Compounding Rifampin Suspensions with Improved Injectability for Nasogastric Enteral Feeding Tube Administration

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INTRODUCTION

Rifampin (RIF) is a semi-synthetic antibiotic with a wide antibacterial spectrum, used mainly in combination with other antitubercular drugs in the initial treatment of pulmonary tuberculosis (TB) or in the treatment of drug-resistant infections.1 TB is still a serious global health problem. The latest estimates of the global burden of TB by the World Health Organization (WHO) are that there were 9.3 million incident cases of TB and 13.7 million prevalent cases of TB in 2007.2 There were also 1.3 million deaths from TB among HIV-negative people in 2007, and an additional 456,000 deaths among HIV-positive TB cases—equivalent to 23% of the total deaths attributed to HIV. Overall, 86% of incident cases occurred in Africa and Asia. In most countries RIF is available in capsules containing either 150 or 300 mg of the drug.

An important element of TB therapy is the actual ingestion of the drugs. Children are especially difficult to dose with TB drugs, given that the formulations are not particularly child friendly. Several studies suggest that if patients cannot swallow RIF capsules, the contents of the capsules can be suspended in a vehicle such as Simple Syrup NF or mixed with applesauce before administration.3–8 However, severely ill patients might not be able to swallow these suspensions and must receive the drug, usually suspended in Syrup NF per manufacturer instructions, through a nasogastric enteral feeding (NG) tube. Medication administration through NG tubes is a common practice.9 For most patients, medications are given in addition to enteral nutrition10,11; however, enteral tubes can be used exclusively to administer medication.12–14 When administering drugs by NG tube, it has been argued that the liquid form is superior to solid as the risk of tube occlusion is less.5,13,15 However, some liquid medications, including RIF suspensions, can also cause tube occlusion, especially of the distal

ABSTRACT

Often medications that have to be administered to patients via a nasogastric enteral feeding tubes are only available as tablets and capsules with no suitable commercial liquids alternatives. In such situations, pharmacists and nurses have to compound the tablets and capsule contents into liquid suspension formulations for dosing. The risk of occlusion of the enteral tubes during administration is reduced by employing liquid suspensions that are composed of small and uniform particles, not subject to rapid rates of settling, resistant to caking, and easily and uniformly resuspended upon agitation. Present techniques often employ a manual process, such as a mortar and pestle, to accomplish the particle size reduction and subsequent incorporation into a suitable liquid diluent. A new compounding device has been invented that employs an automated wet-milling process in a single-use disposable plastic container to compound the suspensions. The two processes were compared using Rifampin capsules and various liquid diluents. A prototype version of the new device was employed in the experiments. The physical characteristics of the compounded suspensions were evaluated by determining sedimentation rate, sedimentation volume, and particle size and shape using laser light scattering, optical microscopy, and scanning electron microscopy techniques. The use characteristic of the compounded suspensions was evaluated using a nasogastric tube injectability test. The results indicated that suspensions prepared using the new device were more resistant to sedimentation and caking and were easier to redisperse into a uniform mixture by gentle shaking. The results were a consequence of the particles generated by the new device which were found to be smaller and more uniform in shape and size. The suspensions prepared using the new device did not cause blockage of the enteral feeding tubes in comparison to those prepared using a mortar and pestle. In conclusion, the results indicate that the wet-milling process employed by the new compounding device produces liquid suspensions that are more suitable for dosing via nasogastric enteral tubes in comparison to the manual mortar and pestle method that is presently employed.
openings of the feeding catheter.\textsuperscript{10} NG tube obstruction may require tube replacement, involving discomfort for the patient, inadvertent positioning in the respiratory tract, increased nursing time, and additional costs, including materials and radiography.\textsuperscript{17,18} It is therefore very important to maintain tube patency. For example, 15 to 50 mL of water should be used to flush before and after giving medication.\textsuperscript{9,15,16,19} Careful selection and preparation of dosage forms will also decrease the incidence of tube clogging and replacement.\textsuperscript{9,13,19}

In order to evaluate if suspension preparation methods influence NG tube clogging, the objective of this study was to use the content of RIF capsules to prepare suspensions according to the capsule manufacturer’s instruction and published reports.\textsuperscript{1–8,20} In addition, these suspensions were prepared using either a mortar and pestle or a prototype compounding mixer. The injectability of the suspensions through a NG tube was measured in vitro to determine which suspension vehicle and preparation method helped to maintain tube patency the best.

**MATERIALS AND METHODS**

**Materials**

Rifampin 300-mg Capsules USP (Lot 62542A, VersaPharm, Marietta, Georgia) were used as supplied. The average total weight of the 300-mg capsules was 360 ± 6.8 mg, which includes 300 mg of the drug. Sterile Water for Irrigation USP (Lot G059279; Baxter, Deerfield, Illinois) was used throughout the study. Ora-Plus (Lot 8273520) and Ora-Sweet (Lot 8313731) were obtained from Paddock Laboratories, Minneapolis, Minnesota. Syrup NF and Vehicle for Oral Suspension, Sugar Free NF were prepared in house from United States Pharmacopeia (USP)—National Formulary (NF)-grade chemicals.

**Method**

**Preparation of Rifampin Suspension Samples**

The following five suspension formulations were prepared:

- **Formulation 1**: The contents of two rifampin capsules (equivalent to 600 mg of the drug) were suspended in 30 mL sterile water for irrigation.
- **Formulation 2**: The contents of two rifampin capsules were suspended in 30 mL Syrup NF.
- **Formulation 3**: The contents of two rifampin capsules were suspended in 30 mL Vehicle for Oral Suspension, Sugar Free NF.
- **Formulation 4**: The contents of two rifampin capsules were suspended in 30 mL of a mixture of Ora-Plus and Ora-Sweet (1:1 v/v).
- **Formulation 5**: The contents of two rifampin capsules were suspended in 30 mL of Ora-Plus.

Suspensions were prepared using two methods.

**Method A**

The contents of the capsules were placed in a small glass mortar and mixed by geometric dilution with 30 mL vehicle using a pestle. To ensure consistency among the different suspensions, each suspension was mixed for 5 minutes using a sequence of 25 seconds of continuous mixing followed by 5 seconds of no mixing.

**Method B**

The contents of two capsules were mixed with 20 mL of the vehicle in a prototype compounding machine for 5 minutes. In this mixer, a sequence of 25 seconds of continuous mixing followed by 5 seconds of no mixing was used. For the injectability test, the suspensions were prepared within 1 hour of testing.

**Description of Prototype Compounding Machine**

**Background**

Healthcare providers such as pharmacists, nurses, physicians, and veterinarians often have to extemporaneously prepare oral liquid formulas from tablets and capsules to dose their patients. Preparation of such liquid formulas involves two steps: (1) the reduction of the tablets or capsule contents into fine particulates and (2) the use of these powders in the compounding of the liquid formulas by the addition of aqueous diluents and pharmaceutical excipients such as flavors, sweeteners, viscosity enhancers, and antimicrobial preservatives. The reduction of the tablets and capsule contents into fine particles is presently undertaken using a variety of dry-grinding techniques. The techniques include use of mortars and pestles, coffee-bean grinders, serrated plastic grinding plates, and devices that “mash” tablets in plastic bags. The grinding techniques have several disadvantages. They are not easily reproducible and often produce coarse powders that are not suitable for the formulating of physically stable liquid preparations that deliver uniform doses of medications. Secondly, the cleaning of the devices is cumbersome and if not done properly leads to the risk of cross-contamination of medications from the repeated use of the device.

**Innovation**

A device (INSTA Formulation System) was invented to provide an alternative method to the dry-grinding process; the innovation employs wet milling. The wet milling process uses a disposable container with an interior abrasive surface. The milling process is achieved by placing the tablets or capsule contents along with water in the containers and providing the proper agitation. The wet milling process produces uniform small particles that are well suited for the compounding of liquid pharmaceutical formulations. The use of disposable plastic containers eliminates the concern of drug cross contamination. The containers are employed to both grind the tablets and capsule contents, and to prepare, store, and dispense the resultant liquid formulations for each prescription. The technology has been granted a patent by the U.S. Patent Office;\textsuperscript{21} has been granted a European Patent and the application is now in the National Phase in the European Union, and has applications under review in Canada and Japan.

A picture depicting the INSTA Formulation System can be found in Figure 1.

**Properties of the Suspensions**

The mean volume particle size, D[4,3], of the suspensions was determined by adding samples to a small volume stirred cell, diluting each sample with demineralized particle-free water until an adequate scattering intensity and obscuration were obtained. The geometric particle size in each sample was then measured by laser light scattering using a 100-mm Fourier transform lens (Malvern Mastersizer X; Malvern Instruments Inc., Westborough, Massachusetts). Photomicrographs of the rifampin particles in the suspensions were taken with an optical polarizing microscope (Lomo, Northbrook, Illinois) with an attached digital camera (Ken-A-Vision; Kansas City, Missouri). The samples were also observed using a Hitachi S-570 LaB\textsubscript{6} Scanning electron microscope (SEM) (Schaumburg, Illinois). Samples were coated with a layer of gold/palladium using a SeeVac Auto Conductavac
IV sputter coater (KDF Sputtering Systems, Rockleigh, New Jersey) before being imaged.

The sedimentation rate of each suspension was measured by pouring 25 to 50 mL of the suspension into graduate cylinders. The boundary between the sediment and the supernatant was determined and used to measure the volume of the sediment. This volume was plotted as a function of time for up to 48 hours. The slope of the initial linear part of the curves represents the sedimentation rates in mL/hr. The sedimentation volume \( F \) was calculated using the relationship:

\[
F = \frac{V_s}{V_0}
\]

Where \( V_s \) is the volume of the sediment and \( V_0 \) is the original volume of the suspension. \( F \) is normally less than 1. When no sedimentation occurs, the volume of the sediment equals the volume of the suspension and \( F = 1 \). The degree of flocculation (\( \beta \)) of the suspension was estimated by comparing the \( F \) of each suspension to that of the suspension with the smallest sedimentation volume (most deflocculated, \( F_\infty \)). In this study, it was the suspensions prepared in Water for Irrigation USP.

If a suspension is completely deflocculated, \( \beta = 1 \). \( \beta \)-values > 1 indicate a more flocculated system. The ease of redispersion of the suspensions was assessed qualitatively by the simple agitation of the preparation in its container or the syringe.

**Nasogastric Tube Injectability Test**

The injectability of the suspensions through a size 8 French polyurethane nasogastric feeding tube (Bard 100 % latex free, Adult/Pediatric feeding tube, 8Fr, 2.7 mm ID, 107 cm length; CR Bard Inc, Covington, Georgia). For each administration, 30 mL of sterile water were initially pushed though the nasogastric tube. Then 30 mL of the suspension containing 20 mg/mL rifampin were pushed through the tube, followed by another 30 mL of sterile water. The tube was then stored in sterile water. This process was repeated every 24 hours. The administration was done with a GENIE Plus infusion and withdrawal syringe pump (Kent Scientific Corp., Torrington, Connecticut) set to deliver 30 mL at a speed of 19 mL/min. Failure was indicated when the tube was dislodged from the syringe due to excessive back-pressure or when the tube became blocked and liquid stopped flowing through the NG tube.

**RESULTS**

In Figure 2, photomicrographs of the rifampin particles in the capsule and after suspension in water, using Method A and B, are shown. The mean volume particle size of the capsule powder was 86.3 ± 31.5 mcm. The particle size of the suspensions prepared using Method A and B are listed in Table 1. For the suspensions...
prepared by Method A, the average particle size was 53.5 ± 4.0 mcm. The average particle size of all the suspension prepared by Method B was 18.9 ± 4.1 mcm. Examples of the sedimentation experienced by suspensions prepared using Method A and B are shown in Figure 3. The decrease in sedimentation volume with time is shown in Figure 3. The results in Figure 4 were used to calculate the sedimentation parameters listed in Table 1. The average sedimentation rate for suspensions prepared by Method A was 2.4 ± 1.7 mL/hr and for Method B it was 0.8 ± 1.1 mL/hr. For Method A, the average $F$ was 0.42 ± 0.21, with an average $\beta$ value of 8.4 ± 4.1. The average $F$ was 0.65 ± 0.35 and $\beta$ 12.9 ± 7.1 for Method B. The results obtained from the injectability test using a syringe pump and 8F NG tubes are listed in Table 2. Failure to pump, which occurred when the tube became dislodged from the syringe or when the tube was blocked, is indicated with a negative (-) sign.

**TABLE 1. Properties of the Suspensions Including Mean Volume Particle Size and Stability Against Sedimentation.**

<table>
<thead>
<tr>
<th>Vehicle</th>
<th>Method Size (mcm)</th>
<th>Sedimentation Rate (mL/hr)</th>
<th>$F$</th>
<th>Degree Flocculation ($\beta$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sterile water A</td>
<td>56.3 ± 9.4</td>
<td>5.34</td>
<td>0.05</td>
<td>1.0</td>
</tr>
<tr>
<td>Sterile water B</td>
<td>24.4 ± 7.2</td>
<td>1.74</td>
<td>0.05</td>
<td>1.0</td>
</tr>
<tr>
<td>Syrup USP A</td>
<td>54.3 ± 8.9</td>
<td>1.86*</td>
<td>0.49</td>
<td>9.8</td>
</tr>
<tr>
<td>Syrup USP B</td>
<td>22.1 ± 6.5</td>
<td>2.26*</td>
<td>0.62</td>
<td>12.4</td>
</tr>
<tr>
<td>Vehicle for Oral Suspension NF A</td>
<td>47.6 ± 8.7</td>
<td>1.82</td>
<td>0.51</td>
<td>10.2</td>
</tr>
<tr>
<td>Vehicle for Oral Suspension NF B</td>
<td>15.6 ± 6.1</td>
<td>0.1</td>
<td>0.91</td>
<td>15.8</td>
</tr>
<tr>
<td>Ora-Plus/ Ora-Sweet (1:1) A</td>
<td>57.6 ± 9.3</td>
<td>1.94</td>
<td>0.51</td>
<td>10.2</td>
</tr>
<tr>
<td>Ora-Plus/ Ora-Sweet (1:1) B</td>
<td>16.7 ± 5.8</td>
<td>0.0</td>
<td>0.96</td>
<td>16.6</td>
</tr>
<tr>
<td>Oral Suspension NF A</td>
<td>54.3 ± 8.9</td>
<td>1.86*</td>
<td>0.49</td>
<td>9.8</td>
</tr>
<tr>
<td>Oral Suspension NF B</td>
<td>22.1 ± 6.5</td>
<td>2.26*</td>
<td>0.62</td>
<td>12.4</td>
</tr>
</tbody>
</table>

*Creaming rate for suspensions in syrup

**TABLE 2. The Injectability of the Suspensions Through an 8F NG Tube Measured with a Syringe Pump Every 24 Hours for Seven Days.**

<table>
<thead>
<tr>
<th>Vehicle</th>
<th>Method</th>
<th>Days</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sterile water A</td>
<td>A</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Sterile water B</td>
<td>A</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Syrup USP A</td>
<td>A</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Syrup USP B</td>
<td>A</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Vehicle for Oral Suspension NF A</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Vehicle for Oral Suspension NF B</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Ora-Plus/ Ora-Sweet (1:1) A</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Ora-Plus/ Ora-Sweet (1:1) B</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>
DISCUSSION

The ease of administration of an RIF suspension with a syringe through a NG tube, its injectability, may depend on the particle size and shape of the drug particles, particularly since the RIF particles (Figures 2 and 5) are acicular in shape rather than isometric.\textsuperscript{22-24} For parenteral injections, it is known that large particles, >25 mcm, and particles with high aspect ratios, the ratio of the longest dimension to the perpendicular dimension at the midpoint >3:1, frequently cause syringe needle blockage. Particle size analysis (Table 1) showed that there was not a significant difference in the mean volume particle size of the suspensions prepared in a mortar with a

FIGURE 4. Sedimentation volume as a function of time for the five suspension formulations prepared using (a) Method A and (b) Method B.

FIGURE 5. SEM photomicrographs of RIF capsule powder suspended in water (A) unmixed (B) mixed in a mortar with a pestle—Method A and (C) using the prototype compounding mixer—Method B.
pestle with the different vehicles. Similarly, the mean volume particle size of the suspensions prepared with the prototype compounding mixer was also not significantly different for the different vehicles. These results showed that size reduction did not depend on the vehicle used. However, although preparation of the suspension with a mortar and pestle reduced the mean volume particle size of all the suspensions by ~33 mcm, regardless of the vehicle used, the reduction in particle size obtained with the prototype compounding mixer was twice as large, 67 mcm. The mean volume particle size of all of the suspensions prepared with the prototype compounding mixer (Table 1) was <25 mcm.

The capsule content had a log normal, positively skewed particle size distribution with a majority of small particles but a significant number of large particles >200 mcm. After mixing in the mortar with a pestle, the distributions tend to become bimodal with a larger number of small particles, >50 mcm, and a separate smaller population of larger particles. The suspensions prepared in the prototype compounding mixer had log normal distributions with no particles larger than 200 mcm. There was also a significant change in the particle shape upon mixing in the prototype compounding mixer. The RIF particles present in the capsule were columnar-shaped, with a width and thickness greater than those of acicular particles. SEM analysis (Figure 5) indicated that the majority of the particles had aspect ratios of 2:1 all the way up to 5:1. After mixing with a pestle in a mortar, the basic particle shape stayed the same but the aspect ratios were reduced to mostly 2:1 and 3:1 with some particles that were isodiametric. The surfaces of many of the larger particles were decorated with tiny irregularly shaped particles. The shape of the majority of particles obtained after size reduction in the prototype compounding mixer (Figure 5) was equant, cubical, and spherical particles, with rounded edges and mostly similar lengths, widths, and thicknesses. The surfaces of these particles were rough with numerous surface irregularities. Overall, the smaller mean volume particle size, narrower size distributions, and more uniform shape of the suspensions prepared in the prototype compounding mixer meant that the particles in these suspensions were more homogenous.

The physical stability of a suspension is normally assessed by the measurement of its rate of sedimentation, the final volume, or height of the sediment, and the ease of redispersion of the product.24 In this study, the suspensions prepared in water settled very quickly, <10 hours, the sediments became compacted, and it was very difficult to disperse the cakes that formed (Figure 2). The sediments of the other suspensions tend to be partially flocculated and, because the viscosities of the vehicles were higher, the sedimentation rates were reduced. Interestingly, the sediment formed in the suspensions prepared in Syrup NF was lighter than the vehicle and floated to the top (Figure 2). Overall, except for the aqueous suspensions, the sedimentation rates (Figure 4) of the suspensions were acceptable. This meant the syringeability of these suspensions were good because they remained sufficiently homogenous for at least the period between shaking the container and removing the dose. As shown in Table 1, the sedimentation rates of the suspensions prepared by Method B were slower than for those prepared via Method A. In fact, within the 48 hours during which the suspensions were observed, those prepared by Method B and using the Vehicle for Oral Suspension, Sugar Free NF, Ora-Plus and Ora-Sweet (1:1 v/v), or Ora-Plus showed hardly any sedimentation with $F$ values $>0.9$ (Figures 3 and 4). The degree of flocculation ($\beta$) of these suspensions were also significantly higher, indicating that they were better at resisting sedimentation. In addition, the sediments produced on storage of these suspensions were easily resuspended by the use of moderate agitation.

The smaller and more uniform particle sizes and greater resistance to sedimentation seem to indicate that RIF suspensions prepared in the more viscous vehicles, compared to water, using Method B should have better injectability during NG tube administration. This was evaluated in vitro using an 8F NG tube attached to a syringe pump. Although most patients receive enteral nutrition in addition to medications by NG tube administration,10,11 in this study, the effect of the daily administration of RIF suspension for 7 days on tube patency was tested in vitro without administration of nutrition solutions. The results in Table 2 indicate that the suspensions prepared in water caused tube blockage after 2 days for Method A and after 3 days for Method B. This was because even though the tubes were flushed with 30 mL of water before and after administration of the suspensions, eventually, dark red RIF particles started to accumulate in the bottom of the NG tube (Figure 6), clogging the two distal openings in the side of the tube. This same observation was seen with the Syrup NF suspensions. Due to the more viscous nature of the syrup, it was more difficult to remove the remaining RIF suspension from the end of the tube, and, eventually, enough residual material accumulated and the tube became blocked after 3 days for Method A and 4 days for Method B (Figure 6). An interesting observation for this suspension was that the NG tube got clogged on the first day if the suspension was injected at a slower rate (<5 mL/min) and the pump was kept in a vertical position. The reason was that the sediment rose to the top (Figure 2), and, towards the end of administration, the concentrated suspension blocked the syringe tip. The results listed in Table 2 were for administration at 19 mL/min with the pump kept in a horizontal position. This reduced syringe blockage by the sediment but did not stop the eventual tube blockage.

The suspensions prepared by Method B using Vehicle for Oral Suspension, Sugar Free NF, Ora-Plus and Ora-Sweet (1:1 v/v), or Ora-Plus did not cause tube blockage within...
the 7 days of testing. Although some RIF accumulated in the end of the NG tube after injection of the suspensions, washing with 30 mL of water before and after injection removed all the residual material. In fact, the Ora-Plus suspension was tested daily for up to 21 days and no NG tube blockage was observed (Figure 6). However, when these suspensions were prepared by Method A, some residual RIF remained in the end of the tubes even after flushing with water and, as shown in Table 2, eventually, the tubes did become blocked.

**CONCLUSION**

Nurses cite RIF as one of the top 20 medications for causing problems with NG tube clogging. This report demonstrates that by preparing RIF suspensions from capsule content, using a prototype compounding mixer and either Vehicle for Oral Suspension, Sugar Free NF, Ora-Plus and Ora-Sweet (1:1 v/v), or Ora-Plus NG tube, patency was maintained from 7 days up to 21 days. Tube blockage was not observed because compared to mixing in a mortar with a pestle this machine produced smaller, more uniform particle sizes with greater resistance to sedimentation. In addition, particles that settled to the bottom did not form a cake and were easy to redisperse by gentle shaking. The suspensions in these vehicles were also not too viscous and showed good flow through the syringe and the 8F NG tubes.

**REFERENCES**