In Vitro Assessment for Dose Preparation and Simulated Administration of Azithromycin Suspensions via Enteral Feeding Tubes

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Abstract
Administration of medication via enteral feeding tubes (EFT) is common in cases where patients are unable to swallow the dosage form or a patient is intubated. The SARS-CoV-2 (COVID-19, coronavirus disease 2019) epidemic created a need to rapidly evaluate potential treatment options to address the global pandemic including evaluation of azithromycin (AZM) as a mono or combination therapy. Due to the complicating medical conditions of COVID-19, in some cases patients may be unable to take medication orally and could require medication administration by alternate routes such as an EFT. The aim of this study was an in vitro assessment for the dose preparation and simulated administration of AZM suspensions, prepared from tablets and capsules, via nasogastric feeding tubes (NGT). AZM tablets and capsules were used to prepare aqueous suspensions from 250 to 2000 mg for administration via NGT. NGT between 8 and 12 French (Fr), from common materials of construction and typical lengths were evaluated. About 20 mL syringes were used with water as the diluent. The preparation and simulated NGT administration steps for AZM suspensions were evaluated in the laboratory studies and included assessment of in-use stability of the aqueous suspensions, chemical compatibility of prepared aqueous suspensions with the syringe and NGT, ease of delivery and accuracy of simulated administration. Analysis of the prepared sample solutions for assay/impurities was performed using chromatographic conditions based on the USP-NF monograph. Verification of dose preparation and simulated administration was performed for intact tablets, crushed tablets, and capsules. Aqueous suspensions prepared from intact tablets and capsules were exposed to dosing materials (enteral syringe and NGT) for a period of up to 4 hours at ambient conditions. Assessment of the ease of dose delivery and analyses of the resulting samples for assay, purity and total degradation products were performed. The laboratory studies verified a procedure to reliably prepare suspensions from AZM tablets and capsules, over a range of 250 to 2000 mg, that can be accurately administered through NGT in sizes of 8 to 12 Fr. No incompatibilities of the prepared aqueous AZM suspension with dosing materials were observed and acceptable stability was demonstrated for up to 4 hours.

Keywords
enteral feeding tube, nasogastric, clogging, compatibility, stability, accuracy

Introduction
Azithromycin (AZM) is a macrolide antibiotic prescribed for the treatment of certain bacterial infections.¹ AZM is commercially available in multiple dosage forms, both generic and branded (Zithromax®, Pfizer Inc.).² Available oral dosage forms include tablets, capsules, and oral powder for reconstitution. Additionally, there is an intravenous powder for solution and an ophthalmic formulation available.

The SARS-CoV-2 (COVID-19, coronavirus disease 2019) epidemic brought about a rapid need to evaluate potential treatment options to help address the global pandemic.³ AZM is one such drug being evaluated as both a mono and combination therapy. Clinical study findings by Gautret et al⁴ suggested that hydroxychloroquine (HCQ) alone or in combination with AZM reduced viral load in COVID-19 patients. While some published data support these results, others do not. For instance, the RECOVERY study by Horby et al⁵ found that AZM provided no difference in clinical endpoints predefined as duration of hospitalization or the...
The proportion of patients discharged from hospital alive within 28 days. Similarly, researchers at the University of Oxford conducting the PRINCIPLE trial closed the AZM arm when they found a low probability of finding an improvement in self-reported recovery and no reduction in hospitalizations or deaths compared with usual care. A keyword search of the World Health Organization’s (WHO) International Clinical Trial Registry Platform (on 21 May 2020) revealed 43 clinical trials, in various stages of recruitment, using AZM in the study design for treatment of COVID-19.

Due to the complicating medical conditions of COVID-19, in some cases, patients may be unable to swallow the dosage form (i.e., tablet or capsule) or they may be intubated. For those patients, feeding and medication administration may need to be performed via enteral feeding tubes (EFT). When administering medication via EFT, the type of tube used as directed by the intended site of insertion and site of the distal end needs to be considered. In this publication, the focus will be on 1 type of EFT, the nasogastric feeding tube (NGT), which is inserted through the nose with the distal end located in the stomach. Other EFT and administration sites exist, including orogastric or percutaneous tubes all of which may target delivery to various regions of the GI system (i.e., stomach, duodenum, jejunum).

An NGT is a common enteral tube for temporary use due to ease of placement and removal, cost, and patient acceptability. Common materials of construction for NGT include polyvinylchloride (PVC), polyurethane (PUR), silicone, or latex. NGT may be characterized as large-bore or small-bore depending upon the external diameter measured in French (Fr) units. In adults, small-bore tubes range from 8 to 12 Fr (2.7–4.0 mm) and are the preferred bore size due to increased comfort to the patient. Large-bore tubes, in adults, typically range from 14 to 18 Fr (4.7–6.0 mm). The Fr size pertains to the external diameter of the tubing but other important NGT attributes to consider for medication administration include the tubing composition, internal diameter, and overall tube length. Softer materials of construction (i.e., silicone and latex) have a smaller internal diameter at respective Fr sizes when compared to other materials (i.e., PVC or PUR). Adult NGT are typically between 90 and 100 cm in length.

The Handbook of Drug Administration via Enteral Feeding Tubes presents individual drug monographs, including enteral tube administration procedures and formulations (i.e., dosage forms) available. Each dosage form presents its own inherent challenges to dosing which need to be evaluated on a case-by-case basis. Key considerations to demonstrate feasibility of medication administration through an EFT include ease of administration procedure, risks of tube clogging, chemical compatibility with common tubing materials of construction and dosing accuracy.

The Guidebook on Enteral Medication Administration contains a chapter for AZM which provides considerations for enteral administration of AZM powder for oral suspension. In response to potential pandemic needs, enteral dosing procedures for alternate AZM dosage forms (tablets and capsules) were developed in vitro. As of March 25, 2020, a search of the published medical literature had failed to identify any additional relevant references which would aid health care providers needing to administer AZM (using tablets or capsules) via feeding tubes. The authors recognize that any literature search is subject to inherent limitations and cannot be considered exhaustive. This manuscript provides the in vitro assessment for the dose preparation and simulated administration of AZM suspensions, prepared from tablets and capsules, via NGT. Multiple dose preparation (i.e., compounding) procedures were evaluated for AZM tablets and capsules with attention placed on the ease of preparation, accuracy of administration (in vitro), in-use stability of prepared suspensions, and chemical compatibility of prepared suspensions with the delivery syringe and NGT. Simulated dosing over a range of 250 to 2000 mg AZM was evaluated to determine the impact of dose size on administration. The relative ease of delivery (i.e., absence of tube clogging) and accuracy of dosing (in vitro) were evaluated using NGT of common materials (PVC, PUR, and silicone) at bore sizes and lengths consistent with those commonly used in adult populations.

Note that the summarized data in this manuscript includes information of an off-label nature, and is based on a laboratory study of physicochemical stability and compatibility with the administration system (dosing syringe and NGT). AZM stored and administered outside the recommended temperature range and method of administration has not been tested or evaluated for safety or efficacy. Any method of administration other than those described in the Prescribing Information is outside the terms of the marketing authorization.

Materials and Methods

Materials

AZM 250 mg tablets (Greenstone LLC, NDC 59762-2198-7; lot number AR8691, North Peapack, NJ) and 250 mg capsules (Haupt Pharma, lot 064223, Latina, Italy) were used to prepare aqueous suspensions from 250 to 2000 mg of AZM for administration via NGT. The AZM tablets (compressed, film coated) contained azithromycin dihydrate (active ingredient) with dibasic calcium phosphate anhydrous, pregelatinized starch, sodium croscarmellose, magnesium stearate, sodium lauryl sulfate, hypromellose, lactose, titanium dioxide, triacetin, and D&C Red #30 aluminum lake (inactive ingredients). The AZM capsules (hard gelatin) contained a blend composed of azithromycin dihydrate (active ingredient) with lactose anhydrous, magnesium stearate, maize starch, sodium lauryl sulfate, gelatin, iron oxide (black) E172, shellac, propylene glycol, sulfur dioxide, and titanium dioxide (inactive ingredients).
The NGT used for the experiments are provided in Table 1. The NGT selected were in the small-bore range (8-12 Fr) and covered common materials of construction (PVC, PUR, and silicone) and typical lengths. Clear, non-sterile, 20 mL enteral syringes (Baxter, ENFit syringe, Ref. H93899120) were used for administration of prepared aqueous suspensions to NGT. Water was used as the diluent (i.e., bottled water). The syringes were composed of polypropylene, polydimethylsiloxane, and silicone and contained no natural rubber latex, bis(2-ethylhexyl) phthalate (DEHP), or bisphenol A (BPA). White, polypropylene tip caps (Baxter, Ref. H93853305) were used during dose preparation and in-use storage.

**Methods**

The preparation and simulated NGT administration steps for AZM suspensions, prepared from tablets and capsules, were evaluated in the laboratory studies. For both dosage forms, evaluation included the assessment of in-use stability of the aqueous suspensions prepared and then held within the dosing syringe, chemical compatibility of prepared aqueous suspensions with the syringe and NGT, ease of delivery (i.e., absence of tube clogging), and accuracy of dosing (in vitro), Figure 1. For tablets, the aqueous suspension dose preparation was evaluated by 2 methods: (1) disintegration of crushed tablet(s) in water and (2) disintegration of intact tablet(s) in water. Capsules were prepared by emptying the contents of the capsule(s) and dispersing the capsule fill in water. The laboratory studies were performed in a manner to simulate the dosing of patients, using a dosing syringe and NGT that would be used in a clinical setting but collecting the effluent into volumetric glassware for analytical testing. A matrix approach (Table 2) to the evaluation was taken for the lowest and highest doses, 250 and 2000 mg respectively. Tubing sizes of 8 and 12 Fr were evaluated to bracket the ranges of typical small bore NGT. The smallest diameter NGT (8 Fr) for each material of construction (PVC, PUR, and silicone) was evaluated as worse case in terms of clogging potential and a test of compatibility of the product in contact with the different tubing material. Larger NGT (12 Fr) were evaluated to confirm the required rinse volume to effectively deliver the full (or complete) dose. For the 12 Fr NGT, only PUR was evaluated as material compatibility was assessed using the smaller diameter tubing. For both 8 and 12 Fr NGT, lengths of approximately 90 cm (35”) or longer were used to represent typical lengths used for adult patients. Acceptable stability of the prepared aqueous suspensions within the dosing syringe was confirmed when held under ambient conditions (light and temperature) for a period of up to 4 hours.

An analysis of the prepared sample solutions for assay (percent of AZM delivered relative to the intended dose) and impurities was performed using chromatographic method.

**Table 1.** Enteral Feeding Tube, Key Information.

| Supplier   | Size (Fr) | Length  | Item #         | Material of construction |
|------------|-----------|---------|----------------|--------------------------|
| Medela     | 8         | 42”     | ENFPV428OLD    | PVC                      |
| Covidien   | 8         | 43”     | 8884720841E    | PUR                      |
| NeoMed     | 8         | 35”     | FTL8.OS-EO     | Silicone                 |
| Covidien   | 12        | 43”     | 8884721252E    | PUR                      |

**Figure 1.** Dose preparation and simulated administration verification workflow.
Table 2. Dose Preparation and Simulated Administration Verification Test Matrix.

| Verification of dose preparation | 250 mg Dose | 2000 mg Dose |
|----------------------------------|-------------|--------------|
| Time 0, syringe stability        | T, CT, C    | T, CT, C     |
| Time 4h, syringe stability       | T, CT, C    | T, CT, C     |

| Verification of simulated administration | 8 Fr PVC | 8 Fr PUR | 8 Fr Silicone | 12 Fr PUR |
|------------------------------------------|----------|---------|---------------|----------|
| 250 mg Dose                              | T, C     | T, C    | T, C          | T, C     |
| 2000 mg Dose                             | T, C     | T, C    | T, CT, C      | T, CT, C |

Note. T = intact tablet; CT = crushed tablet; C = capsule; PVC = polyvinyl chloride; PUR = polyurethane.

conditions based on the USP-NF monograph for AZM tablets.18 Given the compositional similarities of the tablet and capsule formulations, these methods (assay and impurities) were used for analysis of both dosage forms. A common diluent (50/50 v/v, acetonitrile/water) was used for sample preparation for assay and impurities to ensure AZM solubility. The nominal concentration for the sample extractions was 2 to 2.5 mg/mL (purity analysis), with further dilution to the assay method nominal concentration of 1 mg/mL (assay analysis). Analytical dilutions were performed and verified as appropriately sensitive for quantitation of AZM and potential impurities.

Results

Verification of Dose Preparation

The verified dose preparation instructions, for intact tablets and capsules, are outlined in Figure 2. Intact tablets were used to prepare suspensions in the intended 20 mL dosing syringe to minimize manipulation and to ensure acceptable recovery of the administered dose. When evaluating crushed tablet(s), the tablet(s) were placed onto a folded piece of glassine paper and gently crushed using a ceramic pestle. The crushed tablet(s) were transferred to a dosing syringe that contained water and the subsequent steps were in line with the capsule preparation steps, beginning at Step 4. As discussed below, the preparation steps are not fully detailed as the crushed tablet preparation method is not preferred. For capsules, the contents were emptied from the hard gelatin shell and transferred to a 20 mL dosing syringe that contained water to eliminate the need for lengthy times associated with dissolving gelatin if intact capsules were used. The instructions (for intact tablets and capsules) follow closely the practices recommended in the Handbook of Drug Administration via Enteral Feeding Tubes9 for tablets that disintegrate and hard gelatin capsules. Suspensions were prepared at 250 mg (single tablet or capsule) and 2000 mg (8 tablets or capsules) to verify a wide dosing range. A 20 mL dosing syringe was selected to allow enough dilution of the higher doses to ensure good disintegration and dispersion.

Upon completion of suspension preparation steps outlined in Figure 2, the prepared capped syringes were held under ambient light and temperature for 4 hours to generate in-use stability data. Single preparations of each of these samples were tested for assay and impurity content and compared against a control (freshly prepared sample that did not contact a dosing syringe) to establish data supporting the chemical stability of these preparations and compatibility with the syringes and syringe caps. Table 3 contains a summary of the data supporting in-use stability. For both tablets (intact, T and crushed, CT) and capsules (C), the aqueous suspensions were tested immediately upon completion of preparation as a control sample for assay and impurity content. The assay of those initial samples was reported as % of the intended dose (i.e., % of 250 or 2000 mg) with an acceptance criterion of 90.0% to 110.0% of intent. At the 2000 mg dose level, all samples (i.e., T, CT, and C) were within the acceptance limits at the initial time-point. For the 250 mg dose, both the intact tablet (T) and capsules (C) were within the acceptance limits while the crushed tablet (CT) was outside of the criterion, 82.3% of intent. The low assay result for this sample may have been attributed to loss of AZM due to static observed during the crushing process which caused challenges with the quantitative transfer of the product to the dosing syringe. Multiple attempts were made to modify the crushed tablet technique to improve the dose recovery but results consistently demonstrating low recovery when crushing the tablets as part of the 250 mg dose preparation.

The samples held for 4 hours in the capped syringes (under ambient light and temperature) were also analyzed for assay and impurity content. The % of intended dose (i.e., % intent) was reported and compared to the % of intended dose at initial (i.e., % of initial). Following the 4 hour hold in the capped dosing syringe, all samples met 90.0% to 110.0% of initial assay. The purity profile and total degradation was compared to the initial samples and demonstrated acceptable stability of the prepared capped syringes after a 4 hour hold. During this materials compatibility assessment, the syringes were not rinsed after the volume in the syringe was transferred to the volumetric flask. In the simulated administration verification for this study, it was observed that a syringe rinse can increase the delivered dose by approximately 3% or greater. Therefore, a syringe rinse is recommended as part of the dosing instructions.
Figure 2. AZM aqueous suspension dose preparation instructions using 250 mg tablets (top) and 250 mg capsules (bottom).

Table 3. In-Use Stability of Aqueous Suspensions Prepared from AZM Tablets and Capsules Held Within Dosing Syringe.

| Dose (mg) | T, CT, C | Assay (% intent) | Purity | % Total degradation products |
|-----------|----------|------------------|--------|-----------------------------|
|           |          | Initial (% intent) | 4 h (% Initial) | 4 h | Initial | 4 h |
| 250 mg    | T        | 90.3             | 96.8    | Meets criteria              | 1.5  | 1.3 |
| 250 mg    | CT       | 82.3             | 104.4   |                               | 1.1  | 1.1 |
| 250 mg    | C        | 96.3             | 97.1    |                               | 1.0  | 1.0 |
| 2000 mg   | T        | 94.9             | 99.1    |                               | 1.0  | 0.9 |
| 2000 mg   | CT       | 93.2             | 100.4   |                               | 0.9  | 1.0 |
| 2000 mg   | C        | 93.2             | 104.9   |                               | 0.8  | 0.8 |

Acceptance criteria 90.0-110.0 No new impurity >0.2% or change relative to the control >0.2% Not more than 5.0

Note. T = intact tablet; CT = crushed tablet; C = capsule.
In addition to assessing assay and purity changes during in-use stability, a microbial risk assessment was performed to demonstrate acceptability of a 4 hour hold at ambient conditions for these aqueous suspensions. Additionally, the suspension is expected to maintain an acceptable level of microbial quality from preparation through dosing. The short hold-time (4 hours) and broad spectrum of antibacterial activity for AZM reduces the potential risk of microbial contamination and proliferation in the preparation.

**Verification of Simulated Administration**

Dosing accuracy of AZM suspensions prepared from both tablets (intact, T and crushed, CT) and capsules (C) to simulate patient administration were confirmed in laboratory studies and included assessment of material compatibility. Each of the NGT described in Table 2 were staged in the laboratory with the distal tip held within volumetric glassware to collect the delivered dose (in vitro) and all flushes and eluent delivered through the tubing. Upon completion of suspension preparation steps outline in Figure 2, each NGT was prepared for dose delivery (in single replication) including the flushing, delivery of suspension and rinsing steps outlines in Table 5. All materials delivered through the NGT for a given sample were combined into the same glass volumetric flask and further processed for analysis. The study included an evaluation of the effectiveness of rinsing the syringe following delivery of the dose. The assay results were determined as % Intent, based on the target dose of either 250 or 2000 mg AZM for each delivered dose and results are compiled in Table 4. A purity assessment was also performed, quantifying any impurities/degradation products present at reportable levels in the delivered doses as compared to the “control” (analyzed tablets and capsules without any exposure to the delivery devices, eg, syringe, NGT).

The data summarized in Table 4 confirm the utility of a rinse of the syringe following the dose delivery, with as much as a 3% increase in the assay results when a rinse is included. To ensure the highest dose delivery a rinse step is recommended as part of the dosing instructions. All assay results met the acceptance criterion of 90.0% to 110.0% intent, ensuring the accurate delivery of AZM from tablets or capsules via NGT over the dose range of 250 to 2000 mg. Compatibility of the prepared doses with the NGT composed of PVC, PUR, and silicone was demonstrated by acceptable purity assessment of the delivered doses.

**Discussion**

**Dose Preparation**

For tablets, preparation of aqueous suspensions from both crushed (CT) and intact tablets (T) were explored (Table 2 and Table 3). Crushing tablets is a common compounding approach having the advantage of reducing the dosage form to smaller fragments making it a reasonable approach for tablets that do not readily disintegrate. However, the approach does require greater manipulation and can therefore result in dosing accuracy challenges, which were observed in this study. In addition, crushing tablets may be less preferred for tablets that
disintegrate well. The AZM 250 mg tablets used in this study disintegrate quickly in water and intact tablets resulted in the most accurate dose delivery and therefore the preferred preparation method is by using the intact tablets. The assessment of in-use stability was limited to single replications. As the focus was centered around purity and degradation changes, the single replicate determination was deemed acceptable.

Simulated Administration

Dosing and administration instructions were developed and verified through laboratory simulation. A laboratory simulation of patient dosing of AZM tablets and capsules over the dose range of 250 to 2000 mg via NGT of varied material composition was performed. The steps of the dose preparation and delivery were verified to ensure a homogenous suspension that could be accurately dosed via NGT. The experiment was designed to determine if a syringe rinse after initial dose administration is needed. The results (Table 4) demonstrate that under all conditions tested, the % of the dose delivered is within the acceptance criteria but adding the rinse step to the procedure can increase the dose delivered by as much as 3%.

Table 5. Simulated Delivery Instructions for Prepared Suspensions from AZM 250 mg Tablets or 250 mg Capsules via NGT.

| Materials |  |
|-----------|---|
| Product | AZM 250 mg tablets or capsules. |
| Diluents | Water (eg, tap, bottled, sterile) or suitable solution for use in dose preparation and for NGT irrigation/flushing. |
| Oral/Enteral Syringes | 20 mL or larger syringes constructed of polypropylene, PVC or PUR (eg, Universal, Comar®, Baxter ENFit®). Syringes containing natural rubber products were not evaluated. |
| NGT | 8 Fr or larger constructed of PVC, PUR, or silicone. |
| Other | Oral/enteral syringe tip caps, cup, or similar container. |

Step # Administration (250 mg AZM tablets or 250 mg AZM capsules)

1. Flush the NGT with approximately 15 mL of water prior to medication administration.
2. Shake the prepared capped syringe vigorously until a homogenous suspension is observed.
3. Remove the tip cap and administer the prepared suspension via the NGT.
4. Flush the NGT with approximately 15 mL of water immediately after medication administration.
5. Perform a rinse of the syringe to ensure complete delivery of the dose:
   - Remove the tip cap of the syringe and draw up approximately 15 mL of water.
   - Draw air into the syringe until the plunger is at the 20 mL mark.
   - Immediately place a cap on the syringe tip.
   - Shake the syringe vigorously for a minimum of 10 s.
   - Remove the syringe tip cap and administer the rinse via the NG tube.
   - Note: It is normal for a trace amount of material to remain in the syringe.
6. Flush the NG tube with an additional 15 mL of water and cap the NG tube port.
7. Clean all materials carefully and dispose of all supplies.

Note. PVC = polyvinylchloride; PUR = polyurethane.
PVC, PUR, and silicone was demonstrated. Single preparations were evaluated for each type of NGT material, however collectively the repeatability of simulated administration can be assessed.

This assessment covered the in vitro laboratory verification for dose preparation and simulated administration. During the development of administration procedures, the physicochemical properties of the drug, formulation design (eg, presence of functional coatings which may alter drug release), and site of administration need to be considered. Additionally, consideration should be given to potential interactions of the drug with enteral nutrition.

**Conclusion**

The laboratory studies verified an efficient and accurate procedure to reliably prepare stable suspensions from AZM tablets and capsules, over a range of 250 to 2000 mg (1-8 unit doses), that can be administered through NGT of size 8 to 12 Fr. Acceptable chemical stability of the prepared dose(s) through 4 hours at ambient conditions was verified as was the compatibility of the prepared dose(s) with NGT composed of PVC, PUR, and silicone. Finally, the accuracy of the delivered dose by the modified tablet and capsule preparation procedure (Figure 2) and simulated dose procedure (Table 5) was verified to be within 90.0% to 110.0% of intent.

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