AAPS PharmSciTech (2019) 20: 178
DOI: 10.1208/s12249-019-1388-x

Research Article

Theme: Paul Myrdal Memorial Issue - Pharmaceutical Formulation and Aerosol Sciences
Guest Editors: Philip J. Kuehl and Stephen W. Stein

Characterization of Tetracycline Hydrochloride Compounded in a Miracle Mouthwash Formulation

Usir S. Younis,[1,2] Mahdieh Fazel,[1] and Paul B. Myrdal[1]

Received 13 December 2018; accepted 8 April 2019; published online 30 April 2019

Abstract. Miracle mouthwash (MMW) is a commonly prescribed oral formulation compounded with varying active ingredients, depending on purpose of treatment. Due to patient-to-patient customization, the solubility, stability, and solid-state characteristics of the active ingredients may not be known after compounding. This study found that the common antibiotic, tetracycline hydrochloride (HCl), compounded in MMW formulations that contained dexamethasone elixir and diphenhydramine, underwent significant physical-chemical changes. Simulated patient conditions demonstrated appreciable fluctuations from the target content of 50 mg tetracycline HCl per teaspoon over 15 days. The lowest tetracycline content sampled was 32.5 mg, while the highest content sampled was 53.0 mg. Although tetracycline HCl went into solution after compounding, tetracycline did not remain in solution. In fact, the amount of tetracycline in solution declined exponentially, with over two-thirds of tetracycline precipitating out within the first day of compounding and 14% remaining in solution after 15 days. Crystals that formed within the MMW formulation were analyzed using differential scanning calorimetry (DSC), thermogravimetric analysis (TGA), and powder X-ray diffraction (PXRD), which confirmed a solvent-mediated phase transformation of tetracycline HCl to tetracycline hexahydrate. For tetracycline in solution, pH had a significant effect on chemical degradation. Therefore, tetracycline HCl compounded in MMW formulations can have significant physical-chemical stability changes, possibly impacting patient dosing.

KEY WORDS: tetracycline hydrochloride; miracle mouthwash; magic mouthwash; stability; tetracycline hexahydrate.

INTRODUCTION

"Miracle" or "magic" mouthwash (MMW) formulations are compounded, oral formulations that are commonly dispensed in both inpatient and outpatient pharmacy settings. MMW is prescribed for the relief of oral and/or esophageal discomfort caused by chemotherapy, radiation-induced mucositis, canker sores, and other forms of oral cavity damage or irritation, such as oral thrush (1). Although MMW is a frequently used and a generally recognized treatment method, there are numerous variations of MMW containing both over-the-counter and prescription medications. There is no standard compounding recipe for MMW for the specific condition being treated, either in adults or children. When the pharmacy receives a prescription for MMW, the pharmacist compounds the formulation based on the physician's instructions, or uses their pharmacy's internal formulae for the condition at hand, adjusting the dose for either an adult or adolescent patient. Typically, multiple active ingredients with different mechanisms of action are utilized in combination, including various antibiotics, antihistamines, antifungals, corticosteroids, antacids, and local anesthetics (2). As MMW formulations are typically aqueous based, US Pharmacopeia compounding standards recommend that the beyond use date for water containing oral formulations should not exceed 14 days past its preparation date (3). Even within this relatively short storage period, minimal information is known about the physical and chemical stabilities of the multiple active ingredients and various excipients compounded in aqueous-based MMW formulations. This lack of information may be of concern, especially with formulations containing the antibiotic, tetracycline hydrochloride (HCl), considering its known solubility and stability characteristics (4,5).

Paul B. Myrdal Deceased

Electronic supplementary material The online version of this article (https://doi.org/10.1208/s12249-019-1388-x) contains supplementary material, which is available to authorized users.

[1] Department of Pharmaceutical Sciences, University of Arizona, 1230 N. Cherry Avenue, Biosciences Research Laboratories (BSRL) Building, Tucson, AZ 85719, USA.
[2] To whom correspondence should be addressed. (e–mail: usirsyounis@gmail.com)

The chemical stability of tetracycline is strongly dependent on pH, with the highest relative stability around pH 4.0–5.0 and increased degradation under more acidic, neutral, and alkaline conditions (4). Allen and Erickson found that the pH of tetracycline HCl extemporaneously compounded in sweetened, oral liquids—such as Ora-Sweet and Ora-Plus combinations (pH 2.7) or a cherry syrup preparation (pH 2.6)—significantly impacted chemical stability and, thus, shelf life (6). Temperature (7–37°C) has also been shown to have a significant impact on aqueous, chemical stability over a couple weeks (4–6). Since tetracycline is zwitterionic, the solubility of tetracycline in water is also pH dependent. Minimum solubility is observed between pH 4.5 and 6.0, with solubility increasing below and above this range (4,7). Despite this information, little is known about the solubility and stability of tetracycline compounded in MMW formulations, specifically throughout the dosing intervals patients are prescribed. The purpose of this study is to determine the stability of tetracycline HCl compounded in common MMW formulations containing dexamethasone elixir and diphenhydramine HCl. Based on previous studies using tetracycline, we hypothesize that tetracycline hydrochloride compounded in a common miracle mouthwash formulation (containing dexamethasone elixir and diphenhydramine hydrochloride) will have variable stability.

MATERIALS AND METHODS

Materials

Reference standard tetracycline hydrochloride was purchased from Research Products International (RPI) Corp. (Mt. Prospect, IL, USA). Tetracycline hydrochloride capsules were obtained from Fry's Food and Drug Pharmacy in Tucson, AZ (inactive ingredients including, but not limited to, lactose, magnesium stearate, and sodium lauryl sulfate). Dexamethasone was purchased from LKT Laboratories, Inc. (St. Paul MN, USA). An 8 fl. oz. bottle of Children's Benadryl® (12.5 mg diphenhydramine/5 mL) was purchased over-the-counter from a pharmacy in Tucson, AZ. The inactive ingredients in Benadryl® include citric acid, FD&C blue no.1, FD&C red no. 40, flavors, glycerin, poloxamer 407, polysorbate 20, purified water, saccharin sodium, sodium benzoate, sodium chloride, sodium citrate, and sorbitol solution. HPLC grade methanol (MeOH) was purchased from Honeywell Burdick & Jackson (Muskegon, MI, USA), while HPLC grade acetonitrile (ACN) was obtained from Fisher Chemical (Fair Lawn, NJ, USA). Ethanol was obtained from Decon Labs, Inc. (King of Prussia, PA, USA). Dibasic ammonium phosphate $(NH_4)_2HPO_4$ and sodium hydroxide (NaOH) were both purchased from Sigma Aldrich (St. Louis, MO, USA). A Millipore (Billerica, MA, USA) Milli-Q Ultrapure Water purification system with a 0.22-μm filter was used for water.

Methods

High-Performance Liquid Chromatography

Reverse-phase high-performance liquid chromatography (HPLC) was used to analyze drug concentrations from known standards and experimental formulations. All samples were analyzed with a Waters 2690 separation module couple with a Waters 996 photodiode array ultraviolet detector (Waters Corp., Milford, MA, USA). A Waters Symmetry C18 5 μm 3.9 mm × 150 mm column was used for all samples. An isocratic separation method was developed to quantify tetracycline. Sample injection volume was 20 μL, with a mobile phase composition of 80:20% (*v*/*v*) 0.02 M ammonium phosphate dibasic (pH 7.0): acetonitrile at a flow rate of 0.7 mL/min. The total run time of the isocratic method was 6 min, with tetracycline eluting at approximately 3.7 min, with UV detection at 270 nm. A gradient separation method was used to characterize tetracycline in MMW formulation samples. Injection volume was 20 μL, with an initial mobile phase composition of 80:20% (*v*/*v*) 0.02 M ammonium phosphate (dibasic, pH 7.0): acetonitrile at a flow rate of 0.7 mL/min. After 6 min, the mobile phase linearly changed over 30 s to 50:50% (*v*/*v*) 0.02 M ammonium phosphate (dibasic, pH 7.0): acetonitrile with a flow rate of 0.7 mL/min. The total run time of the gradient method was 22 min. The data from both methods were collected and processed with Waters Empower Pro 2 chromatography software. Quantification of tetracycline was based on peak area from a five-point standard curve.

Preparation of Miracle Mouthwash Formulations

The simulated MMW formulation recipe was created based on a survey of existing common recipes used in clinical and compounding pharmacies throughout Tucson, AZ. The recipe consisted of a 1:1 ratio of Benadryl® (diphenhydramine HCl) to a dexamethasone elixir made in the laboratory (0.5 mg/5 mL of dexamethasone mixed in equal parts distilled water and ethanol), adding tetracycline hydrochloride to a target concentration of 10 mg/mL. MMW formulations created for the chemical stability study used the reference standard tetracycline hydrochloride, while simulated patient formulations contained the contents of a tetracycline hydrochloride capsules. All formulations in this study were placed in amber bottles to prevent any photo-degradation of tetracycline HCl.

Chemical Stability of Tetracycline Hydrochloride Within a MMW Formulation

The recommended dose of tetracycline HCl in MMW formulations is 10 mg/mL; however, preliminary results indicated that stability studies could not be done at this concentration due to drug precipitation. Therefore, in order to investigate inherent chemical stability of tetracycline, a MMW formulation was made with approximately 200 μg/mL of tetracycline HCl for the chemical stability study. This formulation was divided into triplicates for the following conditions: 4°C at pH 4.7 (unadjusted pH of the formulation), 25°C at pH 4.7 (unadjusted pH of the formulation), and 25°C at pH 7.0 (pH adjusted with 0.2 N sodium hydroxide). The higher pH adjustment is possibly observed in MMW formulations containing antacids, such as Maalox®. Each of these formulations were analyzed over a period of 15 days.

Sample Preparation, Sampling, and Analysis of Simulated Patient Doses of MMW

A simulated patient formulation of MMW was prepared using the formulation previously described, with tetracycline HCl capsules. The formulation was split into three equal volumes (representative of volumes a patient would receive if prescribed MMW), stored in amber bottles to protect them from light, and placed into refrigerated conditions (4°C). The pH of each formulation was recorded at the beginning of preparation and at the end of collection to determine if any pH change occurred over time.

Sampling took place the same day the formulation was made, and throughout the course of 15 days. Each time a sample was collected, the bottles were vigorously shaken using a vortexer and 5 mL was poured out (which is about the 1 teaspoon volume as per typical directions given to the patient). In order to determine the total concentration of tetracycline HCl in the daily dose, a sample was diluted with methanol, and filtered with a 0.2 μm PVDF membrane. To determine the concentration of tetracycline HCl in solution of a given dose, a sample was taken and filtered with a 0.2-μm PVDF membrane, then diluted with methanol if needed. Concentrations of these samples were analyzed by the previously described HPLC method.

Solid-State Characterization

A MMW formulation was compounded using tetracycline HCl capsules and placed in refrigerated conditions (4°C). After 15 days, the formulation was vigorously shaken, and the crystals that remained in the formulation were collected and dried. The crystals were dried by vacuum filtration (set up within a chemical safety hood), where the crystals were placed on top of the filter and the vacuum left on low overnight (or until any moisture was visibly gone and filter paper was dry to the touch). The crystal solid-state characteristics were analyzed using differential scanning calorimetry (DSC), thermal gravimetric analysis (TGA), and powder X-ray diffraction (PXRD).

The crystals were visually inspected with a Leica MZ9.5 stereomicroscope (Leica Microsystems, Buffalo Grove, IL, USA). Thermal analysis was performed with a Q1000 DSC with an autosampler (TA Instruments, New Castle, DE, USA). Indium was used for the calibration of the DSC. Samples were weighed into a standard aluminum pan and crimped with an aluminum lid. Samples were heated at 5°C/min up to 160°C. Reference tetracycline HCl collected from a capsule was analyzed for comparison, heated at 5°C/min up to 220°C. A nitrogen purge of 40 mL/min was used. A TA Instruments Q50 TGA was used for thermogravimetric analysis. Samples were placed into an empty aluminum pan and heated at 5°C/min up to 150°C. Reference standard tetracycline HCl collected from a capsule was analyzed for comparison, heated at 5°C/min up to 220°C. Weight loss as a function of temperature was analyzed under nitrogen at 60 mL/min purge. Powder X-ray diffraction patterns of all samples were collected at room temperature with a PanAnalytical X'pert diffractometer (PANalytical Inc., Westborough, MA, USA) with copper (Kα) radiation (λ = 1.5406 Å) at 45KV (40 mA target current). Scans were taken between 2-Theta of 5.00° and 50.00° per minute at ambient temperature. Samples were placed on a silica zero background holder, and diffraction was measured with an X-celerator detector.

RESULTS

Simulated Patient Doses

As demonstrated in Fig. 1, significant fluctuations in tetracycline content (based on the tetracycline HCl starting material) were observed in the simulated patient doses. The target dose was 50.0 mg of tetracycline HCl in each teaspoon. The lowest content of tetracycline HCl was approximately 32.5 mg (seen in simulated dose, sample 2 on day 5). The highest content of tetracycline HCl seen was 53.0 mg (seen in simulated dose, sample 3 on day 12). Sampling took place for 15 days, 1 day longer than the recommended use of MMW. On day 15, the average content of tetracycline HCl for all three simulated patient formulations was 37.9 ± 2.05 mg out of the target 50.0 mg. There were no significant pH changes throughout the course of the study.

Preliminary studies revealed that most of the tetracycline HCl went into solution after compounding. However, the tetracycline did not stay into solution for long. The amount of tetracycline in solution (based on the tetracycline HCl starting content) declined exponentially over time. The most drastic decline was seen within the first 24 h of compounding (Fig. 2), where the average amount of tetracycline in solution for the three simulated patient formulations was 46.7 ± 4.20 mg at $t = 0$ days, while the average amount of tetracycline in solution was 14.0 ± 2.91 mg at $t = 1$ day. Therefore, after 24 h, approximately 30% of the drug remained in solution. Tetracycline continued to precipitate until day 5 of sampling, where the amount of tetracycline in solution started to level off. On the final day of sampling, an average of 4.68 ± 0.50 mg of tetracycline HCl remained in solution, around 9.4% of the compounded target content per teaspoon dose.

Solid-State Characterization

Throughout the course of the study, all various formulations of MMW were visually monitored. Crystal formation was observed with all MMW formulation combinations after 24 h of compounding, along with a color change (from an original pink color due to the Benadryl®, to a dark yellow/brown). After 15 days, the crystals from the simulated patient doses were collected and dried for 72 h. The crystals were sticky and difficult to separate into agglomerates small enough to be seen under the microscope. This was in contrast to the fine powder within the capsules. When visualized under a microscope, the size and shape of the crystals obtained (Fig. 3b) were larger in comparison to the contents inside the tetracycline HCl capsule (Fig. 3a). The size for the raw material crystals ranged from 0.01 mm to 0.03 mm, while the crystal agglomerates obtained from the simulated MMW formulation were around 100 times larger. Crystals from the simulated patient doses were analyzed by differential scanning calorimetry (DSC) and compared to the raw powder collected from tetracycline HCl capsules. An overlay of these thermograms can be seen in Fig. 4. The DSC profile of tetracycline HCl capsules showed one endotherm

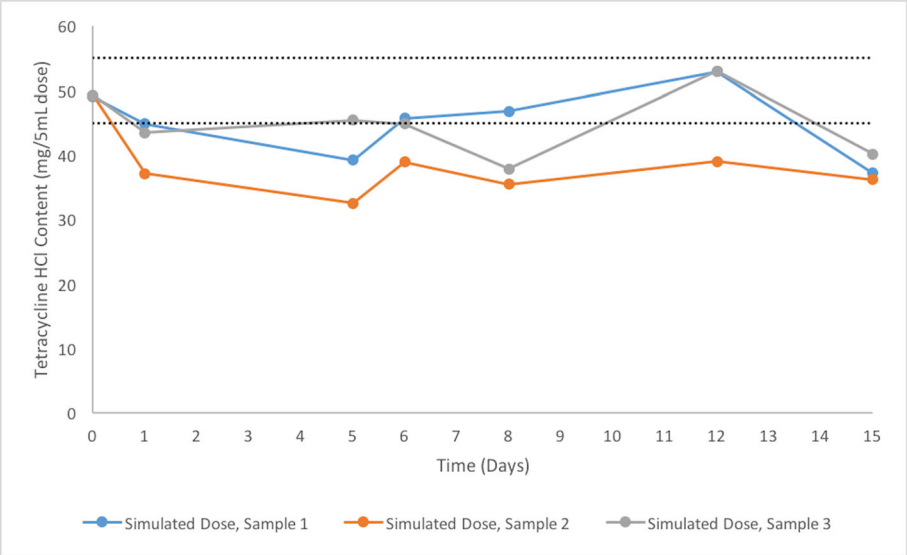

Fig. 1. Tetracycline HCl content (mg/5 mL dose) from three samples of a simulated patient MMW formulation over the course of 15 days. Dashed lines represent the 90–110% acceptable target content range as specified by the USP (3)

(down), with a peak of 211.13°C, and identified to be a final melting point. In comparison, the DSC profile of the solid material gathered from the simulated patient doses showed an endotherm at a peak temperature of 102.87°C, an indication of desolvation.

Thermogravimetric analysis (TGA) studies were performed, and weight loss as a function of temperature was analyzed to determine solvent loss from the crystals, in comparison to the tetracycline HCl capsule raw powder material, which can be seen in Fig. 5. The crystals gathered from the simulated patient formulations showed a total weight loss of 15.53%, beginning at an onset temperature similar to its DSC profile (approximately 50°C). In comparison, no significant weight loss was seen in the tetracycline HCl capsule raw powder material. Weight loss attributed to desolvation from the crystals gathered from the simulated patient formulations were used to estimate a stoichiometry of 4.54:1 water/drug molecule.

To further elucidate what crystals precipitated in the MMW formulation, the crystals collected were analyzed *via* powder X-ray diffraction (PXRD). Differences were seen between the diffraction patterns of the solvated crystals when compared to tetracycline HCl raw capsule powder material, across the full range of 2θ. Verification of the formation of tetracycline hexahydrate was confirmed when the diffraction pattern of the collected crystals matched those of tetracycline hexahydrate within the Cambridge Structural Database System (8), seen in Fig. 4.

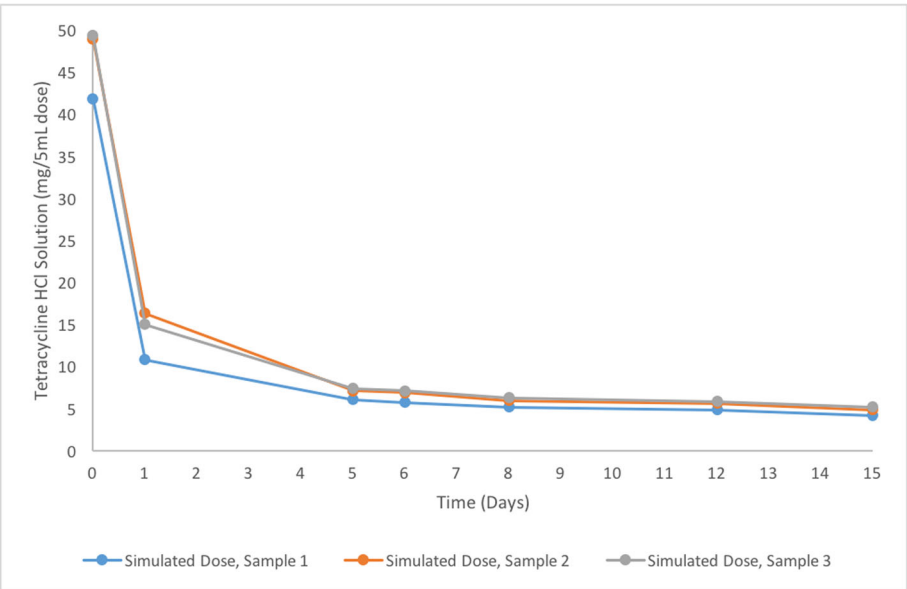

Fig. 2. Amount of tetracycline HCl in solution (mg/5 mL dose) in the three simulated patient MMW formulations over the course of 15 days at 4°C

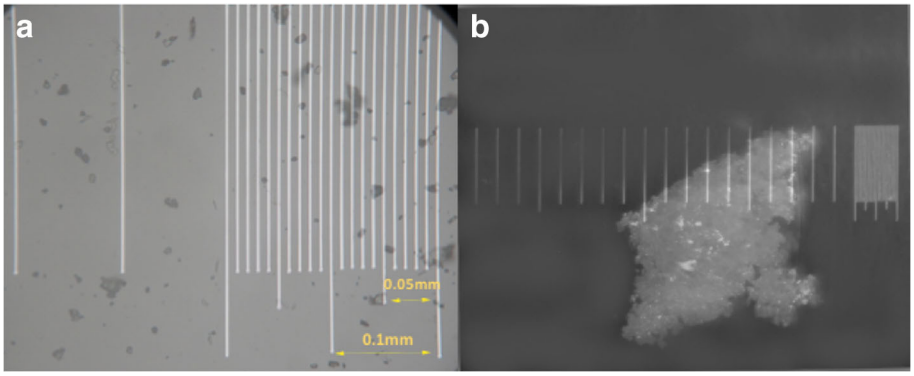

Fig. 3. **a** Tetracycline HCl capsule raw material. **b** Crystals obtained from simulated patient MMW formulation.

Chemical Stability Determination

The effects of pH and temperature on the chemical stability of tetracycline (based on the original tetracycline HCl) in the MMW formulation were analyzed using recommended storage conditions for aqueous-based oral formulations provided by the USP (3) (see supplemental figure). Degradation of tetracycline in solution was found to be significant after compounding in the pH 7.0 adjusted formulation stored at 25°C. After 16 days, about 31% of tetracycline remained in the pH 7.0 adjusted formulation. Increased stability was seen in the pH unadjusted formulations (pH 4.7) stored at 25°C and 4°C, with approximately 63% and 64% of tetracycline remaining after 16 days, respectively. No significant pH change was noted in any of the samples over the course of the study.

DISCUSSION

The simulated patient doses of the MMW formulation had a theoretical 50 mg content of tetracycline HCl contained with each teaspoon dose. As shown in Fig. 1, the lowest content of tetracycline (based on the starting content of tetracycline HCl) was 32.5 mg, or 35% less than the target content (seen in simulated dose sample 2 on day 5), while the highest content of tetracycline HCl seen was 3 mg more than the target content (seen in simulated dose sample 3 on day 12). Not only were there intra-day variances in content between the three different simulated patient formulations, but day-to-day differences in content were also apparent. On the last day of sampling, the average content of tetracycline for all three simulated patient formulations was 37.9 ± 2.05 mg out of the target 50.0 mg, about 25% less than the intended dose. Figure 1 also provides a target specification range of ± 10% of the desired dose (45–55 mg/mL). Using these criteria, overall 13 out of 21 doses would be out of specification.

In addition to finding significant variability of the total dose delivered, it was also determined that the physical state of tetracycline was changing during storage. In essence, the tetracycline HCl converted in the MMW formulation from a predominantly solution formulation to a suspension formulation over the course of the 15 days. As shown in Fig. 2, nearly all of the drug was in solution after compounding ($t = 0$ days). Twenty-four hours after compounding, an average of 14.0 mg

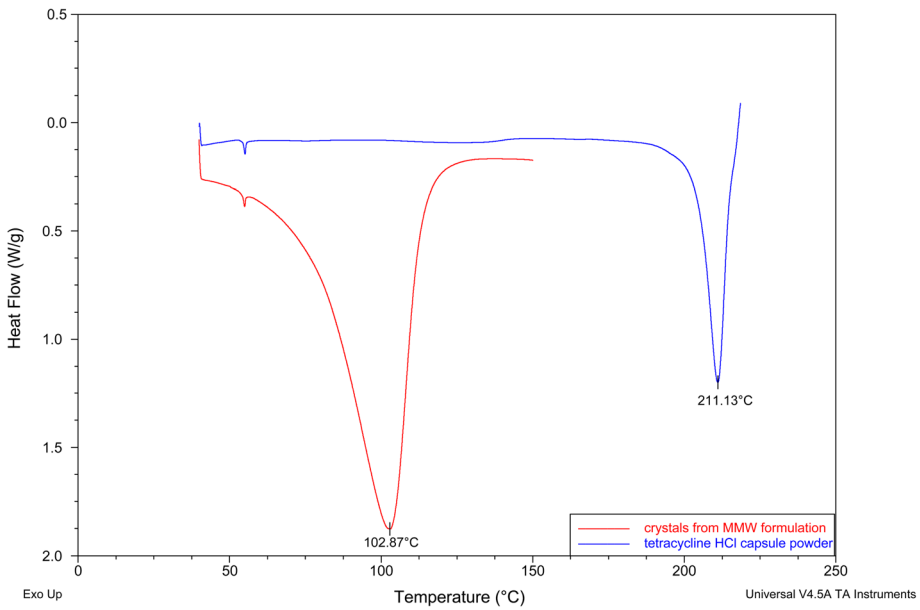

Fig. 4. DSC overlay of tetracycline HCl capsule raw powder material and crystals obtained from the simulated patient MMW formulations

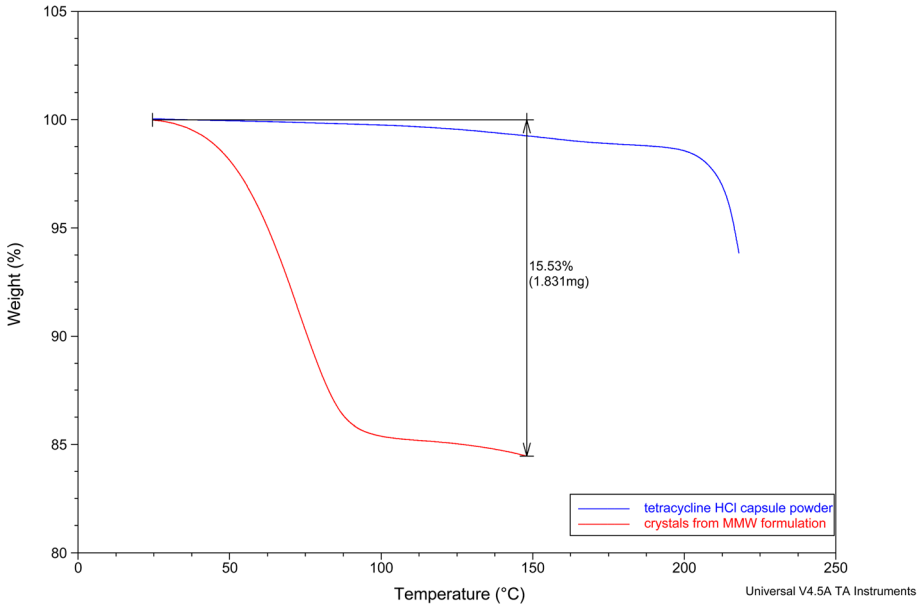

Fig. 5. TGA overlay of tetracycline HCl capsule raw powder material and crystals obtained from the simulated patient MMW formulations

of tetracycline HCl was in solution in a 5-mL dose, which corresponds to 28% of the target dose still in solution. Twelve days after compounding, an average of 5.41 mg of tetracycline HCl was left in solution in a 5-mL dose, corresponding to about 11% of the target tetracycline HCl dose. The percent of the tetracycline in solution in a given dose will depend on the actual content delivered, which will be the amount of tetracycline in solution plus the amount of tetracycline in suspension. These data indicate that tetracycline HCl in this type of MMW formulation is not a physically stable preparation upon storage, converting from a largely solution formulation to a predominately suspension formulation. To the extent that tetracycline must be in solution to be absorbed, the changes in the tetracycline concentration in solution could impact the local bioavailability of the drug (9).

The formation of crystals noticed after 24 h of compounding MMW are the likely cause for the inconsistent doses collected on each day of sampling in the simulated patient MMW formulation. The crystals formed at the bottom of the vial and broke off into larger agglomerates when the formulation was shaken before sampling, as a patient is instructed to do every 4–6 h. Therefore, the content of tetracycline could vary significantly per dose, depending on the amount of crystals collected within a given sample. Since MMW formulations are typically stored in amber bottles to minimize light exposure, it is possible that patients are unaware of the crystal formations. If a patient did not shake the bottle before dosing, they would only be receiving predominantly the tetracycline in solution, which varies from approximately 28% remaining in solution (after 24 h of compounding), to only around 11% in solution (at 14 days after compounding). Therefore, the patient would receive subtarget doses of tetracycline if they did not appropriately shake the bottle, as soon as 24 h after the formulation was made. It is also possible that the dose of tetracycline could significantly exceed the target dose over time, due to the conservation of mass early on in dosing. As the volume of MMW decreases with continued patient use, the total content per teaspoon dose of tetracycline would eventually increase (due to the observed crystal sedimentation in the MWW formulation) and could result in a significantly higher tetracycline dose. It has been observed that high doses of tetracycline could result in possible acute toxicity, with symptoms including nausea, vomiting, and diarrhea, especially in those with a pre-existing renal condition (10). It is possible that actual patient dose variability could significantly exceed those found in this study, considering this study paid special attention to obtaining a uniform suspension by using a vortexer to vigorously mix the contents of the bottle before each sample was collected.

Analysis of the crystals collected using thermal analysis illustrated a clear desolvation of tetracycline. The DSC thermal profile of the tetracycline HCl capsule raw powder material did not exhibit the desolvation endotherm (peak temperature of 102.87°C) illustrated in the DSC thermal profile (Fig. 4) of the crystals collected within the MMW formulation. TGA analysis (Fig. 5) resulted in a 15.53% weight loss in the crystal sample collected, with a calculated 4.54 water/tetracycline mole ratio. PXRD analysis (Fig. 6) demonstrated a difference in the crystal patterns between the tetracycline HCl capsule solid material and the collected crystals from the MMW formulation. While an approximate 5:1 stoichiometric ratio of water to tetracycline is possible as an intermediate in the dehydration of tetracycline hexahydrate (11), PXRD data confirmed the identity of the crystals obtained in the MMW formulation as tetracycline hexahydrate.

The solvent-mediated phase transformation of tetracycline HCl to tetracycline hexahydrate in a simulated MMW formulation has not been previously reported in literature. This is an example of how a conversation to a hydrate may lead to unfavorable pharmaceutical property differences in regard to solubility and physical stability (12), and it follows the general principle that the hydrate form of a compound will have a lower solubility than its original phase (13).

The chemical stability of tetracycline was better in the unadjusted, acidic environment of the MMW formulation, in

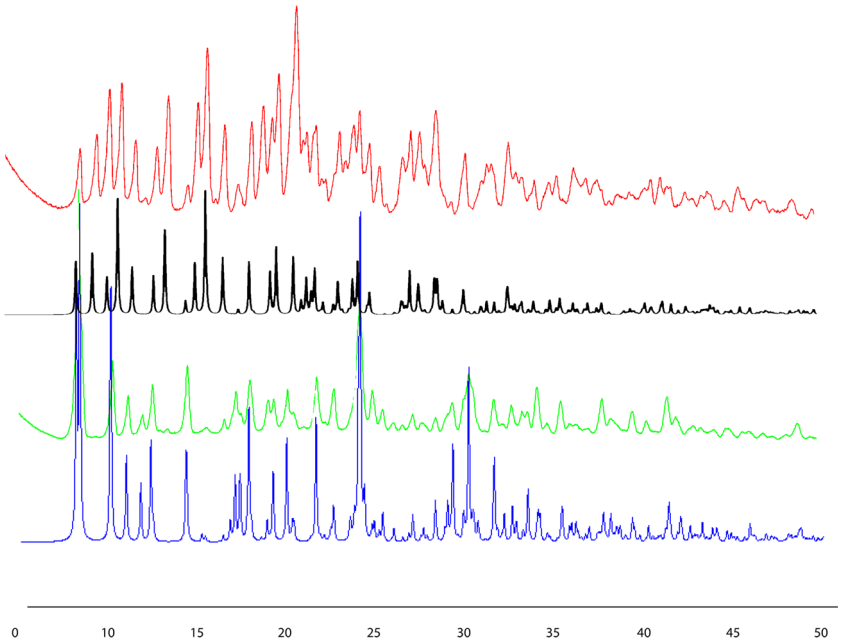

Fig. 6. PXRD pattern overlay of (starting from the top) tetracycline HCl capsule raw powder material (first-red), tetracycline HCl from literature (second-black) (8), tetracycline hexahydrate from crystals obtained from the simulated patient MMW formulations (third-green) and tetracycline hexahydrate from literature (fourth-blue) (8)

comparison to the pH 7.0 adjusted formulation. The pH 7.0 adjusted formulation was less stable than pH 4.7 with, only 31% of tetracycline remaining in the MMW formulation after 16 days of initial compounding at 25°C. This data is consistent with the study performed by Loftin *et al* (5), which found tetracycline to degrade more quickly at pH 7.0 at 22°C, than pH 5.0 at 22°C. Further, work completed by Wu and Fassihi (4) illustrated that tetracycline was less stable in a buffered, aqueous solution at pH 6.0 than a buffered, aqueous solution at pH 4.0 under the same storage conditions. Another example where low pH had a significant chemical stability effect on tetracycline HCl was seen in Ora-Sweet and Ora-Plus combinations (pH 2.7), or a cherry syrup preparation (pH 2.6). These extemporaneously compounded, sweetened, oral liquids significantly impacted chemical stability and thus, shelf life (6).

After analyzing chemical stability in regard to temperature, it was seen that there was not a significant affect between the degradation of tetracycline at 25°C and 4°C (pH 4.7), with approximately 63% and 64% of tetracycline remaining after 16 days, respectively. Although not observed in the one configuration in this study, temperature (7–37°C) has been shown to have a significant impact on aqueous chemical stability over a couple weeks (4–6), especially for lower and higher pH values. Further, considering 90% of tetracycline precipitated out of the MMW formulation after 15 days of compounding, overall chemical degradation of the drug in the unadjusted pH 4.7 formulation would actually be minimal. However, with tetracycline being a zwitterionic compound an increase in solubility at higher and lower pH values could be a significant consideration. Tetracycline's solubility at pH 7.0 is nearly five times higher than its solubility at pH 4.7 and correspondingly, chemical stability decreases (4). Similarly, a decrease in pH will increase solubility. This chemical degradation could impact not only shelf life (10% drug loss) but even more extensive degradation could be observed, which is concerning since chemical degradants of tetracycline have been shown to produce renal toxicity (14). Therefore, each MMW formulation compounded with tetracycline HCl will have a pH based on the excipients present in that formulation, and chemical stability should be a consideration.

Our work not only highlighted the physical and chemical problems that arose when tetracycline hydrochloride was compounded with dexamethasone and diphenhydramine (a recipe that would be seen in a clinical setting), but it also provides insight to the dosing inconsistencies that patients could be receiving after being prescribed a similar formulation. Our work emphasizes how currently prescribed medications, such as miracle mouthwash, are compounded without the understanding or knowledge of how certain active compounds will react within a formulation containing various other components. These studies build the foundation for the standardization of compounded miracle mouthwash formulations.

CONCLUSION

Solubility, stability, and solid-state characterization studies were conducted on tetracycline HCl formulated within a MMW formulation containing diphenhydramine and a dexamethasone elixir. It was determined that tetracycline precipitates out of the MMW formulation in the form of tetracycline hexahydrate. As a result, dose content uniformity was significantly affected, as well as the availability of tetracycline in solution. It was also shown that the tetracycline in solution undergoes chemical degradation over a 15-day sampling period. While MMW formulations containing tetracycline at pH values ranging from 4.5 to 6.0 will have the lowest solubility and may be in suspension, chemical stability will be

a lesser concern since a small fraction of tetracycline would remain in solution. On the other hand, pH values greater than 6.0 or less than 4.5 will increase tetracycline solubility significantly, which in turn makes chemical degradation a greater concern since more drug is in solution. This study emphasizes the practical implications of compounded formulations, and the importance of prioritizing drug solubility to chemical stability.

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