Compounding of oral liquid formulas of two hazardous drugs, tacrolimus 1 mg/mL and hydroxyurea 100 mg/mL, using unopened capsules and a safe self-contained technology

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Introduction

- The compounding of oral liquids using capsules involves the opening of the capsule shell, the removal of the encapsulated powder and its incorporation into the liquid diluent, usually using a mortar and pestle.
- For hazardous medications, the process must be undertaken using the proper personnel safeguards such as gowning and in a controlled environment using a negative pressure hood.
- A novel automated wet-milling technology innovation enables the compounding to be performed within a self-contained single-use multipurpose specialized plastic container using the whole unopened capsule. [Figure 1]
- The container compounds, stores and dispenses the compounded product with no required product transfers.
- The use of whole capsules in a totally self-contained procedure eliminates the possibility of aerosolization of powders and exposure of personnel to hazardous medications.
- A study was undertaken using hydroxyurea and tacrolimus capsules to demonstrate the effectiveness of the process.

Methods

- Tacrolimus and hydroxyurea capsules were compounded into 1 mg/ml and 100 mg/ml oral liquid suspensions respectively.
- The requisite amount of the diluent, Ora-Blend®, is placed into the specialized plastic containers followed by the capsules.
- The containers are capped and placed inside the sealed holders within the milling unit [Figure 2].
- The specially textured container surface combined with a high RPM planetary motion from the machine results in a wet milling process that converts the contents into a fine uniform suspension. [Figure 3]
- A special milling cycle was developed to dissolve the gelatin shell and mill the contents.
- Following compounding, the container serves the roles of storage and dispensing of the compounded product. [Figure 4]
- Dose uniformity and chemical stability studies were undertaken using HPLC methods.

Equipment and Materials

Figure 1: Enclosed wet milling device that produces uniform particles leading to palatable high-quality liquid formulas with the required dose uniformity

Figure 2: Milling unit closed and opened showing containers in place

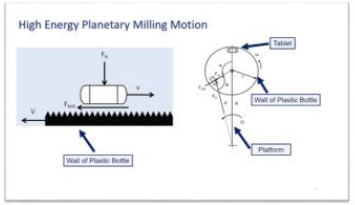

Figure 3: Mechanism of the wet milling process in the specialized plastic container

Figure 4: Compounding process for oral liquids using specialized plastic containers

Results & Discussion

- Both compounded formulas were found to have a smooth texture and the required characteristics for proper dose withdrawal.
- The dose uniformity results were within 7% for the tacrolimus formula and within 2% for the hydroxyurea formula of the label claim. [Table 1]
- A beyond use date (BUD) of 90 days at room temperature was assigned to both compounded product. [Table 2 and Figure 5]
- The stability study results were within 3% for the tacrolimus formula and within 8% for the hydroxyurea formula of the initial concentration.

Table 1: Dose Uniformity Results for tacrolimus and hydroxyurea suspensions as % of label claim

	1 mg/ml tacrolimus	100 mg/ml hydroxyurea
Aliquot 1	1.07	100.1
Aliquot 2	0.95	98.1
Aliquot 3	1.00	98.2
Average	1.01	98.8
%RSD	5.5	1.1

Days	% Initial and % RSD at 25° C	
	1 mg/ml tacrolimus	100 mg/ml hydroxyurea
14	99.3 ± 5.1	98.8 ± 1.1
30	---	93.1 ± 1.3
60	101.0 ± 1.7	92.5 ± 0.7
90	102.7 ± 2.6	94.5 ± 1.3

Table 2: Stability data for 1 mg/ml tacrolimus and 100 mg/ml hydroxyurea suspensions

Figure 5: Stability data as percent of initial concentration at 25° C

Conclusions

- The data demonstrate the ability of the novel wet-milling technology to compound liquid formulas from whole capsules.
- The process results in formulas with excellent dose uniformity.
- Use of a fully-enclosed compounding environment and whole capsules eliminates the potential exposure of personnel to aerosolized hazardous medication powders.
- The process provides a new and efficient way to safely compound oral liquid hazardous medications from capsules.
- Automation provides efficiency and helps to standardize the compounding process.
- The employment of a single-use disposable container for compounding, storage, and administration eliminates the need for cleaning and the risk of cross contamination.
- The exclusion of cleaning procedures provides environmental benefits by the elimination of hazardous waste liquids.

Disclosures

Authors of this presentation have the following to disclose concerning possible financial or personal relationships with commercial entities that may have a direct or indirect interest in the subject matter of this presentation.

- Joe B. D'Silva: Chief Scientific Officer and CEO, P&C Pharma
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References

1. Marsha S. H. Lam, "Extemporaneous Compounding of Oral Liquid Dosage Formulations and Alternative Drug Delivery Methods for Anticancer Drugs" Pharmacotherapy. 31(2) (2011):164-192
2. Heeney M.M., Whorton M.R., Howard T.A., Johnson C.A., and Ware R. E., "Chemical and functional analysis of hydroxyurea oral solutions" J. Pediatr. Hematol. Oncol., 26(3) (2004 Mar):179-184
3. Jacobson P.A., Johnson C.E., West N.J., and Foster J.A., "Stability of tacrolimus in an extemporaneously compounded oral liquid" Am. J. Health Syst. Pharm. 15:54(2) (1997 Jan):178-180
4. Friciu, M., Zaraa, S., and Leclair, G., "Stability of Extemporaneously Compounded Tacrolimus in Glass Bottles and Plastic Syringes" Can. J. Hosp. Pharm. 70(1) (2017 Jan-Feb):51-53