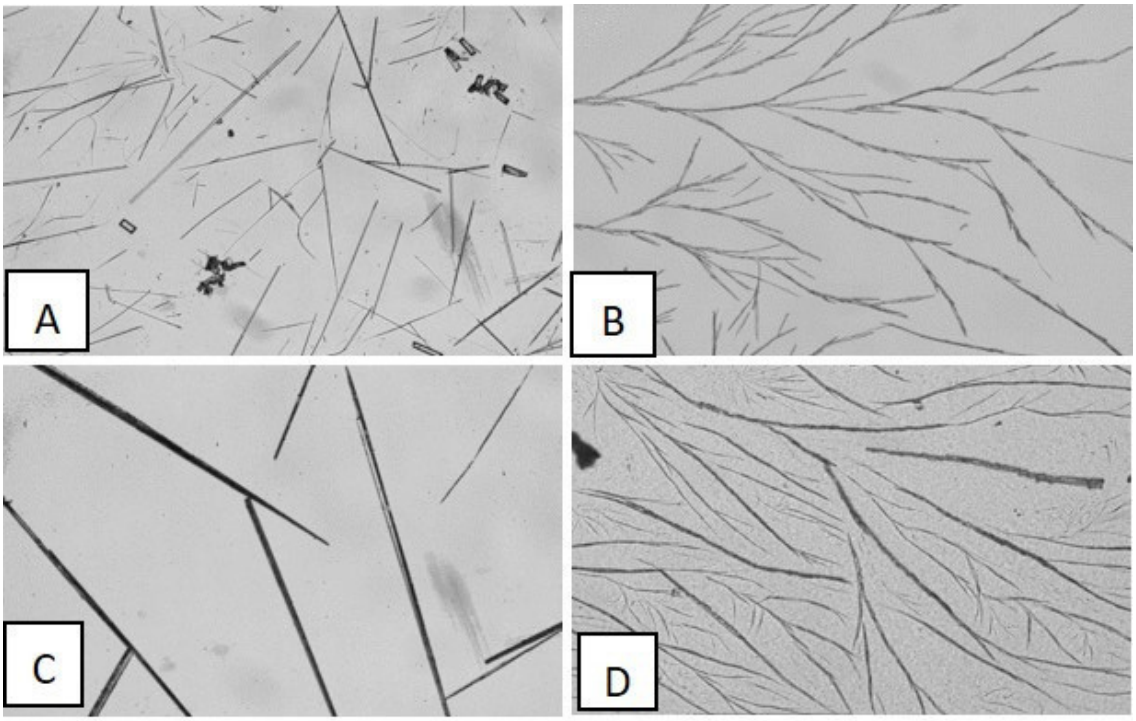

Figure 7 Bright field micrographs of crystal structures formed after drying from (A) tinidazole solution (B) tinidazole-Carbopol gels (C) dimetridazole solution (D) dimetridazole-Carbopol gels.

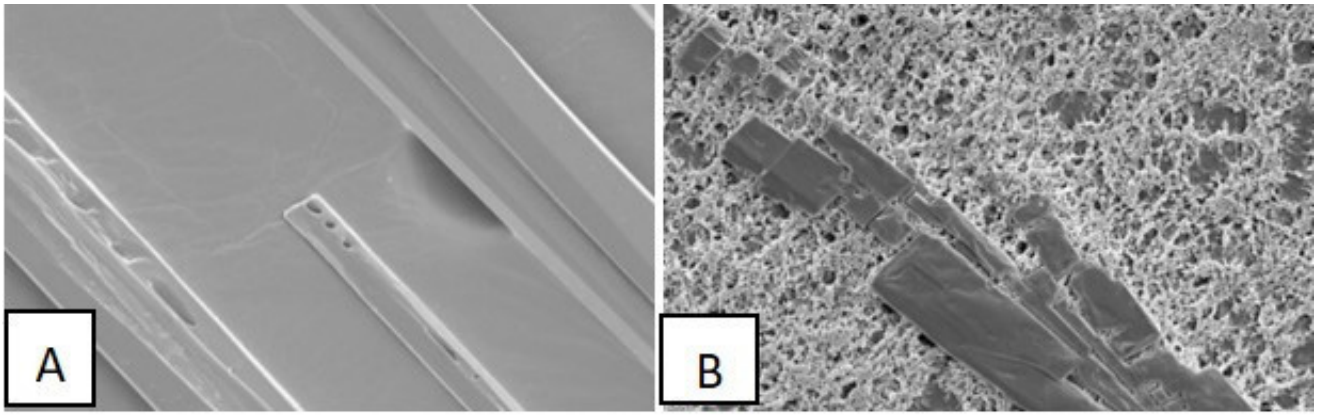

Figure 8 SEM images of metronidazole crystal structures after drying from a (A) metronidazole solution (B) marketed gel (MetroGel®)

straight and linear, while the crystals that precipitated from the commercially available metronidazole gel were branched and curvilinear (Figure 8).

Polarized light microscopy

The observations from polarized light microscopy (Figure 9) revealed birefringent crystals in all cases, having habits similar to those observed using light microscopy of the metronidazole solutions, marketed metronidazole gel, (0.75%) product, and the custom-made metronidazole gels (with and without propylene glycol). As before, branching occurred when the drug was recrystallized in the presence of Carbopol, while linear crystals were the result of growth from aqueous solution.

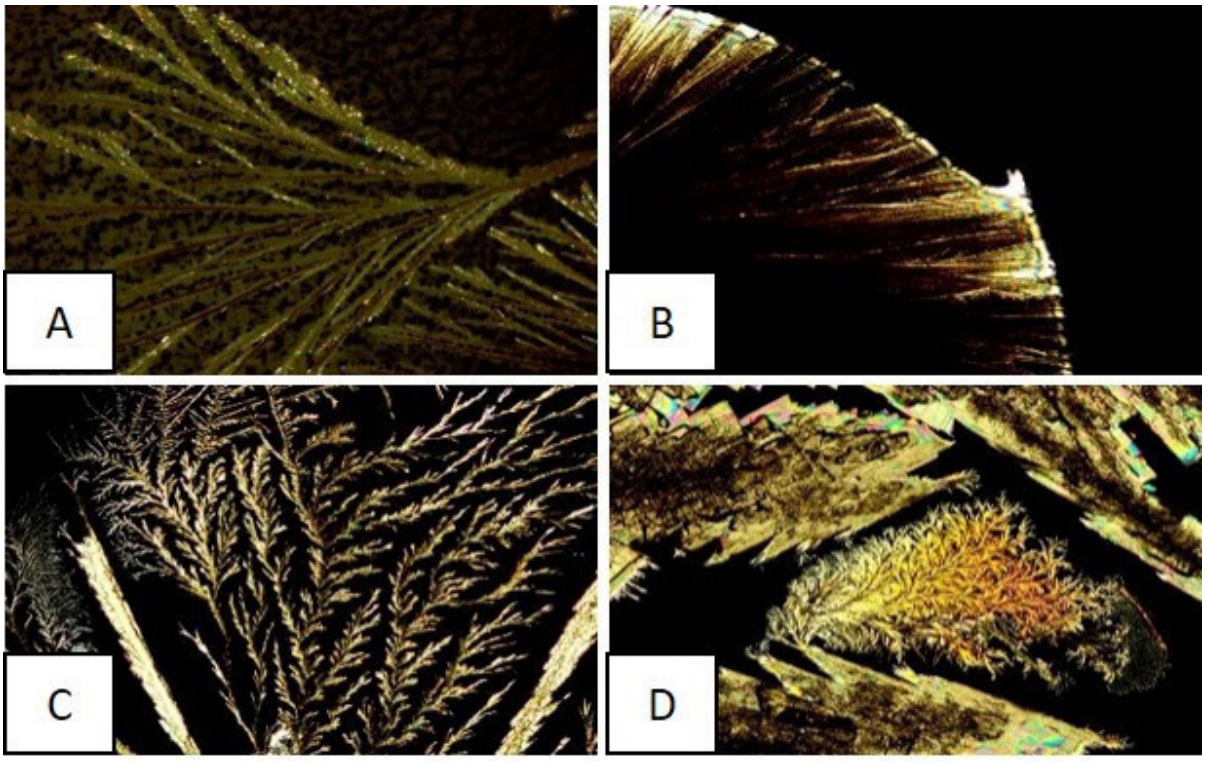

Figure 9 Polarized light micrographs of metronidazole crystal structures formed after drying from (A) marketed gel (MetroGel®) (B) metronidazole solution (C) custom made Carbopol gel after addition of sodium hydroxide (D) custom made Carbopol gel after addition of sodium hydroxide and propylene glycol.

Fourier transform infrared spectroscopy (FTIR)

Spectra from FTIR studies indicate absorption bands at 1535cm^{-1} and 1367cm^{-1}, which correspond to the nitro group associated vibrations in metronidazole. The absorption bands at 3100cm^{-1} and 3204cm^{-1} indicate the stretching vibrations of the hydroxyl group in the metronidazole. Both characteristic absorption peaks also appeared at similar wavenumbers in the crystals precipitated from gel with sodium hydroxide and gel with sodium hydroxide and propylene glycol. However, the OH stretch peak lost it characteristic shape and appeared at a relatively higher wavenumber in the case of metronidazole gel, which could be due to hydrogen bonding interactions between metronidazole and Carbopol. A similar shift was also reported by Szente, Virág *et. al.,* due to stable H bond formation between metronidazole and Carbopol (10). This reveals that the differences in crystal habits observed for metronidazole solid (as received) and metronidazole precipitated from Carbopol gels are due to hydrogen bond interactions (Figure 10).

Differential Scanning Calorimetry (DSC), and Powder X-ray diffraction (PXRD)

Figure 11 shows that the crystals precipitated from drying of metronidazole solution had a melting endotherm with an onset at 159°C, which is consistent with the reported melting point for $P2_1/c$ crystal form (CSD refcode MNIMET) (7). There was a slight depression in melting temperatures (153-157°C) measured for crystals that precipitated from the different Carbopol gels (marketed gel, custom made gel with and without the propylene glycol addition) possibly due to melting point depression induced by the polymer but unlikely due to polymorphic transformations of metronidazole.

The PXRD patterns collected for precipitates from

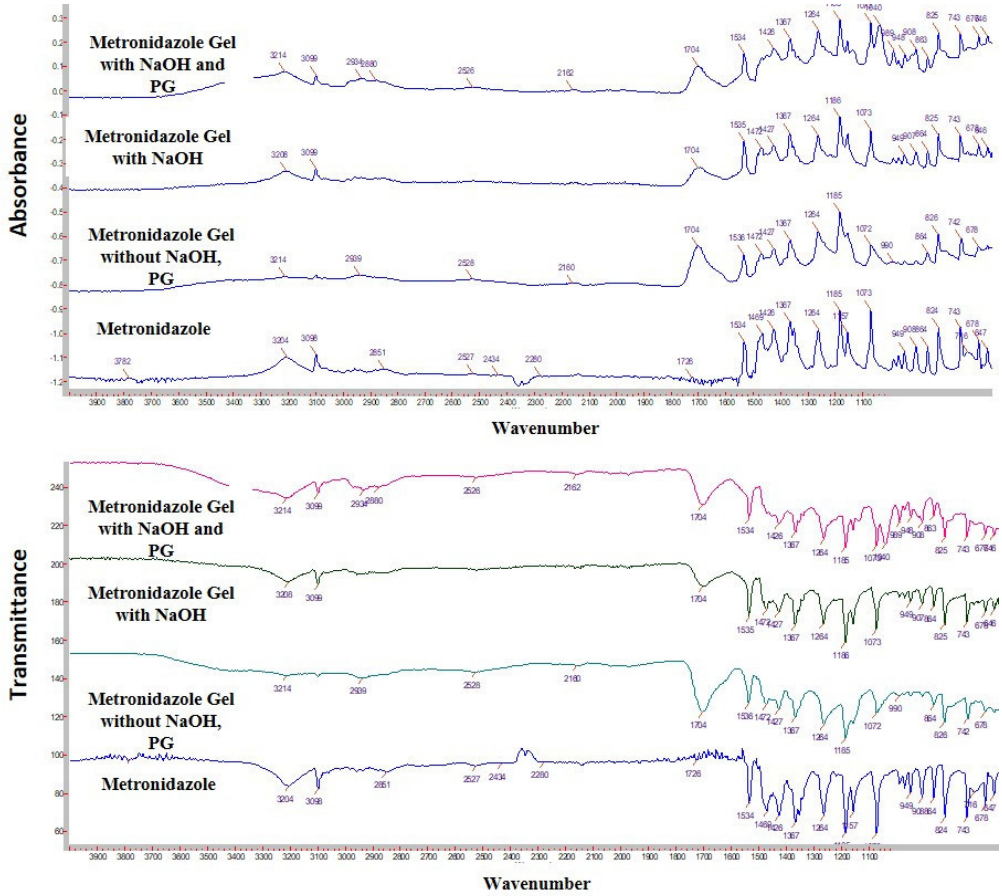

Figure 10 FTIR spectra of metronidazole and custom made gels

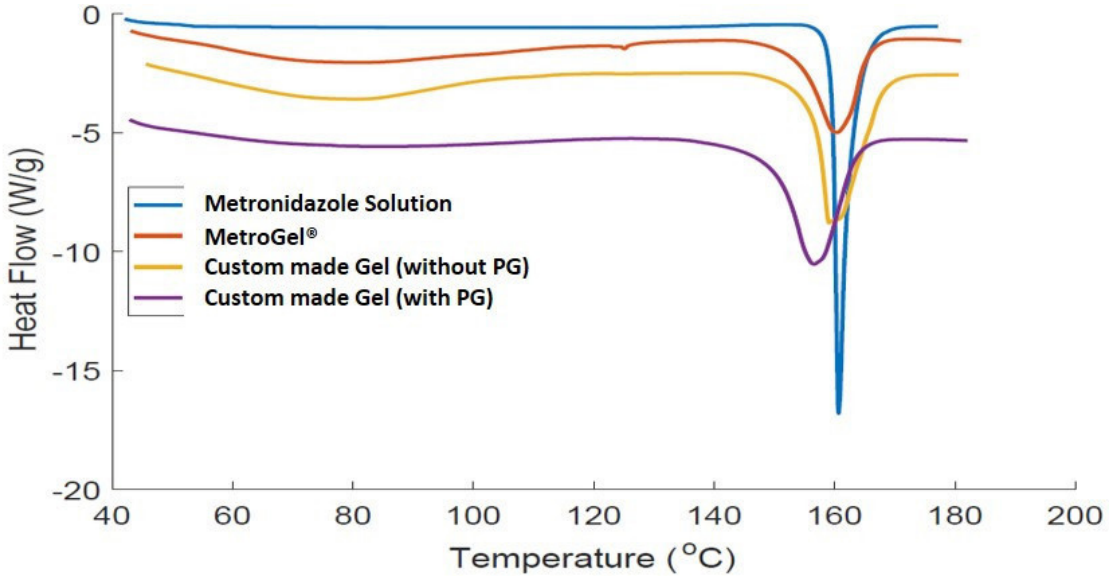

Figure 11 DSC of metronidazole crystals grown from gels and aqueous solution

both solution and the different gels (marketed gel, custom made gel with and without the propylene glycol addition) were all consistent with the calculated diffraction pattern for the reported P21/c crystal form (CSD refcode MNIMET) (7). The PXRD studies also indicated that there was no change in the polymorphic form of metronidazole, despite the differences in branching and curvature observed for the metronidazole crystals grown under different conditions (Figure 12). The most intense diffraction peak in the patterns for crystals precipitated from Carbopol gels occurred at 13.8° 2θ, reflecting that growth in the presence of polymer favored the (002) planes. Comparison with the reference crystal structure shows that (002) primarily expresses the nitro group of the molecule (Figure 13). This appears to reinforce the study with tinidazole and dimetridazole above, which suggested that the observed branching of all the 5-nitroimidazole crystals was the result of interaction between Carbopol and this moiety. In contrast, the most intense diffraction peak for metronidazole crystals precipitated from aqueous solution without the polymer, occurred at 12.4° 2θ, reflecting that growth in the absence of Carbopol favored the (011) planes, which primarily express the hydroxyl group of the metronidazole molecule (Figure 13). The (011) faces are more expected to be more polar than (002), and favor interaction with water.

CONCLUSIONS

The highly branched, curvilinear microstructures observed in the metronidazole gel 0.75% products following dose application, drying, and metamorphosis were identified to be crystalline formations of metronidazole. The absence of these metronidazole crystals from dried HPMC gels may be due to a change in the growth environment that inhibits metronidazole crystal growth. The role of propylene glycol in intensifying the branching is not yet fully understood, but the appearance of branching appears to be limited to formulations that contain Carbopol. Based on the crystals formed with the preparations of metronidazole, tinidazole and dimetridazole, branching is more likely a result of interactions between the nitro moiety expressed on faces of the growing crystals and the Carbopol. Essentially, the overexpression of (002) through branching helps optimize energetically favorable interactions between the crystal and the polymer in the surrounding medium. Although the crystal habit of metronidazole is dictated by different crystallization conditions, the polymorphic form

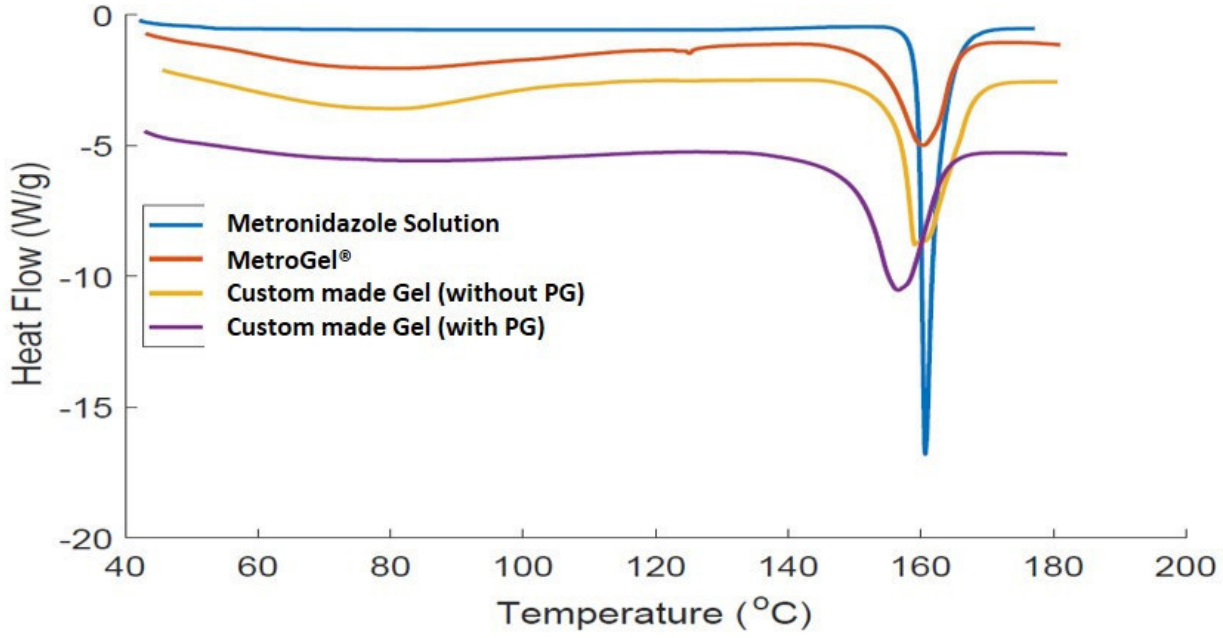

Figure 12 PXRD of metronidazole precipitating from gels and aqueous solution.

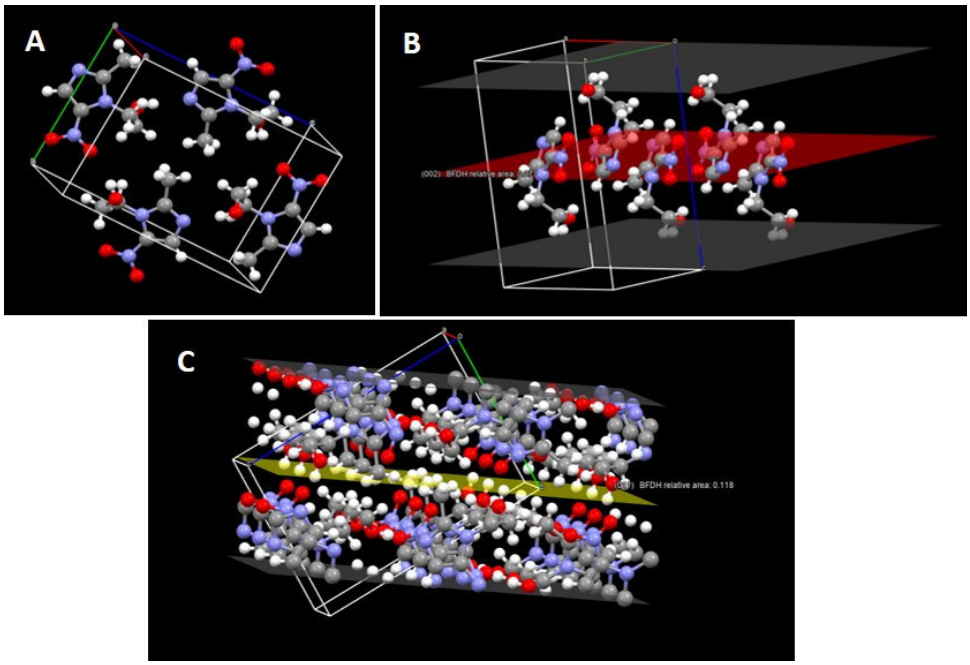

Figure 13 Crystal structure of metronidazole (CSD refcode MNIMET) (A), crystal structure highlighting (002), which is the predominant growth plane for precipitate from Carbopol gels (B), crystal structure highlighting (011), which is the predominant growth plane for precipitate from aqueous solution (C).

remained the same in all cases.

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DECLARATION OF INTEREST

None.

DATA AVAILABILITY STATEMENT

The data is included within the article.

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