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Formulation and Stability of an Extemporaneously Compounded Oral Solution of Chlorpromazine HCl

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Abstract
Chlorpromazine is a phenothiazine antipsychotic which is often used in hospice and palliative care to treat hiccups, delirium, and nausea. With the discontinuation of the commercial oral solution concentrate, there is a need to prepare this product by extemporaneous compounding. This study was initiated to identify an easy-to-prepare formulation for the compounding pharmacist. A stability study was also conducted to select the proper storage conditions and establish the beyond-use date. Chlorpromazine HCl powder and the Ora-Sweet® syrup vehicle were used to prepare the 100 mg/mL solution. Once the feasibility was established, a batch of the solution was prepared and packaged in amber plastic prescription bottles for a stability study. These samples were stored at refrigeration (2–8°C) or room temperature (20–25°C) for up to 3 months. At each monthly time point, the samples were evaluated by visual inspection, pH measurement, and high performance liquid chromatography (HPLC). A separate forced stability study was conducted to confirm that the HPLC method was stability indicating. A clear and colorless solution of 100 mg/mL chlorpromazine HCl was obtained by dissolving the drug powder in Ora-Sweet® with moderate agitation. The stability study results indicated that this solution product remained unchanged in visual appearance or pH at both refrigeration and room temperature for up to 3 months. The HPLC results also confirmed that all stability samples retained 93.6–101.4% of initial drug concentration. Chlorpromazine HCl solution 100 mg/mL can be compounded extemporaneously by dissolving chlorpromazine HCl drug powder in Ora-Sweet®. The resulting product is stable for at least three months in amber plastic prescription bottles stored at either refrigeration or room temperature.

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TITLE

Formulation and Stability of an Extemporaneously Compounded Oral Intensol Solution of Chlorpromazine HCl

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ABSTRACT

Objective. Chlorpromazine is a phenothiazine antipsychotic which is often used in hospice and palliative care to treat hiccups, delirium, and nausea. With the discontinuation of the commercial oral solution concentrate, there is a need to prepare this product by extemporaneous compounding. This study was initiated to identify an easy-to-prepare formulation for the compounding pharmacist. A stability study was also conducted to select the proper storage conditions and establish the beyond-use date.

Methods. The chlorpromazine HCl pure powder and the Ora-Sweet® vehicle were used to prepare the 100 mg/mL solution. Once the feasibility was established, a batch of the solution was prepared and packaged in amber plastic prescription bottles for a stability study. These samples were stored at refrigeration (2-8°C) or room temperature (20-25°C) for up to three months. At each monthly time point, the samples were evaluated by visual inspection, pH measurement, and high performance liquid chromatography (HPLC). A separate forced stability study was conducted to confirm that the HPLC method was stability indicating.

Results. A clear and colorless solution of 100 mg/mL chlorpromazine HCl was obtained by dissolving the drug powder in Ora-Sweet® with moderate agitation. The stability study results indicated that this solution product remained unchanged in visual appearance or pH at both refrigeration and room temperature for up to three months. The HPLC results also confirmed that all stability samples retained 93.6-101.4% of initial drug concentration.

Conclusion. Chlorpromazine HCl solution 100 mg/mL can be compounded extemporaneously by dissolving chlorpromazine HCl drug powder in Ora-Sweet®. The resulting product is stable for at least three months in amber plastic prescription bottles stored at either refrigeration or room temperature.

KEYWORDS

Chlorpromazine, intensol, stability, compounding, buccal, sublingual, hiccup

INTRODUCTION

Chlorpromazine (Thorazine®) is a phenothiazine antipsychotic used in hospice and palliative care to treat hiccups, delirium, and nausea/vomiting at the end of life (EOL).[1,2,3] Currently chlorpromazine is commercially available as 10, 25, 50, 100, and 200 mg oral tablets and a 25 mg/mL solution for injection (all strengths expressed as the HCl salt form and thereafter).[4] The concentrated oral solutions, also known as "intensol" formulations, are often preferred over tablets and injectables for symptom management in hospice outpatient, because the intensols can be easily given sublingually or buccally in patients with dysphagia from advanced disease.[5] Family members may be uncomfortable giving an injectable medication in a home setting or have difficulty crushing tablets and mixing them in food prior to administration, so the intensols provide a valuable alternative product formulation. Chlorpromazine was previously available commercially as a 100 mg/mL oral solution concentrate.[4] Unfortunately this product was discontinued by the manufacturer, creating a need for an extemporaneously compounded product. It is important to point out that the discontinuation was not due to any safety or efficacy reasons of the drug product.[4] This study was initiated to develop a formulation and procedure suitable for the compounding pharmacist. A long-term stability study was also conducted to select the storage conditions and establish the beyond-use date.

METHODS

Sample Preparation

The calculated amount of chlorpromazine HCl powder (MP Biomedical LLC, Solon, OH; lot M2896) was accurately weighed and transferred into a pre-calibrated amber plastic prescription bottle or a glass volumetric flask. About 75% batch size of Ora-Sweet® syrup (Paddock Laboratories, Minneapolis, MN; NDC 0574-0304-16, lot 1356809) was added to the container followed by moderate intermittent agitation. A clear solution was typically obtained within 30 minutes. The remaining Ora-Sweet® was added to the mark, and the solution was mixed thoroughly. The density of this solution was determined to be 1.30 g/mL (for the purpose of sample volume calculations as discussed below). A preliminary taste assessment was performed by three volunteers with a dose of 0.30 mL taken sublingually.

Stability Study

Based on the procedure described above, a 250 mL batch of the chlorpromazine HCl solution in Ora-Sweet® was prepared in a volumetric flask for best accuracy. The solution was aliquoted into six amber plastic prescription bottles, 35 mL each. Three bottles were stored at refrigeration (2-8°C) and three at room temperature conditions (20-25°C).

Stability evaluation was performed immediately after preparation and after 1, 2, and 3 months of storage. At every time point, the three bottles from each temperature condition were pulled for analysis and returned to storage after sampling. About 0.5 mL from each bottle was taken for pH measurement (SevenEasy pH meter, Mettler-Toledo Inc., Columbus, OH), and about 1 mL for visual inspection followed by HPLC analysis. Due to the viscous nature of the solution, it was not possible to pipet the 1 mL samples accurately

based on volume. Instead, the aliquot from each sample was directly weighed in a tared 10 mL volumetric flask. The target weight was calculated based on the density reported above. This sample was visually inspected against a light background for clarity, color, precipitation, and microbial growth. The sample was then serially diluted with HPLC mobile phase for HPLC analysis (see below).

High-performance Liquid Chromatography (HPLC)

The HPLC analysis was performed using a Shimadzu model LC-2010A instrument (Shimadzu Scientific Instruments, Marlborough, MA). The chromatographic parameters were adapted from a stability indicating assay previously published by Kollmorgen et al.[6] A Symmetry C_{18} column (3.5 µ, 4.6×150 mm, Waters, Milford, MA) was used and maintained at 40°C throughout analysis. The mobile phase consisted of water:methanol (36:64 v/v) with 0.1% trifluoroacetic acid; the flow rate was 0.5 mL/min. Each injection volume was 10 µL, and the UV detection was set at 254 nm. Under these conditions, the retention time of chlorpromazine was approximately 8.3 minutes. All samples for HPLC analysis were prepared by diluting the samples to a nominal concentration of 0.05 mg/mL using the mobile phase.

Standards of chlorpromazine HCl solutions were prepared at each time point for calibration purpose. Solutions of 0.03, 0.04, 0.05, 0.06, and 0.07 mg/mL were prepared by dissolving the calculated amount of chlorpromazine HCl powder in the mobile phase. A calibration curve was constructed at each time point by linear regression of the peak area of chlorpromazine against chlorpromazine concentration. The curve was found to be linear over the concentration range of the standards with a typical $r^2 = 0.999$.

Forced Degradation Study

A short-term forced degradation study of chlorpromazine was conducted under extreme pH, sunlight, ultraviolet (UV) light and oxidative stress conditions. This study was intended to verify the ability of the HPLC assay to separate the potential degradation products from the parent drug. Three samples of 0.05 mg/mL chlorpromazine HCl solution were prepared in the mobile phase with 0.5 N HCl, 0.5 N NaOH, and 3% H_2O_2. These samples were incubated at 60°C for up to 3 days. Three additional samples of 0.05 mg/mL chlorpromazine HCl solution prepared in HPLC mobile phase were exposed to sunlight (on a windowsill) and UV light at 254 & 365 nm for 3 days. The UV light was generated by a standard laboratory hand-held UV lamp (Model ENF-240C, Spectronics Corporation, Westbury, NY).

Significant degradation was observed in all conditions except 0.5 N NaOH, and the degradation products were well separated from the parent molecule by the HPLC method with no interfering peaks observed. Therefore, the HPLC method was considered as stability-indicating and suitable for the stability evaluation of chlorpromazine HCl oral solution.

RESULTS AND DISCUSSION

The USP grade of chlorpromazine HCl pure powder is available commercially via multiple vendors, such as Sigma-Aldrich and Spectrum Chemical. This provides an ideal drug source to prepare a concentrated solution. The commercial chlorpromazine HCl tablets were also considered as the drug source, but they were not selected due to the presence of insoluble excipients. These insoluble excipients are undesirable for the buccal/sublingual delivery route and may negatively impact the drug absorption process. Ora-Sweet® is a commonly used syrup vehicle, which provides flavoring and sweetness for taste-masking. Ora-Sweet® also contains effective preservatives to prevent microbial growth over long-term storage.

The chlorpromazine HCl powder was found to dissolve in Ora-Sweet® to yield a clear and colorless solution of 100 mg/mL. A recommended compounding procedure for the pharmacists is provided in Appendix A. The batch size of 20 mL is selected based on the typical dose range and 2-week refill schedule used for hospice outpatients. The amber prescription bottles are required for long-term storage, because chlorpromazine is light sensitive based on previous reports and current findings from the forced stability study.[7,8] Triplicate samples were prepared following the recommended compounding procedure. The initial potency (drug concentration) was determined by HPLC to be 99.1 ± 5.5 mg/mL. This is within the ±10% of the nominal potency and is considered satisfactory.

The palatability of the compounded chlorpromazine HCl solution was assessed by three volunteers. Despite the taste masking effect of the Ora-Sweet® vehicle, the solution tasted bitter. Additionally, the solution exhibited an anesthetic numbing effect in the mouth for about 2-3 hours after administration. However, the bitter taste and numbing effect are

not expected to be a main concern for hospice patients given that intensol preparations are typically reserved for symptom management in patients with dysphagia and decreased level of consciousness related to advanced disease.

For the long-term stability study, the initial sample pH and potency values are reported in Tables 1 & 2. Over the three months of storage at refrigeration (2-8°C) or room temperature (20-25°C), all samples remained clear, colorless, and free of visible precipitation or microbial growth. No significant change in pH was observed for any samples (Table 1). The stability-indicating HPLC analysis also confirmed that all samples retained 93.6-101.4% initial drug concentration (Table 2) with no new peaks observed. Overall, the chlorpromazine HCl solution 100 mg/mL was found to be stable in amber plastic prescription bottles at both refrigeration and room temperature for up to three months.

CONCLUSION

A concentrated oral solution of chlorpromazine HCl was formulated to treat hiccups, delirium, and nausea in hospice and palliative care patients. The 100 mg/mL solution can be conveniently prepared by dissolving USP grade of chlorpromazine HCl drug powder in Ora-Sweet®. The resulting solution product is stable for at least three months in amber plastic prescription bottles stored at either refrigeration or room temperature.

APPENDIX A. Compounding Procedure for Chlorpromazine HCl Oral Solution 100 mg/mL (20 mL batch)

1. Calibrate a suitable amber plastic prescription bottle for 20 mL
2. Weigh out 2.0 g of chlorpromazine HCl powder accurately
3. Transfer the drug powder into the pre-calibrated amber plastic bottle
4. Add ~15 mL of Ora-Sweet® to the bottle
5. Apply moderate intermittent agitation until the drug powder dissolves (~ 30 minutes)
6. QS with additional Ora-Sweet® to the 20 mL mark and mix well
7. Label the bottle with a 90 day expiration date and store at room temperature

NOTE: It is important to use amber bottles or other light resistant containers for long-term storage, because chlorpromazine is light sensitive.

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Table 1. pH Results of Chlorpromazine HCl Solution Stability Samples

Storage Temperature (°C)	pH [a]			
	Time 0	1-month	2-month	3-month
2 – 8	3.57 ± 0.43	3.50 ± 0.02	3.51 ± 0.01	3.71 ± 0.05
20 – 25		3.52 ± 0.01	3.48 ± 0.01	3.77 ± 0.02

[a] Mean ± SD of three replicate samples (n = 3).

Table 2. HPLC Results of Chlorpromazine HCl Solution Stability Samples

Storage Temperature (°C)	Initial Drug Concentration[a] (mg/mL)	% initial concentration remaining[a]		
		1-month	2-month	3-month
2 – 8	104.9 ± 2.0	97.1 ± 1.8	101.4 ± 1.0	94.2 ± 0.9
20 – 25		97.2 ± 0.1	101.4 ± 1.2	93.6 ± 1.6

[a] Mean ± SD of three replicate samples (n = 3).