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Original Research

Enhancing extemporaneous preparations in Thai Hospitals: exploring variation, common formulations, and challenges and needs related to extemporaneous preparations

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Abstract

Objective: This study aimed to assess the diversity of extemporaneous preparations, identify the prevalent formulations, and highlight the challenges and opportunities for standardization and improvement of extemporaneous preparation practices. **Methods:** A survey was conducted among 88 Thai hospitals representing the public and private sectors. The questionnaire gathered information on general hospital characteristics, detailed aspects of extemporaneous compounding, and the specific extemporaneous formulations used. **Results:** The survey revealed significant variations in extemporaneous preparations among Thai hospitals, with oral liquids, semisolids, and eye preparations commonly employed. The primary oral liquid formulations used were suspensions, syrups, and solutions. Specific medications frequently used in extemporaneous preparations were also identified. The challenges encompassed space, personnel, skills, raw materials, equipment, standardized formula information, preparation process information, funding, and other factors. **Conclusion:** A survey among Thai hospitals revealed significant variations in extemporaneous preparations in 88 participating hospitals. Common formulations used in extemporaneous compounding include oral liquid preparations, such as suspensions, syrups, solutions, semisolid preparations, and eye preparations. Stakeholder involvement, implementation of standardized operating procedures, resource allocation, comprehensive training programs, and collaboration among hospitals, pharmaceutical companies, and regulatory agencies are recommended to enhance extemporaneous compounding practices.

Keywords: Extemporaneous compounding; variation; formulations; standardization; challenges; opportunities; Thai hospitals

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INTRODUCTION

Extemporaneous preparation, as defined by the United States Food and Drug Administration (US FDA), encompasses a procedural framework involving the preparation, combination, mixing, or alteration of drug ingredients to deliver bespoke medications that are meticulously tailored to address the unique therapeutic requirements of individual patients.[1]

Extemporaneous compounding involves the preparation of customized medicines to meet specific patient needs that cannot be fulfilled by commercially available medications provided by the pharmaceutical industry.[1-4] It plays a crucial role in healthcare, particularly in hospital settings, where patient-specific medications are often required to address

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unique therapeutic needs.[5] Extemporaneous compounding, also known as compounding, is indispensable in delivering specialized care tailored to patients with unique requirements, including infants, children, and older adults.[6,7] It addresses the challenge of unavailable commercial medications in suitable dosage forms for these populations, such as liquid formulations for children or individuals with difficulty swallowing tablets.[6,7] Furthermore, compounding plays a crucial role in drug shortages and the treatment of rare diseases.[8] This process involves modifying various drug products, including ointments, eye drops, oral dosage forms (solid and liquid), and intravenous infusions.[9] Compounded medicines effectively address a wide range of therapeutic requirements, such as tailored dosing for pediatric patients, customized drug combinations, medications suitable for patients with specific excipient allergies, and medicines for orphan drugs that are not commercially available.[2,10]

Compounding practices vary among hospitals due to institutional policies, resource availability, and the expertise of healthcare professionals.[11] Evaluating the compounding practices employed in hospitals helps identify improvement areas and ensure quality control.[12] This evaluation encompasses the assessment of compounding techniques, adherence to standard operating procedures, utilization of compounding equipment, and training provided to the healthcare professionals involved in the compounding process.[13]

The Professional Pharmacy Standards for Thai Hospitals, specifically Domain 4 concerning the procurement, distribution, and control of medicines, mandates that the preparation or compounding of medications that are not commercially available but essential for patients (extemporaneous compounding preparations) must be conducted by well-trained pharmacists or personnel.[14] Prescription formulas must be developed and formulated based on scientific principles. Pharmacists should always consider the quality and safety of preparations.

The prescription formula must undergo rigorous development and formulation based on scientific principles, strongly emphasizing quality and safety. This should provide comprehensive information on the properties and stability of the drug. Regular reviews of prescription formulas are necessary, with specific attention to the common issues encountered while preparing special extemporaneous preparations, which often stem from a lack of information exchange.[14] Thailand's regulations regarding compounding differ from those governing pharmaceutical manufacturing because of the exemption for pharmacists.[15,16] When formulating individual products prescribed by physicians for specific patients, compounding in Thai hospitals is not required to comply with many processes encompassed by current Good Manufacturing Practices (cGMP).[15,17]

Jaidee examined the pharmaceutical production system in 58 Thai community hospitals and revealed that 27 hospitals (46.5%) offered pharmaceutical production services, encompassing a range of 9–53 formulations for internal and external use.[18] Furthermore, Pitchayajittipong et al. reported that extemporaneous preparations constitute the highest number of pharmaceutical products in Thai hospitals.[19]

This study aimed to address the existing gap in comprehensive reporting by investigating the extent of variation in extemporaneous preparations in Thai hospitals. Through a meticulous examination of the current state of practice, identification of challenges, and exploration of potential areas for improvement, this study aims to provide valuable insights into the distinctive landscape of compounding in Thailand compared with other countries.

Research questions:

What is the extent of variation in extemporaneous preparations among Thai hospitals?

What are the common formulas used in extemporaneous preparations in Thai hospitals?

Are there any opportunities to standardize and improve extemporaneous preparation practices in Thai hospitals?

By addressing these research questions, this study aims to address two primary objectives: first, to determine the magnitude of variation in extemporaneous preparations within Thai hospitals, problems or challenges for standardization and enhancement in extemporaneous compounding practices, and second, to explore the formulation processes employed in the preparation of these extemporaneous preparations within hospital settings.

METHODS

Study population

The study population comprised 395 hospitals in Thailand that reported having on-premise pharmaceutical production facilities. These hospitals were selected based on their prior participation in a comprehensive survey conducted by Pichayajittipong et al.[19] These hospitals were included to gather robust data and valuable insights regarding extemporaneous pharmaceutical production practices within the country. This meticulous approach ensured the representation of a diverse and representative sample of hospitals engaged in pharmaceutical production, thereby enhancing the validity and generalizability of the findings. Ethics approval was obtained from the Research Ethics Committee of Ubon Ratchathani University (No. UBU – REC – 22/2563) to ensure adherence to ethical standards.

Study design

A cross-sectional survey design was employed to investigate extemporaneous pharmaceutical production practices in Thai hospitals. Before initiating the study, formal permission was obtained from the hospital directors to ensure their cooperation. Subsequently, the relevant personnel at each hospital were identified and invited to complete a comprehensive questionnaire. The questionnaire was made available in two formats: a standard self-administered paper questionnaire and an online questionnaire accessed through

a QR code. The inclusion of multiple formats was aimed at optimizing response rates and enhancing data quality. The data were collected between January 2022 and March 2022. To ensure the content validity of the questionnaire, three experts in the field of hospital pharmacy production meticulously evaluated the clarity, completeness, and relevance of the questions and scoring.

Survey instrument

The questionnaire consisted of three parts. Part 1 aimed to gather general hospital information, including respondent characteristics, the number of pharmacy production staff, types of pharmaceutical products, and other relevant details. Part 2 focuses on the detailed aspects of extemporaneous compounding formulas produced in Thai hospitals, specifically identifying problems or needs related to extemporaneous preparations. Finally, Part 3 centered on the extemporaneous formulation itself, requesting participants to share the specific formulas used in their hospitals. Extemporaneous formulas were requested from the hospitals and collected for analysis. These formulas encompass various crucial aspects, including general formulation information, formulation details, such as active ingredients, pharmaceutical excipients, strength, dosage form, manipulation techniques employed during compounding, and considerations related to packaging, storage conditions, and stability.

Data collection and analysis

Survey responses were collected via post or online platforms, facilitating a convenient and efficient data collection process. The collected data were exported to Microsoft Excel (Microsoft Corporation, Redmond, Washington, United States) for comprehensive analysis. Descriptive statistics were employed to examine and interpret the collected data, providing valuable insights into the extemporaneous pharmaceutical production practices of the participating hospitals. The extemporaneous formulas collected through a dedicated data collection form were meticulously transferred to a Microsoft Excel spreadsheet for rigorous analysis.

RESULTS

This study presents the findings of a survey conducted to investigate the extemporaneous compounding practices in Thai hospitals. The survey questionnaire consisted of three parts, each targeting different aspects of extemporaneous compounding. The results provide valuable insights into the respondent characteristics, types of extemporaneous preparations, specific formulations used, and the challenges faced during the compounding process.

General Information

In this study, 395 hospitals engaged in pharmaceutical production were contacted, and 88 agreed to participate. The participating hospitals represented both the public and private sectors, with public hospitals comprising the majority of respondents (n=79, 89.77%) (Table 1). Most respondents had 1–10 years of work experience (n=78, 88.64%). General hospitals were the most prevalent type of institution involved in extemporaneous production, accounting for 42.86% of the participating hospitals (n=21). The pharmaceutical production departments within these hospitals typically consisted of 1–5 pharmacists and 1–5 pharmacy technicians, as shown in Table 2. These findings shed light on the composition and characteristics of the participating hospitals and provide important contextual information for the study's exploration of extemporaneous preparation practices.

Detailed Aspects of Extemporaneous Compounding in Thai Hospitals and Identification of Problems or Needs Related to Extemporaneous Preparations

Extemporaneous Compounding in Hospitals

A survey conducted in Thai hospitals revealed three primary types of extemporaneous preparations: oral liquid, semisolid, and eye preparations (Table 3). A total of 61 extemporaneous medicinal formulations were identified. Among the oral liquid extemporaneous preparations, suspensions were reported by 82 hospitals (22.84%) reported suspensions, 50 hospitals (13.93 %) reported syrups and 17 hospitals (4.74 %) reported solutions.

Further analysis focused on a subset of 88 hospitals, highlighting the list of specific medicines used in extemporaneous preparations and their corresponding indications. Notably, the frequently prepared formulations included oseltamivir, isoniazid, spironolactone, furosemide, and sodium bicarbonate (Table 4). For instance, oral liquid oseltamivir, employed to treat an influenza infection, was reported in 68 hospitals (77.27%). The most prevalent semisolid formulations were urea cream, hydroquinone cream, misoprostol gel, trichloroacetic acid cream, and salicylic acid cream. Additionally, commonly used medications, such as amphotericin B, cefazolin, and ceftazidime eye drops, have been used to treat eye infections. Eye extemporaneous preparations encompassed both anti-infective agents (e.g., amikacin eye drops) and non-anti-infective agents (e.g., dexamethasone, tropicamide/phenylephrine), with amphotericin B, cefazolin, ceftazidime, sodium chloride, and vancomycin being the most commonly prepared formulations (Table 5).

Challenges and Needs Related to Extemporaneous Preparations

The survey data identified challenges and obstacles in the extemporaneous preparation of different formulations. These challenges are categorized into nine main areas: insufficient space, inadequate personnel, lack of preparer skills, scarcity of raw materials, absence of equipment/facilities, absence of standardized formula information, inadequate preparation process information, and insufficient funding. Within the liquid preparation category, the most prevalent challenges included insufficient building space, workforce shortage, lack of skilled personnel, shortage of raw material supplies, equipment-related challenges, lack of a master formula, and budget constraints. Similarly, in semisolid preparations, challenges were noted in terms of space, raw material supplies, equipment, and budgets. Eye preparations also encounter

Table 1.Population and sample by type of hospital

Types of the hospital				Survey in 2019					Survey in 2022 (n= 395 hospitals)			
				Population (n=1,347)	Percentage of population	Sample (n=750)	Percentage of sample	Responding sample group (n=395)	Responding sample group (n=88)	Percentage of responding sample group (From 88 hospitals)	Respond Rate for each hospital group (From 395 hospitals)
Public hospitals	**Ministry of Public Health (MoPH)**	**Office of the Permanent Secretary (OPS)**	Regional hospitals	33	2.45	33	4.40	18	5	5.68	27.78
			Regional hospitals with Thai traditional medicine policy	1	0.07	1	0.13	0	0	0	0
			General hospitals	80	5.94	80	10.67	49	21	23.86	42.86
			General hospitals with Thai traditional medicine policy	3	0.22	3	0.40	2	0	0	0
			Community hospitals	736	54.64	260	34.67	151	41	46.59	27.15
			Community hospitals with Thai traditional medicine policy	42	3.12	42	5.60	29	0	0	0
		Non-Office of the Permanent Secretary		57	4.23	57	7.60	34	3	3.41	8.82
	Non-Ministry of Public Health (Non-MoPH)	10 - 30 beds		35	2.60	67	8.93	26	9	10.23	34.62
		31 - 90 beds		28	2.08						
		91–150 beds		17	1.26						
		> 150 beds		34	2.52	34	4.53	16	0	0	0
Private hospitals		31-100 beds		174	12.92	161	21.47	61	8	9.09	13.11
		101-300 beds		95	7.05						
		> 300 beds		12	0.89	12	1.60	9	1	1.14	11.11
		Total		**1347**	**100**	**750**	**100**	**395**	**88**	**100**	**22.28**

Table 2. Characteristics of the respondents (n=88)		
Characteristics	Number	Percentage
1. Position and responsibility		
1.1 Head of the pharmacy department	31	35.23
1.2 Head of the pharmacy production department	15	17.05
1.3 Pharmacists in pharmacy production department	42	47.72
2. Types of the hospitals		
2.1 Public	79	89.77
2.2 Private	9	10.23
3. Work experience of respondents in pharmaceutical production area (years) (Range 1–26 years, Mean±SD =6.84±5.12)		
• 1–10 years	78	88.64
• 11–20 years	8	9.09
• 21–30 years	2	2.27
4. Pharmacy workforce in the production department		
4.1 Number of pharmacists (Range 1–17, mean±SD =2·34±2.56)		
• 1–5	80	90.91
• 6–10	4	4.55
• 11–15	2	2.27
• 16–20	2	2.27
4.2 Number of pharmacy technicians (Range 0-15, mean±SD =1.95±1.96)		
• 0	1	1.14
• 1–5	85	96.59
• 6–10	1	1.14
• 11–15	1	1.14
• 16–20	0	0·00

Table 3**.** Number of hospitals that provide extemporaneous preparations (n= 88 hospitals, 61 medication items)			
Types of extemporaneous preparations	**Dosage for[m]a**	**Number of hospitals[b]**	**Percentage**
Oral liquid extemporaneous preparations	Suspensions	82	22·84
	Syrups	50	13·93
	Solutions	17	4·74
	Drops	1	0·28
	Elixirs	1	0·28
	Unspecified	54	15·04
Semisolid extemporaneous preparations	Creams	12	3·34
	Gels	3	0·84
	Unspecified	1	0·28
Eye extemporaneous preparations	Eye drops	138	38·44
Total		359	100·00

[a] A single extemporaneous preparation may consist of multiple strengths or dosage forms
[b] A hospital may possess multiple types of extemporaneous preparation

Table 4. The top ten extemporaneous preparations

	List of medicine	Indication	Type of extemporaneous	Number of hospitals	Percentage (Based on 88 hospitals)
1	Oseltamivir oral liquid	Treatment of influenza infection	EL[a]	68	77.27
2	Amphotericin B eye drops	Treatment of fungal and yeast eye infections	EE[b]	24	27.27
3	Cefazolin eye drops	Treatment of bacterial eye infections	EE	24	27.27
4	Isoniazid oral liquid	Treatment of tuberculosis	EL	18	20.45
5	Ceftazidime eye drops	Treatment of bacterial eye infections	EE	16	18.18
6	Vancomycin eye drops	Treatment of bacterial eye infections	EE	15	17.05
7	Spironolactone oral liquid	Treatment of heart failure and high blood pressure	EL	15	17.05
8	Gentamicin eye drops	Treatment of bacterial eye infections	EE	13	14.77
9	Furosemide	Treatment of heart failure and high blood pressure	EL	14	15.91
10	Sodium bicarbonate	Cerumenolytics	EL	11	12.50

[a]EL=Oral liquid extemporaneous preparations; [b]EE = Eye extemporaneous preparations

Table 5. Extemporaneous preparations grouped by category and the corresponding number of hospitals that manufactured them

	Liquid extemporaneous preparations	No. of hospitals		Liquid extemporaneous preparations	No. of hospitals		Eye extemporaneous	No. of hospitals		Semisolid extemporaneous	No. of hospitals
1	Acetazolamide oral liquid	4	*21*	Methadone oral liquid	1	*40*	Amikacin eye drops	9	*56*	Conjugated estrogen cream	1
2	Acyclovir oral liquid	2	*22*	Metronidazole oral liquid	2	*41*	Amphotericin B eye drops	24	*57*	Hydroquinone cream	4
3	Aminophylline oral liquid	4	*23*	Norfloxacin oral liquid	2	*42*	Atropine eye drops	2	*58*	Misoprostol gel	3
4	Amlodipine oral liquid	1	*24*	Omeprazole oral liquid	4	*43*	Cefazolin eye drops	24	*59*	Salicylic acid cream	1
5	Bambuterol oral liquid	1	*25*	Oseltamivir oral liquid	68	*44*	Ceftazidime eye drops	16	*60*	Trichloroacetic acid cream	2
6	Captopril oral liquid	1	*26*	Phenobarbital oral liquid	7	*45*	Cyclosporin eye drops	2	*61*	Urea cream	5
7	Carbamazepine oral liquid	2	*27*	Phenytoin oral liquid	3	*46*	Dexamethasone eye drops	3			
8	Chloral hydrate oral liquid	1	*28*	Prednisolone oral liquid	3	*47*	Ganciclovir eye drops	1			
9	Clonazepam oral liquid	1	*29*	Propranolol oral liquid	3	*48*	Gentamicin eye drops	13			
10	Doxycycline oral liquid	3	*30*	Pyrazinamide oral liquid	4	*49*	Methylprednisolone eye drops	3			
11	Enalapril oral liquid	3	*31*	Pyridoxine oral liquid	1	*50*	Phenylephrine eye drops	2			
12	Ethambutol oral liquid	3	*32*	Ranitidine oral liquid	8	*51*	Serum eye drops	2			
13	Furosemide oral liquid	12	*33*	Rifampicin oral liquid	6	*52*	Sodium chloride eye drops	15			
14	Hydrochlorothiazide oral liquid	9	*34*	Sodium bicarbonate oral liquid	11	*53*	Tropicamide eye drops	1			
15	Ibuprofen oral liquid	1	*35*	Spironolactone oral liquid	14	*54*	Tropicamide/ Phenylephrine eye drops	5			
16	Isoniazid oral liquid	17	*36*	Ursodeoxycholic acid oral liquid	2	*55*	Vancomycin eye drop	15			
17	Ketoconazole oral liquid	2	*37*	Vitamin D oral liquid	2						
18	Levothyroxine oral liquid	4	*38*	Vitamin E drops	1						

19	Lidocaine oral liquid	1	*39*	Zinc oral liquid	4						
20	Magnesium chloride oral liquid	1									

obstacles in terms of space, workforce, skilled personnel, and raw material supply. These findings highlight the importance of addressing these challenges to optimize extemporaneous compounding practices and ensure the provision of high-quality pharmaceutical products.

The extemporaneous drug preparation process has revealed specific challenges for each formulation category. The primary concern in the liquid formulation category included a lack of standard formula information, with 81 hospitals (22.56%) reporting this challenge. Insufficient equipment and facilities were also prevalent issues, with 77 hospitals (21.45%) facing this challenge. Additionally, 62 hospitals (17.27 %) identified inadequate space as a significant obstacle.

In the semisolid formulation category, the most common challenge was the lack of standard formula information, reported by 13 hospitals (3.62%), followed by insufficient equipment/facilities, mentioned by 11 hospitals (3.06%). Inaccurate preparation processes were also a significant challenge, as identified by nine hospitals (2.51%).

For eye drop formulations, the top three problems were lack of space, affecting eight hospitals (2.23%), followed by insufficient personnel, reported by five hospitals (1.39%). In addition, a lack of expertise and inadequate equipment/facilities were identified as challenges by three hospitals (0.84%) each. These findings underscore the importance of addressing these specific challenges to enhance the extemporaneous preparation process and ensure the quality of compounded medications.

In an open-ended questionnaire, the study participants emphasized the critical need for stakeholder involvement in addressing the challenges associated with extemporaneous drug preparations. They strongly recommended implementing standardized operating procedures, allocating adequate resources (including equipment, personnel, and funding), and developing comprehensive training programs to enhance staff expertise. Additionally, fostering collaborative efforts among hospitals, pharmaceutical companies, and regulatory agencies has been highlighted as a significant contributor to optimizing extemporaneous drug preparation processes and ultimately improving the quality of patient care. Furthermore, to further enhance extemporaneous drug preparations, participants proposed the following strategies: instituting rigorous protocols for quality assurance and control to ensure the safety and efficacy of pharmaceuticals, adhering to current standards and continuously monitoring patient outcomes for validation; maintaining meticulous documentation of procedures and patient-centric information to ensure consistency and personalized care; systematically evaluating the stability of preparations to determine optimal storage conditions and shelf life; offering continuous education and proficiency evaluations for pharmacy staff; cultivating robust channels of communication among healthcare providers to facilitate the exchange of knowledge and best practices; encouraging ongoing research and development efforts to discover novel formulations and enhance extemporaneous preparations; and safeguarding adherence to regulatory mandates through vigilant oversight and the development of relevant guidelines.

The extemporaneous formulation

In the 88 participating hospitals, the most frequently used oral liquid extemporaneous preparations were oseltamivir, isoniazid, spironolactone, furosemide, and sodium bicarbonate. Eye drop preparations, prepared using aseptic techniques under laminar airflow hoods, frequently contain amphotericin B, cefazolin, ceftazidime, gentamicin, and vancomycin. Notably, only three central hub hospitals in the northern and northeastern regions of Thailand provided detailed formulas.

The participants provided liquid extemporaneous and eye drop formulas but not semisolid formulations provided from the participants. The following are comprehensive descriptions of the preparation processes and storage conditions of the most prevalent extemporaneous oral liquids and eye preparations.

Oseltamivir, an antiviral agent used for influenza management, often has limited availability in commercial products. A formulation of oseltamivir suspension (10 mg/ml) was prepared by grinding 600 mg of powder from eight 75 mg capsules to a fine, uniform consistency using a mortar and pestle. The powder was then blended with simple syrup or other vehicles (e.g., Ora-sweet®, Ora-sweet® SF) to form a smooth paste. The resulting suspension was transferred to a 60 mL amber glass bottle and stored at 2–8 °C for up to 10 days.

Isoniazid, an anti-tuberculosis agent, was prepared as a 10 mg/ml suspension using 300 mg of powder from three 100 mg tablets. The resulting powder was ground and combined with a carboxymethylcellulose-based (CMC)-based vehicle. The suspension was transferred to a 30 mL amber glass bottle and stored at 2–8 °C for up to 21 days.

Spironolactone, used for treating bronchopulmonary dysplasia, edema, and hypertension, was prepared as a 25 mg/ml suspension using 300 mg of powder from twelve 25 mg tablets. The powder was then mixed with a syrup containing sodium benzoate. The suspension was transferred to a 30 mL amber glass bottle and stored at 2–8 °C for up to 30 days.

Furosemide, used to treat hypertension, was prepared as a 1 mg/ml suspension using 100 mg of furosemide powder blended with a 50 ml suspending vehicle containing 10% NaOH and syrup. The suspension was transferred to an amber glass bottle and stored at 2–8 °C for up to 30 days.

Sodium bicarbonate ear drops (5 ml/bottle) were used as the cerumenolytic agents. A 5% v/v solution was created using 66.67 ml of 7.5% sodium bicarbonate and 30 ml of 99.5% glycerin, and the final volume was adjusted to 100 ml. The ear

drops were stored below 40 °C for up to 14 days.

The most frequently used eye drops for extemporaneous preparations prepared under aseptic conditions in a laminar airflow hood include the following:

Amphotericin B eye drops were available at concentrations of 0.15 % (1.5 mg/ml) and 0.3 % (3 mg/ml). For example, to formulate 0.15% formulation, a 50 mg/vial of amphotericin was reconstituted with 10 mL of preservative-free sterile water for injection, then the mixture of 1.5 ml (7.5 mg) was transferred to a 5 ml sterile ophthalmic container, and 3.5 ml of sterile water for injection (SWFI) was added. These eye drops were stored in bottles at 2–8 °C for 7 days.

Cefazolin eye drops were available at 1.0% (10 mg/ml) and 5.0% (50 mg/ml). For example, to obtain the 1.0% formulation, 1 g/vial of cefazolin was reconstituted with 10 ml of normal saline solution (NSS) for injection, 0.5 ml (50 mg) was transferred to a 5 ml sterile ophthalmic container, and add NSS 4.5 ml. The 1.0% cefazolin eye drops were stored in bottles at 2–8 °C for up to 4 days, while 5.0% cefazolin eye drops were stored for 28 days in a freezer.

Ceftazidime eye drops (5 %, 50 mg/ml) prepared at 50 mg/ml concentration necessitated the reconstitution of 1 g/vial ceftazidime with 10 ml of NSS. The mixture was drawn into a syringe, 2.5 ml (250 mg) was transferred to a 5 ml sterile ophthalmic container, and added NSS 2.5 ml. Ceftazidime eye drops could be stored at 2–8 °C for 7 days.

Gentamicin eye drops were available at concentrations of 1 % (10 mg/ml) and 1.4 % (14 mg/ml). For example, to obtain the 1% formulation, 80 mg of a 2 ml ampoule of gentamicin injection was drawn 1.25 ml (50 mg) into a 5 ml sterile ophthalmic container, and 3.75 ml of NSS was added. The 1.0% gentamicin eye drops were stored in bottles at 2–8 °C for 30 days, while 1.4% gentamicin eye drops were stored for 28 days.

5%Vancomycin (50 mg/ml) eye drops were prepared using a 1 g vancomycin vial reconstituted with 10 ml of SWFI. The mixture (5 ml, 250 mg) was drawn and transferred to a 5 ml sterile ophthalmic container. Vancomycin eye drops could be stored at 2–8 °C for up to 14 days.

(Table 6) shows the variations in strength, stability, and storage conditions of the various extemporaneous preparations. For example, acetazolamide oral liquid has a strength of 10 mg/ml and a stability of 7 days in some hospitals and 30 days in one hospital when refrigerated. Amikacin eye drops have a strength of 2.0% (20 mg/ml) and a stability of 7 days in some hospitals and 30 days in one hospital when refrigerated. The aminophylline oral liquid exhibited two different concentrations, 5 and 10 mg/ml, with a stability of 30 days. Storage conditions also varied for amphotericin B eye drops, with some preparations requiring refrigeration; one hospital stored them in a freezer.

DISCUSSION

This discussion presents an analysis of the survey results, which aimed to investigate extemporaneous compounding practices

Table 6. Example of extemporaneous preparations exhibit variations in terms of strength, stability, and storage condition

Extemporaneous preparations	**Strength**	**Stability**	**Storage condition**
Acetazolamide oral liquid	10 mg/ml	7 days 30 days	Refrigerate
Amikacin eye drops	2.0% (20 mg/ml)	7 days 30 days	Refrigerate
Aminophylline oral liquid	5 mg/ml 10 mg/ml	30 days	Refrigerate
Amphotericin B eye drops	0.15% (1.5 mg/ml) 0.30% (3 mg/ml)	7 days 28 days	Refrigerate Freezer
Cephazolin eye drops	1.0% (10 mg/ml) 5.0% (50 mg/ml)	4 days 28 days	Refrigerate
Gentamicin eye drops	1.0% (10 mg/ml) 1.4% (14 mg/ml)	30 days 28 days	Refrigerate
Enalapril oral liquid	1 mg/ml	14 days 30 days	Refrigerate
Ethambutol oral liquid	50 mg/ml	28 days, 30 days	Refrigerate
Furosemide oral liquid	2 mg/ml	7 days, 30 days	Refrigerate
Propranolol oral liquid	2 mg/ml	30 days, 45 days	Refrigerate
Pyrazinamide oral liquid	40 mg/ml	30 days, 60 days	Refrigerate
Rifampicin oral liquid	50 mg/ml	28 days, 30 days	Refrigerate

in Thai hospitals, focusing on the extent of variation, common formulas used, and challenges related to standardization and improvement.

The survey revealed that among the 395 hospitals that reported having pharmaceutical production facilities, 88 agreed to participate, representing both the public and private sectors. The participating hospitals were predominantly general. This finding aligns with previous research, highlighting the significant role of public hospitals in providing specialized care and catering to the unique therapeutic needs of patients through extemporaneous compounding.[20] These findings provide important contextual information on the characteristics of hospitals and the number of workforce members engaged in extemporaneous production.

The survey identified three primary types of extemporaneous preparations used in Thai hospitals: oral liquids, semisolids, and eye preparations. Among the extemporaneous oral liquid preparations, suspensions were the most frequently reported formulations, followed by syrups and solutions. This is consistent with previous studies showing that the compounding process tends to be performed in pharmaceutical practices in developing nations.[20] Oral and semisolid dosage forms are predominantly prescribed as extemporaneous products. Many studies have reported that a higher proportion of extemporaneous preparations are compounded for pediatric patients; for example, in Indonesia, children aged 0–5 years receive a higher proportion of extemporaneous preparations, with approximately 71.5% of drugs administered to children being compounds, including divided powders (88.36%) and oral suspensions (8.06%).[21] In Thailand, 73.5% of pediatric preparations are prescribed off-label medications.[22] Similarly, newborns admitted to neonatal care units (NCU) also receive compounded preparations in Brazil. In Estonia, more than 90% of hospitalized newborns, on average, receive two extemporaneous preparation products.[20]

Some common extemporaneous oral liquid formulations have also been reported in other countries, such as Malaysia (e.g., acetazolamide, amlodipine, captopril, and clonazepam).[23] Most extemporaneous oral liquids prepared from commercially available solid oral dosage forms typically involve techniques such as tablet trituration or capsule opening, followed by the addition of water or another suitable vehicle.[24] These methods allow for the conversion of solid forms into liquid forms for ease of administration, especially when a commercially available liquid formulation is unavailable or is suitable for the patient's specific needs.[24]

This study revealed variations in the concentrations of oral liquid medicines (e.g., aminophylline solutions of 5 mg/ml and 10 mg/ml).[25] This variation must be clarified and standardized to prevent errors in concentration, as mentioned in a previous study.[25] Another study reported that medication errors involving liquid medications in pediatric patients highlighted a lack of standardized concentrations. The variability in concentration leads to errors during care transitions, potentially resulting in therapeutic failure or toxicity. Pharmacists reported a similar awareness of errors related to concentration variability.[25]

According to the stability of the extemporaneous preparations, all preparations in this study followed the United States Pharmacopeia (USP) 2019, which suggests that the appropriate beyond-use date (BUD) for non-aqueous formulations is below six months.[26] Specifically, water-containing oral and topical formulations without moisture have 14 and 90 days BUD, respectively.[26] This study found that some preparations from different hospitals had different BUD; for example, acetazolamide suspensions at 10 mg/ml had a reported BUD of 7 days in one hospital and 30 days in another. However, both are correct as per the USP and according to the results of a study that investigated the shelf life of acetazolamide for at least 120 days at less than 30°C regarding its physical and chemical stability.[27] These results highlight the need for further research and interventions to study the stability of these extemporaneous preparations, which have never been reported in stability studies.[26]

The findings of this study show the current situation of current practices in extemporaneous preparations in Thailand. The study revealed variations in the concentrations of commonly used oral liquid medicine and BUD. Therefore, awareness of the standards of extemporaneous formulations is needed, especially in terms of standardized concentrations and BUD, to improve patient safety.

Opportunities for Standardization and Improvement in Extemporaneous Preparation Practices

The survey findings highlighted various challenges and needs related to extemporaneous preparation. These challenges are categorized into nine main areas: insufficient space, inadequate personnel, lack of compounding pharmacist's skills, scarcity of raw materials, absence of equipment/facilities, absence of standardized formula information, inadequate preparation process information, and insufficient funding. The participants emphasized the critical need for stakeholder involvement and recommended implementing standardized operating procedures, allocating sufficient resources, and comprehensive training programs to enhance staff expertise. Collaborative efforts among hospitals, pharmaceutical companies, and regulatory agencies are also considered crucial for optimizing extemporaneous drug preparation processes.[5,20,28-30] The participants proposed specific strategies, such as quality assurance and control protocols, meticulous documentation, stability testing, training and assessment programs, communication and collaboration channels, research and development initiatives, and regulatory guidance to enhance extemporaneous preparations further. Many previous studies reported that standard guidelines and procedures, such as the quality control of extemporaneous products, were also required.[2,3,12,20,28,29,31]

Overall, the survey findings shed light on the extent of variation in extemporaneous preparations among Thai hospitals, identify common formulas used in extemporaneous preparations, and reveal opportunities for standardization and improvement in extemporaneous preparation practices. These findings provide valuable insights for healthcare professionals, policymakers, and stakeholders to enhance the quality, safety, and efficiency

of extemporaneous preparations.

Despite the valuable insights provided by this study regarding extemporaneous preparation in Thai hospitals, several limitations should be acknowledged. First, it relied on self-reported data from a limited sample size of 88 hospitals out of the 395 initially contacted. This may introduce a potential bias, as the participating hospitals may not fully represent the diversity of extemporaneous compounding practices across all Thai hospitals. Therefore, the findings may not be generalizable to the entire Thai hospital population engaged in extemporaneous preparations.

Second, this study utilized a cross-sectional survey design that captured a snapshot of extemporaneous compounding practices at a specific point in time. This design limited the ability to establish causal relationships and track changes in practice over time. Longitudinal studies or qualitative approaches can provide a more in-depth understanding of the dynamics and evolution of extemporaneous compounding practices in Thai hospitals.

Third, this study focused primarily on quantitative data collected through a structured questionnaire. While this approach allowed for systematic data analysis, it may have limited the exploration of the nuanced aspects of extemporaneous compounding practices. Incorporating qualitative methods such as interviews or focus groups could provide a richer understanding of the experiences, perspectives, and contextual factors influencing extemporaneous preparation practices. Furthermore, this study did not specifically address the outcomes or clinical implications of extemporaneous preparation. While the study identified the common formulas used and the challenges faced, the impact of these practices on patient outcomes or safety was not assessed.

Despite these limitations, this study offers valuable insights into extemporaneous compounding practices in Thai hospitals, contributing to the existing knowledge base and highlighting opportunities for standardization and improvement. Future research should aim to address the limitations present in extemporaneous compounding practices and their impact on patient care in order to advance our understanding in this area. By evaluating the clinical effectiveness and safety of extemporaneously compounded medications, future research can provide a more comprehensive understanding of their role in patient care. Furthermore, it is essential for future studies to specifically focus on the context of Thai hospitals in order to enhance our understanding of the impact of extemporaneous preparations on patient care within this setting.[29,30]

The findings provide practical insights that can be applied to real-world healthcare settings. This study highlights the need to standardize extemporaneous compounding practices within Thai hospitals. The challenges identified, such as limited space, inadequate personnel, and lack of standardized formula information, underscore the importance of establishing clear guidelines and protocols for extemporaneous preparations. Policymakers can utilize these findings to create guidelines to ensure the quality, safety, and consistency of extemporaneously compounded medications. Policymakers should create an enabling environment that supports the provision of safe, effective, and high-quality extemporaneously compounded medications in Thai hospitals.

CONCLUSION

This study aimed to investigate the extent of variation in extemporaneous preparations, explore the common formulas employed, and identify opportunities to standardize and improve extemporaneous compounding practices within Thai hospitals. A survey conducted among Thai hospitals revealed significant variations in extemporaneous preparations in 88 participating hospitals. Common formulations used in extemporaneous compounding include oral liquid preparations, such as suspensions, syrups, solutions, semisolid preparations, and eye preparations. This study identified several opportunities for the standardization and improvement of extemporaneous preparation practices, with challenges arising in terms of space, personnel, skills, raw materials, equipment, standardized formula information, preparation process information, funding, and other pertinent factors. To enhance extemporaneous compounding practices, this study recommends stakeholder involvement, implementation of standardized operating procedures, resource allocation, comprehensive training programs, and collaboration among hospitals, pharmaceutical companies, and regulatory agencies. This study contributes to the advancement of knowledge in the field of extemporaneous compounding by providing valuable insights into these aspects. These findings expand our understanding of the types of preparations utilized and shed light on the challenges encountered by hospitals, thus informing future research and interventions.

CONFLICT OF INTEREST

None

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AUTHOR CONTRIBUTIONS

Teeraporn Supapaan: Conceptualization, Methodology, Data collection, Formal analysis, Writing-original draft preparation; Chinnawat Jamlongpeng**:** Data collection, Formal analysis; Natthapon Yangyuen**:** Data collection, Formal analysis; Komkrit Srisawai: Data collection, Validation, Writing-reviewing and editing; Lersak Prachuabaree: Validation, Writing-reviewing and editing; Wannaporn Wattanawong: Data collection, Writing-reviewing and editing; Jirana Anansushatgul: Data collection, Validation, Writing-reviewing and editing; Thanatcha Songmuang: Data collection, Validation, Writing-reviewing and editing; Saksit Sripa: Conceptualization, Methodology, Writing-reviewing and editing; Chonladda Pitchayajittipong: Methodology, Formal analysis, Writing-original draft

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