The Stability Study of Extemporaneous Preparations Prepared in The Outpatient Pharmacy of Tuanku Fauziah Hospital Stored in Patient's Setting

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Abstract

Introduction: There are concerns about the stability of extemporaneous preparations after being dispensed to and stored by patients.

Objectives: The objective of this study was to investigate the stability of extemporaneous preparations prepared using simple syrup and X-Temp® syrup in the outpatient pharmacy of Tuanku Fauziah Hospital (HTF) when they were stored in the refrigerator and at room temperature in patient's setting.

Methods: The study was carried out in August 2015. Extemporaneous Baclofen Suspension 10mg/ml, Clonazepam Suspension 0.1mg/ml, Propranolol Suspension 1mg/ml, Spironolactone Syrup 2.5mg/ml and Frusemide Syrup 5mg/1ml were included in this study. These medications were prepared using both simple syrup and X-Temp® syrup as vehicle according to the standard formulas in the Ministry of Health (MOH) Extemporaneous Formulation 2015. Each type of syrups were stored in both kitchen cupboard at room temperature and domestic fridge for 14 days and 30 days to mimic the storage at patients' home. At the end of the specified study periods, the syrups were assessed in terms of visual and odour, pH level and sterility. The syrups were considered stable if no changes were detected in all the criteria.

Results: All preparations showed no changes in colour, odour and pH except Baclofen Syrup prepared with simple syrup that turned darker when stored at room temperature for 14 days and 30 days, and when stored in the fridge for 30 days. All preparations passed the sterility test except Propranolol Suspension prepared using X-Temp® syrup and stored under the room temperature for 30 days in which seven Gram-negative bacilli colonies were detected.

Conclusion: Extemporaneous preparations using either simple syrup and X-Temp® syrup were stable up to 30 days, except for baclofen syrup which was only stable for 14 days, if stored in the refrigerator.

Keywords: stability, extemporaneous, preparation, outpatient

NMRR ID: NMRR-16-296-29084

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Introduction

Extemporaneous preparation is defined as the preparation, mixing, assembling, packaging and labelling of a medicinal product based on a prescription order from a licensed practitioner for the individual patient (1). Despite the meaning, extemporaneous preparation is best described as the off-license use of a medicine, whereby a licensed medicine is reformulated into a preparation that is acceptable or appropriate for the patients (2-8). It is usually prepared due to lack of commercially available formulations for patients with specific needs (1).

Compounding of extemporaneous preparations consists of two main components which are the active ingredients and the excipients. Active ingredient is defined as any component that provides pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man or animals (9). Meanwhile, excipients are the vehicles and diluents for the active ingredient (10). The active ingredient or the oral medication (tablet or capsule) will be crushed and triturated using mortar and pestle, followed by the addition of the excipients and they are mixed until a homogenous solution or suspension is formed. There are many kinds of excipients that can be used as the vehicle or suspending agent during extemporaneous preparation. The examples include acacia, tragacanth, hydroxymethycellulose, sugar, carboxymethylcellulose, sorbitol and glycerin (11).

Normally, extemporaneous preparations are required by patients who are unable to swallow the oral solid medications such as neonates, paediatric patients and patients having throat problems. Therefore, most of the extemporaneous preparations involve the process of compounding of oral solid medications into oral liquid forms such as solutions or suspensions (2). In practice, however, commercially prepared solution or suspension will be preferred as the first choice for the patients. However, the choices are usually only limited to commonly used medications. Studies showed that most of drug manufacturers have little interest in supporting the research on developing oral liquid formulations for infants and children. This is probably due to the limited resources, small size of paediatric market and possible liabilities (3-5). In addition, the manufacturers may be reluctant to share the stability data of a drug in a liquid dosage form because the efficacy and safety of the drug in the paediatric population have not been evaluated (6).

Due to this problem, compounding extemporaneous preparations is still a significant practice in the Ministry of Health Malaysia (MOH) healthcare facilities including the Tuanku Fauziah Hospital (HTF). Among the medications that are prepared extemporaneously in HTF are frusemide, spironolactone, propranolol and baclofen syrups. In HTF, extemporaneous preparations are prepared according to the MOH Extemporaneous Formulary 2015 (12). Prior to the preparation, the details of the preparation, such as dose, frequency, strength, total quantity and expiry date, will be determined by interpreting the prescription with reference to the standard strengths of syrup formulation available in the guideline (12).

In HTF, simple syrup and X-Temp® Syrup are the two commercially available vehicles that are normally used as excipients in compounding extemporaneous preparations. Simple syrup (66.7% w/w) contains sugar as the important component in extemporaneous preparation to act as diluent, binder and flavouring agent (13). Meanwhile, X-Temp® syrup is another vehicle that contains specialised suspending system formulated to assist in the extemporaneous preparations of oral liquid, non-soluble, aqueous dosage forms. It is an orange flavoured, sweetened (sugar-free) excipient containing suitable preservatives. X-temp® syrup also consists of purified water, sorbitol, glycerin, microcrystalline cellulose, carboxymethylcellulose sodium and sucralose as suspending agent (14).

Based on the current practice in HTF, expiry dates of extemporaneous preparations using simple syrup and X-Temp® syrup are 14 days and 30 days respectively. However, the stability of the extemporaneous preparation after being dispensed to the patients has not been fully studied especially when they are stored at home. Since there were lack of other similar studies conducted in Malaysia, the results of this study were hoped to provide more evidence for the pharmacists to make informed choices when choosing the vehicles of extemporaneous products to improve the stability the drug preparations. The objective of this study was to investigate the stability of extemporaneous preparations prepared using simple syrup and X-Temp® syrup in the outpatient pharmacy of HTF when they were stored in the refrigerator and at room temperature in patient's setting.

Methodology

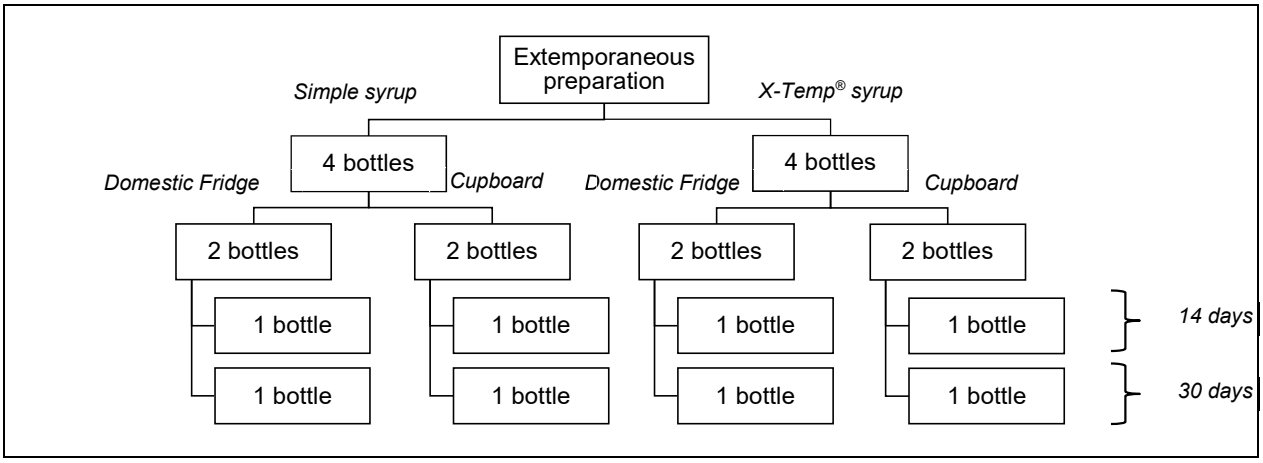
Extemporaneous Preparations

The extemporaneous preparations included in this study were extemporaneous preparation prepared in the outpatient pharmacy department of HTF using simple syrup or X-Temp® syrup with the prepared volume more than 10,000ml a year based on the record in 2014. Syrup medications that were available commercially in HTF and extemporaneous preparations using vehicles other than simple syrup or X-Temp® syrup were excluded. Considering the inclusion and exclusion criteria, the extemporaneous preparations included were Baclofen Suspension 10mg/ml, Clonazepam Suspension 0.1mg/ml, Propranolol Suspension 1mg/ml, Spironolactone Syrup 2.5mg/ml and Frusemide Syrup 5mg/1ml.

These preparations were prepared during the first week of August 2015 according to the standard formulas and methods in the MOH Extemporaneous Formulary 2015 (12). In total, ten types of preparations were prepared, as each of the five included preparations were prepared using both simple syrup and X-Temp® syrup as excipients. The active ingredients and excipients used for each type of preparations were of the same manufacturer as well as batch of expiry. The total volume prepared for each medication was 40 ml for each excipient. The preparations were then divided into four bottles of 10 ml each. Two of the bottles were stored in the domestic fridge while the other two were stored in the kitchen cupboard at room temperature. The domestic fridge and the kitchen cupboard were located at one of the researcher's home in Perlis. For each set of the preparations, one bottle was stored for 14 days while the other was stored for

a period of 30 days. The summary of the storage conditions for each type of extemporaneous preparation was shown in Figure 1.

Figure 1: Summary of the storage conditions for each type of extemporaneous preparation



Stability Tests

In this study, three main aspects were tested for the stability of the extemporaneously compounded medications, which included physical examination, pH and sterility. The tests were carried out on the samples at the beginning of the study (day 0) and at the end of the specified study period (day 14 or day 30). The syrups were considered stable if no changes were detected in all tests.

Physical examination was conducted to examine the visual appearance and odour of the products. The photos of each test samples were taken at the designated time using the same camera and used to record any significant visual changes. The odour of each test samples was recorded and verified by two investigators.

The pH test was conducted using pH indicator strips by MColorpHast™. The paper was dipped in the solution and the changes in colour were matched with the pH chart available along with pH test strip. The readings were taken and verified by two investigators.

For the sterility test, the extemporaneous samples were sent to the Pathology Unit of HTF to check for microbial contamination.

Results

The temperature in the domestic fridge was around 2°C to 8°C and kitchen cupboard was 27°C. All syrup preparations retained their initial colour from Day 0 to Day 30 except Baclofen Syrup prepared with simple syrup (Table 1). It was found that Baclofen Syrup prepared using simple syrup stored at room temperature for 14 days and 30 days turned to a darker colour. On the other hand, the same preparation stored in fridge showed no significant changes in visual appearance up to 14 days, but the colour turned darker after 30 days.

No changes in odour were detected after 30 days of the study for all samples. Similarly, the pH values of the test samples were constant throughout the period of study (Table 2). The results showed that the test samples were free from any microbial growth except for Propranolol Suspension 1mg/ml prepared using X-Temp® syrup as excipient and stored under the room temperature (in cupboard) for 30 days. There were seven colonies of Gram-negative bacilli detected in the sterility test (Table 3).

Table 1: Results of the visual appearance test

Medication	Storage temperature	Vehicle	Colour change	
			Day 14	Day 30
Baclofen Suspension 5mg/ml	27°C	Simple	Yes *	Yes *
		X-Temp®	No	No
	2-8°C	Simple	No	Yes *
		X-Temp®	No	No
Spironolactone Syrup 2.5mg/ml	27°C	Simple	No	No
		X-Temp®	No	No
	2-8°C	Simple	No	No
		X-Temp®	No	No
Frusemide Syrup 5mg/mml	27°C	Simple	No	No
		X-Temp®	No	No
	2-8°C	Simple	No	No
		X-Temp®	No	No
Propranolol Suspension 1mg/ml	27°C	Simple	No	No
		X-Temp®	No	No
	2-8°C	Simple	No	No
		X-Temp®	No	No
Clonazepam Suspension 0.1mg/ml	27°C	Simple	No	No
		X-Temp®	No	No
	2-8°C	Simple	No	No
		X-Temp®	No	No

* The colour of the preparation turned darker

Table 2: Results of the pH test

Medication	Storage temperature	Vehicle	pH		
			Day 0	Day 14	Day 30
Baclofen Suspension 5mg/ml	27°C	Simple	5	5	5
		X-Temp®	4	4	4
	2-8°C	Simple	5	5	5
		X-Temp®	4	4	4
Spironolactone Syrup 2.5mg/ml	27°C	Simple	5	5	5
		X-Temp®	4	4	4
	2-8°C	Simple	5	5	5
		X-Temp®	4	4	4
Frusemide Syrup 5mg/mml	27°C	Simple	4	4	4
		X-Temp®	4	4	4
	2-8°C	Simple	4	4	4
		X-Temp®	4	4	4
Propranolol Suspension 1mg/ml	27°C	Simple	4	4	4
		X-Temp®	4	4	4
	2-8°C	Simple	4	4	4
		X-Temp®	4	4	4
Clonazepam Suspension 0.1mg/ml	27°C	Simple	5	5	5
		X-Temp®	4	4	4
	2-8°C	Simple	5	5	5
		X-Temp®	4	4	4

Table 3: Results of the sterility test

Medication	Storage temperature	Vehicle	Microbial growth		
			Day 0	Day 14	Day 30
Baclofen Suspension 5mg/ml	27°C	Simple	NG	NG	NG
		X-Temp®	NG	NG	NG
	2-8°C	Simple	NG	NG	NG
		X-Temp®	NG	NG	NG
Spironolactone Syrup 2.5mg/ml	27°C	Simple	NG	NG	NG
		X-Temp®	NG	NG	NG
	2-8°C	Simple	NG	NG	NG
		X-Temp®	NG	NG	NG
Frusemide Syrup 5mg/ml	27°C	Simple	NG	NG	NG
		X-Temp®	NG	NG	NG
	2-8°C	Simple	NG	NG	NG
		X-Temp®	NG	NG	NG
Propranolol Suspension 1mg/ml	27°C	Simple	NG	NG	NG
		X-Temp®	NG	NG	7 colonies of Gram-negative Bacilli
	2-8°C	Simple	NG	NG	NG
		X-Temp®	NG	NG	NG
Clonazepam Suspension 0.1mg/ml	27°C	Simple	NG	NG	NG
		X-Temp®	NG	NG	NG
	2-8°C	Simple	NG	NG	NG
		X-Temp®	NG	NG	NG

Abbreviation: NG – no growth

Discussion

Stability refers to the chemical and physical integrity of the dosage unit and, when appropriate, the ability of the dosage unit to maintain protection against microbiological contamination (15). The stability of pharmaceutical products could be influenced by their formulation, storage conditions and even containers. An extensive survey of the literature and investigation of 83 oral liquid formulations prepared extemporaneously by Glass and Haywood in 2006 found that the instability of the formulations is primarily due to interactions between drug substance and the excipients rather than degradation of the active pharmaceutical ingredient (16). It is thus important to consider not only the stability of the drug substance but the entire formulation. A study by Muśko and Sznitowska in 2012 found that propranolol hydrochloride suspensions prepared in three different compounding vehicles, i.e. Ora-Sweet, modified Ora-Sweet and simple syrup with glycerol and sorbitol, were stable with more than 95% of initial concentration remaining after being stored for 35 days in a dark place at 25°C and 4°C. However, suspensions prepared with modified Ora-Sweet should not be stored at 4°C due to crystallization of their buffer substances (17).

The colour of Baclofen syrup prepared using simple syrup turned darker after being stored for 14 days under room temperature. The same preparations that were stored in the fridge showed no colour changes up to 14 days, but not after 30 days. The suggested stability of Baclofen suspension 5mg/ml using simple syrup as vehicle is 35 days if refrigerated and protected from light (12). This implied that the changes in colour could be due to the storage temperature and light. Another possible reason was the chemical reactions that occurred between the active ingredient and the material of the storage bottles used in this study. The bottles in use were made from of plastic material and thus were susceptible to several reactions including migration of the drug through the plastic into the environment, transfer of environmental moisture, oxygen, and other elements into the pharmaceutical product, leaching of container ingredients into the drug and also the risk of adsorption or absorption of the active drug or excipients by the plastic surface (8). Therefore, it may be possible that either of the reactions happened and caused the colour of the baclofen syrup turned darker.

Extemporaneous Frusemide 5g/ml syrups prepared in this study were found to be stable in all storage conditions. A study by Shoosanglertwijit in 2011 found that extemporaneously compounded frusemide suspensions at the concentration of 2mg/ml made from two different suspending vehicles were

stable for at least 60 days when stored in glass bottles protected from light at three controlled temperatures. At least 93% of the initial frusemide concentration remained in both compounded frusemide suspensions for up to 60 days and there were no substantial changes in the appearance colour or odour of both formulations. The pH values of both formulations kept at certain temperatures demonstrated some changes. Both formulations maintained microbiological stability for 60 days (18). Thaweethamcharoen *et al*. in their research in 2014 found that frusemide syrup and spironolactone suspension prepared by the Pharmaceutical Production of Siriraj Hospital were stable for 360 and 60 days, respectively, when stored in light-resistant containers and 5 ± 3^{o}C condition (19).

There were no changes in the pH of all extemporaneous preparations in this study. The changes in pH were generally associated with drug degradation (2). The most common reactions causing drug degradation are hydrolysis, oxidation and reduction (20). The contributing factors to drug degradation were microbial contamination, exposure to sunlight and storage temperature. Therefore, preventing the extemporaneous preparations from microbial contamination is also important. Such contamination can alter the stability of preparations due to the presence of by-products of microbial metabolism. This may cause a change in the pH values of the preparation and reduce the chemical stability or solubility of the drug. On the other hand, the test samples were not exposed to direct sunlight. Due to photosensitivity properties of some ingredients in the test samples, it is crucial that they are stored in a cool, dark place. In addition, high temperature may also affect the stability of extemporaneous preparation as it can accelerate drug degradation process (20).

The Propranolol Suspension 1mg/ml prepared by using X-Temp® syrup failed the sterility test when it was kept under room temperature for 30 days. Nevertheless, this could be due to microbial contamination introduced by the investigator during the transfer of preparation from one container to another rather than the instability of the formulation. According to the International Pharmacopoeia by the World Health Organization (WHO) and other published literature, the sterility test was carried by direct inoculation of the culture medium method (21-27)**.** A small amount of quantity of the extemporaneous was transferred directly into the culture medium (blood agar). Then, the culture medium plus sample of extemporaneous was incubated for 24 hours. The incubated samples were observed. If no evidence of microbial growth is found, the product complied with the test for sterility and *vice versa* (15,22). If there was evidence of growth, culture and sensitivity test were done to identify the type of bacteria by performing gram stain procedure (21). According to Monica *et al.*, gram staining is a common technique used to differentiate two large groups of bacteria based on their different cell wall constituents (23). The Gram stain procedure distinguishes between Gram-positive and Gram-negative groups by colouring these cells red or violet (24).

The physical, chemical and microbiological stability testing of the drugs in the published literatures included pH and colour observation, standard microbiological testing, and measurements using High Performance Liquid chromatography (HPLC) or Ultra Performance Liquid chromatography (UPLC) (16-20,28). In this study, however, only three main aspects were tested for the stability of the extemporaneously compounded medications, which included physical examination, pH and sterility. Therefore, the main limitation of this study was the lack of analytical data to support the results. The presence of drug components in each extemporaneous preparation should be measured using HPLC to further quantify the exact amount of drugs in the test samples during the study period which was not done since there was no access to the necessary instrument. The second limitation was that actual microbial stability test was not performed according to the standards outlined in the British Pharmacopeia for non-sterile product (15). The study duration was also restricted to only 30 days. If the study was carried out for a longer period of time, we could continue observing the changes of each extemporaneous preparation in order to get better evidences on its stability. In addition, certain factors such as the temperature, humidity and brightness were not monitored and controlled throughout the study. Also, all the tests were only performed once for every sample in this study. The evidence would be stronger if the tests were repeated under the same conditions. The use of a pH meter would be a better choice since it can produce more accurate results. In this study, pH test strip papers were used in which the pH measurement was done only by visual comparison to a table of reference colours which may not be as accurate as a digital pH meter. Further studies should be carried out with improvements to these limitations.

Conclusion

All extemporaneous preparations prepared using X-Temp® syrup were stable up to 30 days if stored in the domestic fridge while syrup preparations prepared using simple syrup were stable up to 30 days if stored in the fridge except for baclofen syrup which was only stable for 14 days if being refrigerated. More studies should be carried out to ensure that the extemporaneous compounded for patients are stable and of high quality.

Acknowledgement

We are grateful to Allah the Almighty for the good health and wellbeing that were necessary to complete this research. We would like to thank the Director General of Health Malaysia for his permission to publish this article. We also want to express our gratitude to Mr. Mohamad Syafuan bin Fadzil for his wisdom and guidance in helping us completing this study. We place on record, our sincere appreciation to Mrs. A'tia binti Hashim, the Head of Pharmacy Department of HTF, for her continuous encouragement. We are also grateful to the Pathology Department of HTF for providing us with all the necessary assistance for the research. We also take this opportunity to express gratitude to everyone who helped and supported us through the journey of completing this study.

Conflict of Interest Statement

No external funding was received and the authors declared no conflict of interest.

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