Physicochemical Evaluation of Compounded Oral Preparations for Respiratory Illnesses, also known as *Mezclitas*

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Objective: Compounded oral solutions for respiratory illnesses such as the common cold and cough are commonly prepared and dispensed by licensed pharmacists in the United States and Puerto Rico (PR). Standard protocols for their preparation and quality assessment and for patient counseling are available for most of the prescribed compounded solutions. However, in PR there is a common prescription approach colloquially referred to as "*mezclitas*": mixtures of antitussives, expectorants, decongestants, and other active ingredients available in commercial solutions for which there are no science-driven compounding guidelines for local pharmacists.

Methods: This study evaluated the physicochemical stability of a commonly dispensed compounded preparation (containing guaifenesin, dextromethorphan, and dexamethasone) that is used for the treatment of respiratory illnesses in PR. The stability indicators tested included clarity, odor, pH, and viscosity. Changes in stability indicators were evaluated for different storage conditions (ambient temperature and refrigerated) over a period of 6 months.

Results: The samples exhibited small changes in color, odor, and viscosity. Although the observed changes were small, they may be indicative of chemical and/or physical transformations that occurred over time. A survey of local pharmacists also evidenced the absence of standardized protocols for the preparation and dispensation of the *mezclitas* in PR.

Conclusions: In spite of the absence of protocols for compounding oral solutions for respiratory illnesses, our study suggests that the stability of such solutions is not heavily compromised. However further chemical and physical testing is needed and the findings of such testing used to develop standardized protocols for the compounding of oral solutions for respiratory illnesses. [*P R Health Sci J 2020;39:189-194*]

Key words: Mezclitas, Compounding, Pharmacist, Common cold and cough, Catarro

In the United States (US) (comprising the 50 states, the District of Columbia, and the outlying territories, but not Puerto Rico [PR]) and in PR, respiratory illnesses such as the common cold and cough, also known in Spanish as "catarro," are often treated with extemporaneously compounded preparations that are assembled according to the specifications of the prescribing physician (1–3). These are prepared and dispensed by a licensed pharmacist following guidelines that are available from the United States Pharmacopeia (USP) Compounding Compendium and the National Formulary, and peer-reviewed publications. For pharmacists in the US compounding medications that are aimed at relieving cold and cough symptoms, the USP provides guidelines regarding drug stability; packaging, storage, and labeling; and patient counseling (3–5). In PR, however, there are unique compound oral solutions using different drug combinations (colloquially referred to as "*mezclitas*") that physicians commonly prescribe to treat cold and cough symptoms; these preparations differ from those prescribed in the US and from those described in the USP and the relevant peer-reviewed publications. Consequently, in terms of guaranteeing the safety and efficacy of a compound preparation prescribed by a physician to treat cough and cold symptoms, licensed pharmacists in PR have little to guide them.

In PR, dispensed *mezclitas* used to treat cold and cough symptoms include a variety of active ingredients with different concentrations; one such combination includes an expectorant, a non-narcotic antitussive, a steroid, and a decongestant (1). Other combinations include expectorants, non-narcotic

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The authors have no conflicts of interest to disclose.

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antitussives, and steroids, with or without decongestants and/or beta-agonists (1). The assignment of specific compounding quality standards for these preparations becomes difficult for pharmacists in PR, given the diversity of the ingredients and concentrations being prescribed coupled with the lack of available scientific data regarding the stability of those preparations. Furthermore, the assignment of reliable beyond-use dates (BUDs) to these compounded preparations by pharmacists in PR is an extrapolation process that involves the expiration dates of each of the components of the preparation and follows the general USP guidelines (4). However, this extrapolation process is also difficult given that the drug concentration, fill volume, and packaging of the compounded product differs from those of the original compounds (6,7). To ensure the safety and efficacy of these preparations, drug-specific stability studies following USP guidelines must be undertaken; the results of such studies will enable pharmacists in PR to assign appropriate BUDs to the extemporaneously compounded oral solutions currently being used to treat cold and cough symptoms (8,9). The stability of any compounded preparation in general will depend on the chemical and physical properties of the ingredients used to formulate it; environmental factors, such as temperature, light, air, and humidity; and the containers in which the ingredients are dispensed (4,10). The physical stability of each ingredient—being the retention of original appearance, uniformity, dissolution, and suspendability—must be tested to safely and accurately assign a BUD to and determine the storage conditions for a compounded preparation (11). In addition to information regarding physical stability, details about chemical stability are needed to define the capacity of each pharmacological ingredient to retain its specific integrity and labeled potency within the specified limits (5). Through these chemical and physical stability studies, specific quality parameters of compounded preparations can be accurately determined (rather than only estimated).

Though many Puerto Rican patients perceive positive effects when using *mezclitas* to treat cold and cough symptoms, the safety and efficacy of many of these preparations remain controversial (3). Additionally, in PR it is anecdotally known that some patients continue to use compounded preparations far past their assigned BUDs, and often stored inappropriately. The stability and, thus, the BUDs of these preparations remain unknown, both to local pharmacists and, as a consequence, to patients, as well. The objective of this study was to evaluate the physical and chemical stability of a common mezclita that is used for cold and cough symptoms in PR.

Methods

Determination of the extemporaneous oral solution to be compounded and evaluated

Face-to-face interviews using a pre-established questionnaire were used to survey a small group of community pharmacists in Puerto Rico. Ten licensed pharmacists, 21 years old or older and with at least 2 years of experience in community pharmacy practice, were interviewed. The selection of the pharmacists that were interviewed was made by convenience and included independent community pharmacists from different regions of the island. No pharmacist was excluded based on his or her demographic information (other than age); however, pharmacists not having a license to practice in PR were excluded from participating in the survey. Pharmacists that were willing to participate were administered a questionnaire in accordance with an IRB-approved protocol (B1080116).

A pre-selection of drugs to be listed on the questionnaire was performed based on the most common drugs and combinations used for compounding extemporaneous preparations for cold and cough symptoms, according to a previously published study (1). The drugs included were guaifenesin, dextromethorphan, phenylephrine, dexamethasone, prednisolone, and albuterol. The questionnaires were also designed to collect information regarding the methodology and approach used by pharmacists to compound these preparations, in terms of preparation protocols, quality assessments, BUD assignment, and patient counseling.

Compounding methods

The *mezclitas* were formulated by mixing together commercial oral solutions of each of the components; the liquid forms of dextromethorphan and guaifenesin were used, and the elixir form of dexamethasone was used. All the drugs were generously provided by one of the surveyed pharmacies. Q-Tussin DM (dextromethorphan, 10mg/5mL; guaifenesin, 100mg/mL), manufactured by Qualitest Pharmaceuticals, and dexamethasone elixir (0.5mg/mL), manufactured by Morton Grove Pharmaceuticals, were used. The amount of each component to be mixed (dextromethorphan, guaifenesin, and dexamethasone) was determined based upon the results of the pharmacist survey. The components were manually mixed at ambient temperatures and transferred to amber colored bottles (4). Three bottles were stored at ambient conditions (24–32°C) and three were refrigerated (2–8°C). The latter 3 bottles were sampled and evaluated for clarity and odor, pH, and viscosity; each bottle was labeled according to the characteristic(s) of interest. Temperature was monitored and recorded throughout the study.

Evaluating the stability of the compounded preparations

Specific stability indicators of the compounded preparations included clarity, odor, pH, and viscosity at ambient and refrigerated conditions (for a total of 6 months); which were evaluated immediately and 7 days, 14 days, 30 days, 2 months, 3 months, 4 months, 5 months, and 6 months after preparation. In each storage condition, 1 bottle held the sample that was used to measure clarity and odor, a second bottle contained the sample for the pH measurement, and a third bottle had the sample that was used to measure the viscosity; each bottle was labeled accordingly. Temperature was continuously monitored and recorded at each sampling point to document any deviation

from pre-established ranges. At each predefined sampling point, samples were drawn from each bottle to test each stability parameter. Before the samples were drawn, the bottles were gently shaken to ensure homogeneity.

Clarity

Clarity was visually assessed at each sampling point and for each storage condition. Five milliliters (mL) was drawn from the clarity–odor bottle and placed in a 5mL glass vial. Physical changes were determined by comparing images of each of the sampled solutions to those of the original solution in terms of color and clarity and using a black background. Changes in the color of each sample were compared using standard colors as established with Roscolux® color filter cards: Light Salmon, Salmon, Deep Salmon and Broadway Pink. The changes in all the samples were documented and evidenced by collecting visual images of those samples (digital photography using standardized shutter speed, aperture, and exposure settings). The visual assessments were always performed by the same investigator and under the same lighting conditions in order to ensure consistency and reproducibility throughout the study. Clarity was analyzed taking into consideration precipitate formation, cloudiness, and changes in color. A binary analysis of change, or lack thereof, was used for all clarity properties.

Odor

Five milliliter samples were drawn from the clarity–odor bottles in both storage conditions and placed in translucent glass vials with no caps. Changes in odor were documented by the same investigator to ensure consistency throughout the analysis. Odor was analyzed as a dichotomous variable.

Potential of hydrogen (pH)

The pH at each sampling point and under both storage conditions was measured in triplicate. The pH meter was calibrated before each measurement. Ten milliliters was taken from each of the pH bottles and placed in each of 2 translucent glass vials. The pH probe was inserted into each glass vial, and the pH values displayed were recorded. The mean pH values and the standard deviations were calculated and recorded. Changes in the pH of the samples were determined by comparing the average pH value at each sampling point to that of the original solution.

Viscosity

Viscosity for each sample was measured using a parallel-plate rheometer with 25mm plates (0.5mm gap). Changes in viscosity were analyzed by comparing the viscosity at each sampling point to that of the original preparation. Five milliliters was drawn from each of the 2 viscosity bottles and poured into each of 2 glass vials; then, 1mL was withdrawn from each vial to measure the viscosity of the formulation at each of the two storage conditions. After each viscosity measurement, the sample was discarded. The mean value and the standard deviation were calculated.

Results

Pharmacist questionnaire

The results from the questionnaire indicated that 8 out of 10 (80%) pharmacists frequently dispensed oral *mezclitas* for the common cold and cough to patients in PR. Of the pharmacists that reported having dispensed them, the most commonly reported compounded preparation was composed of equal parts of guaifenesin, dextromethorphan, and dexamethasone (or prednisolone) (Figure 1, left). Thus, a compounded preparation composed of equal parts of guaifenesin, dextromethorphan, and dexamethasone was prepared for the physicochemical evaluation of the stability.

Additionally, the questionnaire revealed that none of the interviewed pharmacists that reported having prepared and dispensed these compounded oral solutions (0 out of the 8 pharmacists) had used a standard protocol. Furthermore, only 50% (4 out of the 8 pharmacists) of the interviewed pharmacists had assigned BUDs to these preparations, whereas 40% had not assigned BUDs, and 10% did not provide a response to this part of the questionnaire (Figure 1, right). The pharmacists interviewed who routinely assigned BUDs had different strategies for their doing so; most either used the earliest expiration date of the different components in the compound or defaulted to 3 months. Similar inconsistencies were observed with the instructions of use given to patients (summarized in Table 1).

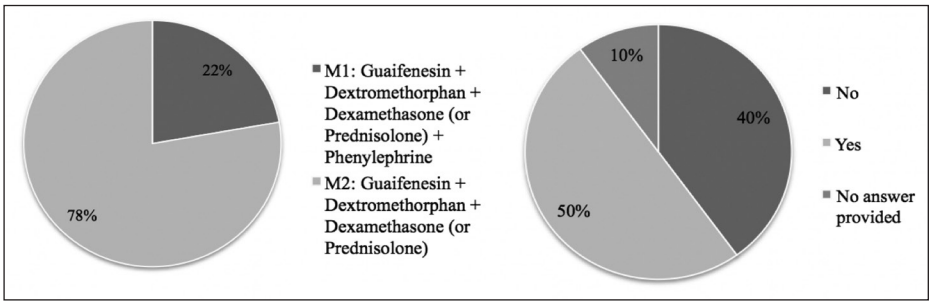

Figure 1. The two most commonly prepared oral solutions for respiratory illnesses reported by the surveyed pharmacists (left). The pharmacists' responses when asked whether they provided BUDs for compounded oral solutions for respiratory illnesses (right). The pie chart on the left shows that 78% of the pharmacists in the study reported that the oral solution that they prepared most frequently was composed of guaifenesin, dextromethorphan, and dexamethasone (or prednisolone) (light gray). The remaining 22% reported that the oral solution that they prepared most frequently was composed of guaifenesin, dextromethorphan, dexamethasone (or prednisolone), and phenylephrine (dark gray). The pie chart on the right shows that 50% of the interviewed pharmacists provided BUDs (light gray), 40% did not provide BUDs (dark gray), and 10% did not answer (white).

Table 1. Beyond use date by type of Formulation (non-sterile preparations).[4]

Non-aqueous Formulation	BUD is not later than the time remaining until the earliest expiration date of any API or 6 months, whichever is earlier.
Water-containing Oral Formulations	The BUD is not later than 14 days when stored at controlled cold temperatures.
Water-containing Topical/ dermal and Mucosal liquid and Semisolid Formulations	BUD is not later than 30 days.

Compounding of the mezclita

Based on the results of the survey, we decided that the mezclita for this study would consist of dextromethorphan, guaifenesin, and dexamethasone. Given that dextromethorphan and guaifenesin were already combined in a single oral syrup, a volume of 40mL of a dextromethorphan–guaifenesin syrup was mixed with 20mL of dexamethasone elixir. These were manually mixed at ambient temperatures and transferred to amber colored bottles. Three bottles were stored at ambient conditions (24–32°C), and three were refrigerated (2–8°C).

Stability evaluation

No significant changes in the clarity of the samples in terms of precipitate formation or cloudiness were observed at any sampling point for either storage condition throughout the duration of the study. Figure 2 shows color images of the samples stored at ambient and refrigerated conditions, throughout the sampling period (6 months), along with standardized control colors. The control colors (Roscolux® standardized color filter cards) were used for comparisons; the upper and lower observed tones of the samples were assessed for differences. In general, all the samples showed a darkening tendency, as time elapsed; that is, as the samples aged from having been freshly prepared to being 6 months old. This may be observed when comparing the first (1) and last (9) sampling point colors (found in the 1st and 9th columns, respectively).

The odor of the compounded oral solutions in both storage conditions changed over the course of the study period. The investigators noticed a sweet scent when the solution was first compounded, and the scent increased in intensity as the study progressed.

Table 2 shows the measured pH values of the samples throughout the sampling period, at ambient and refrigerated conditions, respectively. The samples stored in either storage condition had similar pH values, throughout the study, with very small standard deviations. Samples stored at ambient conditions had an average pH value of 2.90 (±0.12), whereas the samples at refrigerated conditions had an average pH value of 3.09 (±0.11).

Table 2. pH measurements of compounded oral solutions.

Ambient conditions					
Sampling point	**pH 1**	**pH 2**	**pH 3**	**Mean**	**STDEV**
1	3.02	3.05	3.04	3.04	0.02
2	3.00	2.99	2.98	2.99	0.01
3	2.92	2.93	2.9	2.92	0.02
4	3.04	2.98	2.99	3.00	0.03
5	2.72	2.73	2.72	2.72	0.01
6	2.85	2.82	2.81	2.83	0.02
7	2.76	2.74	2.72	2.74	0.02
8	2.91	2.89	2.88	2.89	0.02
9	2.99	2.97	2.97	2.98	0.01
Refrigerated conditions					
Sampling point	**pH 1**	**pH 2**	**pH 3**	**Mean**	**STDEV**
1	3.15	3.13	3.11	3.13	0.02
2	3.23	3.23	3.24	3.23	0.01
3	3.00	3.10	3.08	3.06	0.05
4	3.21	3.20	3.18	3.20	0.02
5	2.99	2.98	2		

Notable variations were observed on the viscosity measures across the sampling points (Figures 3 and 4). The samples at ambient conditions exhibited a decrease in viscosity (17.23 mPa·s ± 4.27) compared to the samples stored in refrigerated conditions (37.93 mPa·s ± 10.07).

Discussion

Based on the results of the pharmacist survey, we believe that the preparation and dispensation of commonly prescribed

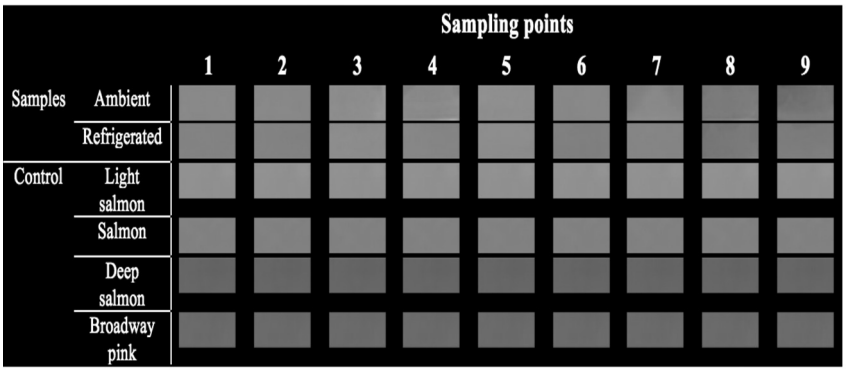

Figure 2. Color-change analysis of the compounded oral solutions at ambient and refrigerated conditions. The colors of the samples are compared with standard colors. Samples at room temperature are shown in the top row, for all sampling points. Refrigerated samples are shown in the second row, for all sampling points. Rows 3 to 6 correspond to color standards: Light Salmon, Salmon, Deep Salmon, and Broadway Pink. The same control colors are repeated in other columns to facilitate comparison.

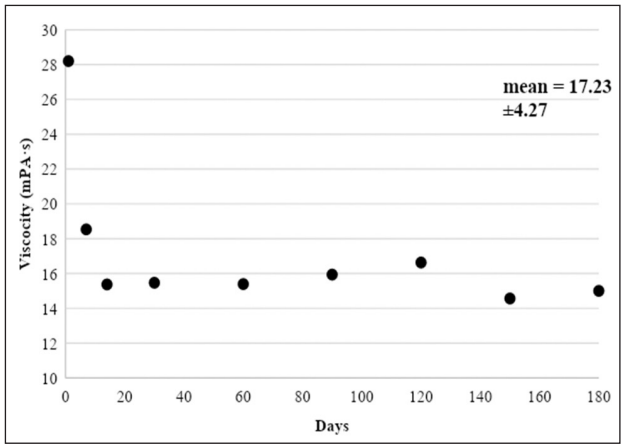

Figure 3. Viscosity of the oral solutions stored at ambient conditions (24°C–32°C). Scatter plot shows the viscosity values of samples over the duration of the study.

mezclitas for cold and cough symptoms must be standardized. A variety of approaches were reported by pharmacists to assign stability parameters, such as BUDs.

Although there are no available guidelines to inform the preparation or stability of *mezclitas*, no significant changes in the measured physical and chemical characteristics were observed that might suggest a deterioration of the safety or efficacy of the preparation. The absence of observed precipitate formation or cloudiness may be indicative of the absence of agglomerates between the components. However, changes in color were observed throughout the study period, which may be a sign of instability and are usually the result of chemical reactions or the degradation of 1 or more of the components of the compounded preparation (12). Additionally, the observed changes in odor throughout the study period may also be suggestive of instability (12). Although these observed changes in color and odor point towards a potential impact on the stability of the formulation, further chemical testing is needed to validate and measure the degree of this instability.

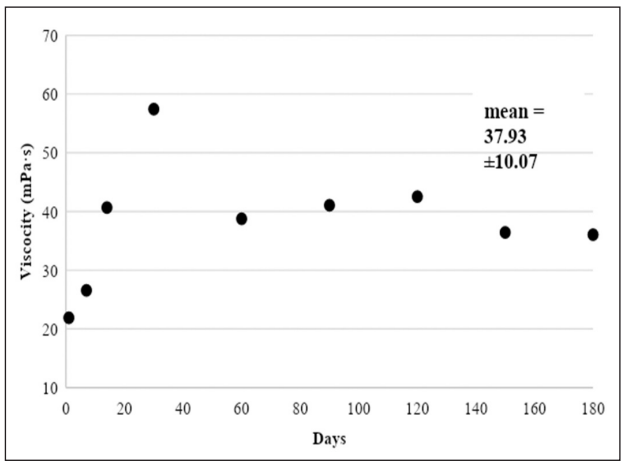

Figure 4. Viscosity of oral solutions stored at refrigerated conditions (2°C–8°C). Scatter plot shows the viscosity values of samples over the duration of the study.

Chemical measures (pH) showed that the solubility of the pharmaceutical compounds present in the preparations were not significantly impacted, as no significant changes in the pH values resulted within the 6-month period (4,12). Further experiments are needed to confirm changes in the solubility of these preparations.

Marked changes in viscosity were observed over time in both the ambient-temperature and refrigerated samples, and notable variations were noted across the sampling points. The samples kept at ambient temperature exhibited lower viscosities compared to the samples in refrigerated conditions. These differences may be associated with structural arrangements that may occur when an element is stored over time. Such arrangements may have impacted the molecular interaction of the components, resulting in the observed variations of viscosity. The viscosity behavior of the preparations was somewhat expected, since with an increase in temperature there is also an associated increase in molecular motion as the molecules begin to move faster and more freely, which is reflected as reduced viscosity (13). At lower temperatures, the molecular interactions are reduced due to a decrease in mobility (higher viscosity). It is important to clarify that these arrangements did not cause changes in the clarity of the samples, as opacity was not observed. These arrangements may occur at molecular levels not detectable to the naked eye.

As this was an exploratory study, it does have several limitations. First, a larger sample of pharmacists would be useful in studying the different methods that pharmacists in PR use when compounding oral solutions for patients with a common cold. However, we believe that, although small, the sample of pharmacists in this study provided a good approximation of current practices in community pharmacies in different regions of PR. Another limitation is that our methods did not allow us to monitor changes in the concentration of the different compounds present in the preparation over time. However, the changes in the measured color and viscosity over time suggest that stability also changed, warranting further studies.

Altogether, this study contributes to the understanding of issues in the formulation, dispensation, and usage of *mezclitas*, commonly compounded preparations that are prescribed to patients with a common cold or cough. The questionnaire's results highlight the lack of control and standardization among pharmacists in PR when it comes to the management of these preparations. Preparation protocols are nonexistent, BUD assigning is highly inconsistent, and stability is unknown. Our preliminary data indicate that there are few stability issues, and that those issues consist mainly of changes in color, odor, and viscosity. Although it is unknown whether the changes observed were derived from the active ingredients, even changes in non-active ingredients may affect the pharmacodynamics and, ultimately, the safety and efficacy of the drugs (9). Thus, these findings highlight the need for further stability studies to assess the chemical stability of the individual drug components, the presence of specific degradation products, and the remaining fraction of active ingredients over time.

Conclusions

Although the commonly compounded oral solutions to treat the common cold or "catarro" in PR and colloquially known as *mezclitas* are prepared by licensed pharmacists in the absence of standardized protocols and science driven stability data, few signs of instability were observed in terms of the physical (color, odor, and viscosity) and chemical (pH) measures. Nevertheless, there is a need for more testing to accurately describe the changes in chemical and physical properties that may occur when such compounds are in storage and that may impact their efficacy.

Resumen

Objetivo: Farmacéuticos en Puerto Rico (PR) y los Estados Unidos comúnmente preparan soluciones orales para tratar síntomas de catarro. En PR específicamente se recetan ciertas combinaciones de fármacos incluyendo antitusivos, expectorantes, descongestionantes y otros ingredientes activos los cuales se han denominado culturalmente como *mezclitas*. Desafortunadamente, no existe una guía actualmente disponible para los farmacéuticos en PR que recomiende su preparación, evaluación de calidad y despacho. Métodos: Este estudio evaluó la estabilidad fisicoquímica de una preparación comúnmente realizada por farmacéuticos en PR para tratar síntomas de catarro que contengan guaifenesina, dextrometorfano, y dexametasona. Indicadores de calidad medidos en este estudio incluyeron claridad, olor, pH y viscosidad, bajo dos condiciones de almacenamiento (nevera y temperatura ambiente) por un periodo de 6 meses. Resultados: Las *mezclitas* mostraron pequeños cambios en color, olor y viscosidad. Aunque estos cambios fueron relativamente pequeños, estos pueden ser indicativos de transformaciones químicas o físicas que ocurrieron durante este periodo de almacenamiento. Un cuestionario a farmacéuticos demostró la ausencia de protocolos estandarizados para la preparación y despacho de estas *mezclitas* en PR. Conclusión: Aunque en ausencia de estos protocolos, nuestro estudio sugiere que su estabilidad no está grandemente comprometida. Más sin embargo, estudios adicionales que midan cambios químicos y físicos son necesarios para traducir estos resultados en protocolos estandarizados para farmacéuticos en PR.

Acknowledgements

The authors would like to thank Mikeas Toledo for his support in the color analysis of the samples.

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