The stability of valproate sodium syrup repackaged in three types of unit dose containers was studied.

Two-milliliter samples of commercial valproate sodium syrup 250 mg/5 ml (of valproic acid) were packaged in polypropylene oral syringes, glass oral syringes, and glass vials (126 of each type). These were stored at 4, 25, or 60°C and assayed for valproic acid concentration using gas chromatography at 0, 5, 10, 20, 30, 90, and 180 days. Polypropylene syringes that were stored for 180 days at 4 and 25°C were rinsed and put in chloroform 50 ml; valproic acid concentration was determined daily for 12 days.

Valproate sodium syrup repackaged in glass oral syringes and glass vials retained 95% of valproic acid label claim after storage at 4 and 25°C for 180 days, while valproate sodium syrup repackaged in polypropylene oral syringes did not retain 90% of label claim after storage for 20 days at 4 or 25°C. All samples
stored at 60°C had greater loss than those stored at lower tempera-
tures. An average of 86% of the drug lost from the polypropylene syringes was recovered in 12 days during the desorption experiment (range 80-92%).

Repackaging valproate sodium syrup in unit dose glass vials or glass syringes resulted in retention of 95% of valproic acid label claim after storage for 180 days at 4 and 25°C. Repackaging of this drug product in polypropylene oral syringes is not recommended.
The Study of Valproate Sodium Formulations in Vitro

by

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INTRODUCTION

The practice of repackaging oral liquid drugs in unit dose packages is widespread in hospitals across the nation, but serious questions have been raised about the stability of these repackaged drugs. Valproate sodium is among many oral liquid drugs repacked in plastic or glass containers. Although information exists concerning the advantages of this type of system [1,4], no information is available dealing with stability of valproate sodium syrup repackaged in these containers.

Because of large workloads in many hospitals, it would be beneficial to be able to repackage valproate sodium syrup in unit dose containers for use as needed. Hospital pharmacists in Oregon reported to us that patients receiving valproate sodium syrup in unit dose plastic oral syringes had serum valproic acid concentrations below those predicted by standard pharmacokinetic principles. Loss of valproate sodium from the plastic containers was felt to be one of the factors that could explain the lower serum valproic acid concentrations. The purpose of this investigation was to determine the stability of valproate sodium syrup repackaged and stored in various types of unit dose containers.
METHODS

Sample Preparations and Storage

Commercial valproate sodium syrup 250 mg/5 ml (of valproic acid)\(^2\) was repackaged in polypropylene oral syringes,\(^3\) glass oral syringes,\(^4\) and glass vials.\(^5\) A 2-ml sample was drawn up into each container, and the containers were capped and coded. One hundred twenty-six samples were prepared for each type of container. Each type of container was then divided into three groups of 42 that were stored at a constant temperature of either 4, 25, or 60°C (± 1°C) in enclosed compartments to prevent exposure to light and varying moisture conditions.

Experimental Procedure

Six samples from each type of container were assayed for initial valproic acid concentration immediately after repackaging. Six containers from each group were withdrawn from the constant temperature compartments 5, 10, 20, 30, 90, and 180 days after repackaging for analysis of valproic acid concentration. A 1-ml sample from each container was diluted to 50 ml with methanol in a volumetric flask. To a 1-ml sample of diluted valproate sodium syrup, 3mM cyclohexane carboxylic acid\(^6\) 150 µl was added, and the concentration of valproic acid was determined using a gas chromatographic procedure [5].
Even though the commercial dosage form contained valproate sodium, valproic acid concentrations were measured in this study because valproate sodium was changed instantaneously to valproic acid in the assay procedure. The concentrations of valproic acid and valproate sodium are directly proportional to each other.

**Desorption Experiment**

The polypropylene oral syringes that were stored at 4 and 25°C for 180 days were used for desorption experiments. After the syrup in the polypropylene unit dose syringe was assayed, the syringe was rinsed with water until no residual valproic acid from the syrup could be observed in the rinse water as determined by gas chromatography. Then, the syringe was soaked in chloroform 50 ml. A 0.5-ml sample was collected and assayed for the amount of valproic acid that was released from the polypropylene container. Samples were obtained 0, 2, 4, and 16 hours, and daily for 12 days after initiation of soaking in chloroform, and the concentration of valproic acid was determined using the gas chromatographic procedure described above.

All experiments for desorption and stability of valproate sodium in the unit dose containers were repeated to assure confidence in the data.
Data Analysis

A factorial experimental design [6] was used to analyze the data. The three factors tested were: time (having seven levels, one for each sampling time); types of containers (at three levels, one for each type of container); and temperature (also at three levels, one for each storage temperature). The mean concentrations of valproic acid for each of the 63 treatments were based on six samples. Analysis of variance was conducted on valproic acid concentrations for each treatment and F-tests were performed at the 0.05 significant level comparing the effects of these factors.
RESULTS

The mean concentrations of valproic acid for each treatment group are given in Table 1. There was a greater loss of valproic acid from the syrup in the unit dose containers as temperature increased. Storage of the drug in polypropylene oral syringes demonstrated this to the greatest extent and that in glass vials the least. There was no significant difference between concentrations of valproic acid repackaged and stored over a period of time in polypropylene oral syringes compared with glass oral syringes and glass vials. Valproate sodium syrup repacked in glass oral syringes and glass vials still retained more than 95% of its label claim (47.5 mg/ml) after storage for 180 days at refrigeration and room temperature. When repackaged in polypropylene oral syringes, valproic acid concentration decreased to 88.5% of the label claim after 20 days storage at room temperature. However, storage at refrigerated temperature in polypropylene oral syringes resulted in retention of valproic acid at 90% of label claim for at least 90 days. Loss of valproic acid from polypropylene oral syringes occurred at the greatest extent during the first 20 days after storage. After this, little loss of valproic acid occurred. During the first 20 days, there was a greater loss from polypropylene oral syringes than from the other types of containers as the storage temperature increased.
As a point of comparison for the results of this study, the valproate sodium syrup stored in the original amber glass container from the manufacturer for 11 months still retained 99% of the label claim.

The percent of drug lost recovered in the desorption experiment was calculated as:

\[
\% \text{ drug lost recovered} = 100 \frac{\text{drug released from container}}{\text{drug lost during storage}}
\]

The average estimated percent of drug lost that was recovered for each day for all syringes studied is plotted versus time in Figure 1. After 12 days, recovery of more drug from syringes ceased. An average of 86% of the drug lost from the syringes was recovered during desorption (range 80-92%).
<table>
<thead>
<tr>
<th>Days</th>
<th>Plastic Syringes</th>
<th>Glass Syringes</th>
<th>Glass Vials</th>
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</thead>
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<td>25°C</td>
<td>60°C</td>
</tr>
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<td>50.2±0.6</td>
<td>50.2±0.6</td>
</tr>
<tr>
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<tr>
<td>180</td>
<td>45.0±2.5</td>
<td>44.8±1.5</td>
<td>****a</td>
</tr>
</tbody>
</table>

*a****Loss of volume and solidification of samples prevented analysis of valproate sodium concentration

*b####No sample taken
Figure 1: A Plot of % Drug Lost Recovered vs. Time After Desorption Initiated.

VALUES REPRESENT MEAN \pm STANDARD DEVIATION FOR 12 SYRINGES
DISCUSSION

The results of this study indicated that valproate sodium syrup can be repackaged in glass oral syringes or glass vials without adversely affecting the stability and shelf-life of the drug for at least 180 days. The loss of drug in these containers was decreased by storage at lower temperatures. However, there was no advantage between storage at refrigerated and room temperature. The loss of valproic acid was significant when the temperature was raised to 60°C.

It is doubtful that repackaging of valproate sodium syrup in polypropylene oral syringes can retain the concentration of drug above 90% of label claim after storage for 20 days even at refrigerated temperature. The loss of drug from polypropylene containers was greater as the temperature increased, but the concentration of valproic acid remained constant after 20 days. Sorption of drug into the plastic material accounted for the major loss of valproic acid from polypropylene containers.
SUMMARY AND CONCLUSIONS

Repackaging valproate sodium syrup in unit dose glass vials or glass syringes can assure that 95% of label claim can be met for up to 180 days when stored at 4 and 25°C. The evidence of rapid loss of valproate sodium due to sorption of the drug into polypropylene unit dose oral syringes presented here precludes using polypropylene oral syringes for repackaging valproate sodium syrup if stored for more than 20 days.
ENDNOTES

1 Valproate sodium is rapidly converted in the stomach to valproic acid, which is the active form of the drug.

2 Depakene, Abbott Laboratories, Inc., North Chicago, IL 60064, lots 21-469-AF and 17-641-AF.

3 Baxa Corporation, Denver, CO 80209, 5-ml amber polypropylene syringes.

4 M.P.L., Inc., SoloPak Division, Chicago, IL 60657, 3-4 ml clear syringes.

5 Wheaton Scientific, Millville, NJ 08332, 15-ml amber vials.

6 Aldrich Chemical Company, Milwaukee, WI 53233.
The PROPHET system, a unique national resource sponsored by the NIH, was used in the data analysis. Information about PROPHET, including how to apply for access, can be obtained from the Director, Chemical/Biological Information-Handling Program, Division of Research Resources, NIH, Bethesda, MS 20184.
BIBLIOGRAPHY


