Developing a Tretinoin Oral Liquid for Patients Who Cannot Take Capsules

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Abstract
Published information on alternative ways to administer commercial dosage forms may not always be the best option for patients and the hospital staff. There are resources available to research information about drugs and excipients. A compounding pharmacist can review the information and, based on training and experience in compounding, develop a formulation to meet the individual needs of a patient. The tretinoin oral suspension formulation included with this article is an example of how to develop a formulation without a published stability study by utilizing various compounding references and databases.
Tretinoin (Vesanoid), commonly known as Retin-A or Renova, is used topically for the treatment of acne vulgaris or photodamaged skin and palliation of fine wrinkles, mottled hyperpigmentation, and tactile roughness of facial skin as part of a comprehensive skin care program. When taken orally, tretinoin is an antineoplastic agent used alone or in combination with the following antineoplastic agents for remission induction in acute promyelocytic leukemia (APL):

- Arsenic trioxide
- Arsenic trioxide-gemtuzumab
- Daunorubicin
- Daunorubicin-cytarabine
- Idarubicin

Tretinoin is also being investigated for post consolidation and maintenance therapy in APL and for use in combination therapy with arsenic trioxide for remission induction in APL.

### Table. Ingredients of Vesanoid (Tretinoin).

<table>
<thead>
<tr>
<th>Name (Active Moiety)</th>
<th>Type</th>
<th>Strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tretinoin</td>
<td>Active</td>
<td>10 milligrams in 1 capsule (6%)</td>
</tr>
<tr>
<td>Beeswax</td>
<td>Inactive</td>
<td>N/A</td>
</tr>
<tr>
<td>Butylated hydroxyanisole</td>
<td>Inactive</td>
<td>N/A</td>
</tr>
<tr>
<td>Edetate disodium</td>
<td>Inactive</td>
<td>N/A</td>
</tr>
<tr>
<td>Hydrogenated soybean oil flakes</td>
<td>Inactive</td>
<td>N/A</td>
</tr>
<tr>
<td>Hydrogenated vegetable oils</td>
<td>Inactive</td>
<td>18%</td>
</tr>
<tr>
<td>Soybean oil</td>
<td>Inactive</td>
<td>70%</td>
</tr>
<tr>
<td>Gelatin</td>
<td>Inactive</td>
<td>N/A</td>
</tr>
<tr>
<td>Glycerin</td>
<td>Inactive</td>
<td>N/A</td>
</tr>
<tr>
<td>Yellow iron oxide</td>
<td>Inactive</td>
<td>N/A</td>
</tr>
<tr>
<td>Red iron oxide</td>
<td>Inactive</td>
<td>N/A</td>
</tr>
<tr>
<td>Titanium dioxide</td>
<td>Inactive</td>
<td>N/A</td>
</tr>
<tr>
<td>Methylparaben</td>
<td>Inactive</td>
<td>N/A</td>
</tr>
<tr>
<td>Propylparaben</td>
<td>Inactive</td>
<td>N/A</td>
</tr>
<tr>
<td>N/A = not applicable</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Tretinoin is only commercially available as a 10-mg liquid-filled capsule. It is a category X drug and hazardous precautions must be used by the nursing and medical staff when administering the drug.

Tretinoin is only commercially available as a 10-mg liquid-filled capsule. It is a category X drug and hazardous precautions must be used by the nursing and medical staff when administering the drug. Although this drug is primarily administered to adult patients, not all patients are able to swallow the capsules. There are cases in institutional settings where patients requiring tretinoin therapy cannot take medications orally (NPO) because they are intubated. These cases present a difficult treatment challenge for the hematology/oncology staff.

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Treatment Options

Although the manufacturer does not recommend using the contents of the tretinoin capsules to extemporaneously prepare a tretinoin oral suspension, there are limited case reports on altering the commercial dosage form to treat NPO patients. In a patient with a nasogastric (NG) tube, the tretinoin capsules were cut open and the contents were partially aspirated into a glass syringe. The residual contents of the capsule were mixed with soybean oil, aspirated into the same syringe, and administered to the patient. Another reported option was to mix the tretinoin capsules with sterile water, heat in a water bath at 37°C to melt the capsules, and create an oily suspension for NG tube administration. Tretinoin has also been administered sublingually by pricking the capsules with a needle and squeezing the capsule contents beneath the patient’s tongue.

None of these options are ideal for administration. There may be loss of drug when aspirating or squeezing the contents of the capsules into a syringe or when administering the drug sublingually. Tretinoin may adhere to the container when melting the capsules in a water bath. The loss could be significant and result in a subtherapeutic dose. Low plasma levels have been reported when tretinoin has been administered through a feeding tube, although patient-specific impaired absorption may have been a factor.

Another concern with these preparation and administration techniques is that tretinoin is a hazardous drug. If the first two techniques are not being done in a biological safety cabinet (BSC) or barrier isolator, the person preparing the dose(s) may be unnecessarily exposed to the hazardous drug. Equipment, such as the glass syringe or the water bath, may also be contaminated. The sublingual administration technique is exposing the person administering the tretinoin to a category X drug. Many healthcare systems are implementing policies that restrict the manipulation of hazardous drugs to pharmacy personnel so that the dose(s) can be prepared in a negative-pressure hazard room within a BSC or barrier isolator.

Developing a Formulation for Tretinoin Oral Suspension

After several failed and nominally successful attempts by the inpatient pharmacy staff to prepare tretinoin doses for the intubated patients in the intensive care units, a request was sent to the compounding pharmacy to develop a tretinoin oral suspension. A search was done to find a...
published stability study for an oral tretinoin suspension, but there was no information available. Another search was done on the Internet to find out the exact contents of the tretinoin capsules. On the National Library of Medicine website, all of the active and inactive ingredients were listed (see the accompanying Table). Each ingredient was researched in *Trissel’s Stability of Compounded Formulations* and the databases on the International Journal of Pharmaceutical, Inc.’s CompoundingToday.com website to determine the chemical properties and which ingredient and quantities should be included in the new oral suspension formulation. The following information summarizes the results of the search.

**Tretinoin, also known as all-trans-retinoic acid, is the most stable in an oil base. It is sensitive to heat, air, and especially light.**

**Tretinoin**

Tretinoin, also known as all-trans-retinoic acid, is the most stable in an oil base. It is sensitive to heat, air, and especially light. There were several studies on topical formulations containing water; however, there were no studies on nonaqueous vehicles. The tretinoin in the vegetable-soybean oil vehicle in the commercial capsules had a long shelf-life stability. Based on stability indicating high-performance liquid chromatography analysis, the time to 10% loss of tretinoin ($t_{90}$) was calculated to be 453 days at 25°C, 678 days at 19°C, and 1289 days or 3.5 years frozen.

**Butylated Hydroxyanisole**

Butylated hydroxyanisole (BHA) is a preservative and antioxidant used in concentrations of 0.005% to 0.02%. It is soluble in oil. Antioxidants are used to minimize or retard the oxidative processes that occur with some drugs, such as tretinoin, and excipients, such as oils, upon exposure to oxygen or in the presence of free radicals. Oxidation causes rancidity in oils.

**Edetate Disodium**

Edetate disodium is an adjunct preservative and antioxidant used in concentrations of 0.02% to 0.1%. It is soluble in water.

**Soybean Oil**

Soybean oil is the refined fixed oil obtained from the seed of the soy plant *Glycine soja* (Leguminosae). It occurs as a clear, pale yellow, oily liquid with a characteristic odor and taste. It may be used as an oleaginous vehicle and a solvent in both topical and oral use preparations. It is commonly used as the fat source in total parenteral nutrition. Silicone from plastic syringes can be leached into the soybean oil.

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The availability of all of the ingredients chosen for the new formulation was also researched. All of the ingredients are readily

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available through most chemical wholesalers. An order for the ingredients not routinely stocked in the compounding laboratory was placed with one of the wholesalers to be shipped overnight.

In the meantime, a formulation record sheet was written and is provided in this article. Since tretinoin is a category X drug, all weighing and compounding should be done in a negative-pressure hazard room within a BSC or barrier isolator using antineoplastic precautions. To prevent contamination of the compounding equipment, disposable equipment should be used to prepare the suspension. A disposable mortar and pestle may be used to mix the powders into the soybean oil and the final container, an amber glass bottle, can be calibrated to the desired volume so that the suspension can be brought to the desired amount with the soybean oil. The final mixture is a smooth, yellow liquid that uniformly suspends upon shaking well.

Another method that is good for mixing some hazardous drugs is the syringe method. The powders can be weighed and backloaded into one Luer Lock syringe, and the soybean oil can be drawn up into another Luer Lock syringe. The two syringes are connected with a Luer Lock-to-Luer Lock connector and the contents mixed by pushing the contents back and forth between the two syringes until a smooth, uniform suspension is made. The mixture is then added to a clean, calibrated, glass amber bottle, and soybean oil is added to the desired volume. Since the mixing occurs over a short period of time, there is little concern about the silicone from the syringes leaching into the soybean oil. Because there is no stability studies have been done on tretinoin oral suspension, United States Pharmacopeial Convention standards should be used to determine the beyond-use date. This formulation is a nonaqueous liquid and a 6-month beyond-use date may be assigned. However, since tretinoin is a hazardous drug and sensitive to light, heat and air, a conservative beyond-use date of 30 days may be more appropriate. To prevent contamination of the compound-
erly disposed in a designated hazardous waste container along with any other contaminated equipment, such as gloves.

**Conclusion**

Published information on alternative ways to administer commercial dosage forms may not always be the best option for patients and the hospital staff. There are resources available to research information about drugs and excipients. A compounding pharmacist can review the information and, based on training and experience in compounding, develop a formulation to meet the individual needs of a patient. The tretinoin oral suspension formulation included with this article is an example of how to develop a formulation without a published stability study by utilizing various compounding references and databases.

**References**