Simultaneous nebulization of prescribed inhalation solutions is both preferred and practical for healthcare professionals as well as patients. For example, co-nebulization may decrease administration times and enhance compliance. Revefenacin is convenient, however, mixing revefenacin with other inhaled medications is not approved by the Food and Drug Administration (FDA) as compatibility data is limited.1

Simultaneous nebulization of prescribed inhalation solutions is both preferred and practical for healthcare professionals as well as patients. For example, co-nebulization may decrease administration times and enhance compliance. Revefenacin is convenient, however, mixing revefenacin with other inhaled medications is not approved by the Food and Drug Administration (FDA) as compatibility data is limited.1

The pH of each solution was measured and visual inspection was performed immediately after mixing (time zero [T0]), at 30 minutes (T30), at 60 minutes (T60), and at 360 minutes (T360) after mixing (time zero [T0]), at 30 minutes (T30), at 60 minutes (T60), and at 360 minutes (T360). The mean pH of the revefenacin and albuterol admixture was pH of 5.30 ± 0.04 with a pH difference of -0.4% at T0 vs. T30 and 0.4% at T30 vs. T60. The mean pH of the revefenacin and arformoterol admixture was 5.28 ± 0.03 with a pH difference of -1.6% at T0 vs. T30, and 1.7% at T30 vs. T60. The mean pH of the revefenacin and budesonide admixture was 4.85 ± 0.05 with a pH difference of -0.03% at T0 vs. T30 and 1.0% at T30 vs. T60. Each admixture met compatibility standards with a pH variation of ±10% between time points (Figure 1).

Compatibility of each nebulized drug admixture was met based on unremarkable physical characteristics starting at T0 (Table 2). The approximate nebulization time was 30 minutes for revefenacin plus albuterol, 25 minutes for revefenacin plus arformoterol, and 10 minutes for revefenacin plus budesonide. The notable variance in nebulization time is attributed to using a different nebulization device for the revefenacin and budesonide admixture.

Inability to study admixtures utilizing high-pressure liquid chromatography (HPLC) due to lack of equipment availability was a limitation of the study. Further research is warranted to determine the compatibility of revefenacin with other inhalation solutions indicated for the treatment of COPD.

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Methods

Three drug admixtures were prepared by mixing one vial of revefenacin solution (175 mcg/mL; Mylan Specialty L.P.) with one vial of albuterol sulfate (2.5 mg/mL; Nephron Pharmaceuticals Corporation), one vial of arformoterol tartrate (15 mcg/mL; Sunovion Pharmaceuticals Inc.), or one vial of budesonide (0.5 mg/mL; Nephron Pharmaceuticals Corporation). Triplicates of each admixture were prepared in glassware and solutions were gently mixed for one minute to achieve homogeneity.

The pH of each solution was measured and visual inspection was performed immediately after mixing (time zero [T0]), at 30 minutes (T30), at 60 minutes (T60), and at 360 minutes (T360) at an ambient room temperature of 23.7 °C. Additionally, one admixture each of revefenacin plus albuterol, arformoterol, or budesonide was nebulized at T0 to inspect for changes in the physical characteristics of the solutions and to approximate the time to complete a nebulization treatment. A calibrated pH-100 meter, standard jet nebulizer, and small volume nebulizer were utilized in this study.

Compatibility was defined as a pH variation ±10 % and no visual evidence of physical solution changes at T0 vs. T30 and T30 vs. T60. Physical solution changes were determined by visual inspection, defined as evidence of precipitation, turbidity, and/or discoloration. Nebulized admixtures were considered compatible if there were no remarkable changes in the physical characteristics of the mixed solutions. Note, budesonide is cloudy at baseline as it is a suspension and foams when nebulized with other solutions, such as albuterol.

Table 1: Visual Inspection (VI) of Admixtures

<table>
<thead>
<tr>
<th>Admixtures</th>
<th>VI T0</th>
<th>VI T30</th>
<th>VI T60</th>
<th>VI T360</th>
</tr>
</thead>
<tbody>
<tr>
<td>Revefenacin / Albuterol</td>
<td>Clear, colorless</td>
<td>Clear, colorless</td>
<td>Clear, colorless</td>
<td>Clear, colorless</td>
</tr>
<tr>
<td>Revefenacin / Arformoterol</td>
<td>Clear, colorless</td>
<td>Clear, colorless</td>
<td>Clear, colorless</td>
<td>Clear, colorless</td>
</tr>
<tr>
<td>Revefenacin / Budesonide</td>
<td>Cloudy, colorless</td>
<td>Cloudy, colorless</td>
<td>Cloudy, colorless</td>
<td>Cloudy, colorless</td>
</tr>
</tbody>
</table>

Table 2: Physical Characteristics of Nebulized Solutions

<table>
<thead>
<tr>
<th>Nebulized Admixtures</th>
<th>Physical Characteristics</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Revefenacin / Albuterol</td>
<td>Unremarkable</td>
<td>30 minutes</td>
</tr>
<tr>
<td>Revefenacin / Arformoterol</td>
<td>Unremarkable</td>
<td>25 minutes</td>
</tr>
<tr>
<td>Revefenacin / Budesonide</td>
<td>Mist</td>
<td>10 minutes</td>
</tr>
</tbody>
</table>

Figure 1: pH of Drug Admixtures

Figure 1: pH of Drug Admixtures

Discussion

Under our study methodology, revefenacin proved to be physically and chemically compatible when mixed with albuterol sulfate, arformoterol tartrate, and budesonide for at least 60 minutes at room temperature. The ability to simultaneously nebulize revefenacin with other inhaled solutions serves as an administrative convenience. Further research is warranted to determine the compatibility of revefenacin with other inhalation solutions indicated for the treatment of COPD.

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Conclusion