OPEN ACCESS Freely available online

ISSN: 2153-2435
Pharmaceutica Analytica Acta

Research article

Extemporaneous Compounding of Furosemide Oral Liquid Formulations: A Systemic Review

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ABSTRACT

Small-scale compounding of oral liquid dosage forms lacks long-term safety and efficacy data of commercially available medicines. Medication shortages of furosemide syrup continue to burden healthcare treatment. Extemporaneous compounding of commercially available registered drugs is prohibited, except under exceptional circumstances. Compounding an alcohol-free furosemide oral liquid may be safe for pediatric patients. This study aims to alleviate a nationwide shortage of furosemide syrup *via* a literature review of extemporaneous compounding resources. Investigators performed a literature review and found that 8 of the 13 stability studies of furosemide oral liquids were alcohol-free with at least a 30-day shelf life, and may be suitably compounded for pediatric patients. In the absence of a commercially available furosemide syrup, this review found safe alternatives to extemporaneously compound furosemide oral liquid dosage forms.

Keywords: Syrup; Oral liquids; Furosemide; Dosage forms

INTRODUCTION

Extemporaneous compounding may be defined as a process whereby a health care professional mixes, combines packages or alters ingredients tailored to meet the needs of a particular patient. The Ministry of National Guard Health Affairs (MNGHA) strives to achieve the highest quality of care, ensuring patient safety by utilizing sound scientific principles. Pharmacists rely heavily on reference material to extemporaneously compound medicines, on the assumption that such references have been validated. The purpose of this study was to evaluate the current compounding practice at tertiary care institutions in relation to oral liquid dosage forms, and to establish a reference for the current formulary of compounded non-sterile products based on current evidence [1]. Medication shortages, of furosemide syrup in Saudi Arabia, have placed a burden on health care. Extemporaneous compounding could provide access to a lifesaving medicine that would otherwise not be accessible. In the absence of commercially available dosage forms, prescribers and patients rely on pharmacists to ensure that extemporaneously prepared dosage forms are safe and effective. Oral liquid dosage forms may be needed by pediatric patients, as well as patients who are unable to swallow oral solid dosage forms (tablets or capsules). Such products may, however, lack support in terms of stability, bioavailability, pharmacokinetics, pharmacodynamics, efficacy, and tolerability studies. The evidence base is weak in many situations and guidance is predominantly informed by best practice, scientific and therapeutic principles, and expert consensus. Despite guidance by regulatory authorities, extemporaneous compounding for individual patients has traditionally not been prohibited, nor has it been closely regulated. This may, nonetheless, pose a potential risk if good compounding practices are not followed. The United States Food and Drug Administration (US-FDA) has identified risks associated with pharmaceutical compounding, especially where this veers close to manufacturing without a marketing authorization. The Saudi Food and Drug Authority (SFDA) and the United States Pharmacopeia (USP) chapters<795>Pharmaceutical Compounding-Nonsterile Preparations have provided some guidance on compounding practices [2-7].

A commercially available medicine for human consumption should be registered with SFDA. These medicines have been licensed after extensive trials in safety and efficacy. Registered medicines must follow Good Manufacturing Practice (GMP) guidelines as governed by SFDA. GMP requires validated analytical techniques, and independent quality control; including package inserts packaging,

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Received: 24-Jul-2023, Manuscript No. PAA-23-22316; **Editor assigned:** 27-Jul-2023, Pre QC No. PAA-23-22316 (PQ); **Reviewed:** 10-Aug-2023, QC No. PAA-23-22316; **Revised:** 17-Aug-2023, Manuscript No. PAA-23-22316 (R); **Published:** 25-Aug-2023, DOI: 10.35248/2153-2435.23.14.750

Citation: Joosub I, Anezi MA, Emara Z, Youssif E (2023) Extemporaneous Compounding of Furosemide Oral Liquid Formulations: A Systemic Review. Pharm Anal Acta.14:750.

testing, batch rejections, and reporting of adverse events. Licensed products must have been validated by clinical data prior to registration. Small-scale extemporaneous compounding lacks the vigorous testing and quality controls applied by pharmaceutical manufacturing companies. Copies of registered SFDA medicines in the absence of GMPs may compound potential risks and may be unsafe. Extemporaneous compounding of a commercially-registered medicine should be prohibited unless products do not meet the clinical needs of the patient. These may include instances where the medication is unavailable, the patient has an allergy to the excipients, an elderly who cannot swallow solid dosage forms, or a lower concentration of the registered product is required [4,6,8].

Furosemide is a diuretic that may be used in hypertension, and edematous conditions that are associated with heart failure, liver cirrhosis, and renal diseases. It is a white or slightly yellow crystalline powder, practically insoluble in water, sparingly soluble in ethanol, soluble in methanol and acetone, and freely soluble in alkali hydroxide. Furosemide injectable solutions are prepared with sodium hydroxide to maintain an alkali pH (8.0-9.3). Furosemide is registered commercially with SFDA as tablets, injections, and oral syrup. Although available commercially, periodic recalls within the Kingdom of Saudi Arabia have led to critical shortages. Moreover, commercially available furosemide syrup contains ethanol and propylene glycol, which may be associated with adverse events on the central nervous system, particularly in neonates. Compounding alcohol-free syrup would be an attractive alternative for the pediatric population [9-13].

This study aims to help alleviate a nationwide shortage of furosemide syrup by identifying and compounding an alcohol-free formulation by means of a literature review [11].

LITERATURE REVIEW

The authors were made up of a task force, established by the pharmacy and therapeutic committee. The authors were tasked to review extemporaneous compounding at the Ministry of National Guard Health Affairs in Saudi Arabia. A literature review was used to evaluate stability studies, supporting extemporaneous compounding of furosemide oral liquids. Sources for the literature review included Medline (accessed *via* PubMed), Google Scholar, and United States Food and Drug Administration-approved package inserts. Tertiary references such as "Trissels' Stability of Compounded Formulations" and "Extemporaneous Formulations for Pediatric, Geriatric, and Special Needs Patients" were included in the review. Search terms included 'furosemide', 'extemporaneous compounding' and 'stability'. Abstracts were reviewed for their relevance to stability design. Searches were saved in Endnote citation manager and full-text articles were sought. English language publications were considered. In the absence of full-text articles, abstracts were considered if they were supported by tertiary references mentioned above. The searches were last updated in February 2022 [14,15].

Master Formula Records (MFRs) are the documents or recipes used by pharmacy staff in preparing compounded formulations. MFRs contain necessary information and procedures ensuring safety, consistently, and accuracy. The task force compiled a MFR by extracting relevant information from each study. The retrieved literature was used to evaluate whether formulations were backed by at least one stability study. Studies were included if they incorporated valid chemical stability studies, such as High-Performance Liquid Chromatography (HPLC) and UV-spectrophotometric analyses. The compounded medicine was considered stable if it retained more than 90% of the initial drug concentration. This review included oral liquid dosage forms. It excluded oral solid dosage forms and injectable medicines. Tertiary references with inaccuracies in citations, errors in concentrations, or discrepancies in shelf-lives were excluded from the study. Studies that had no stability data or whose abstracts and full-length articles did not clearly document the MFR were also excluded from this review. Using the criteria described above, the primary investigator assessed each study and tabulated findings.

All data gathered by the principal investigator was independently reviewed by three pharmacists. Reviewers made necessary corrections during the verification process. These included concentrations, stability assay design, shelf-life, and traceable reference standards as listed in the results section. The intent was to formulate an alcohol-free liquid dosage form that would be stable for at least 30 days.

MATERIALS AND METHODS

A total of 34 publications were retrieved from the literature, while only 13 were relevant to our review. These included HPLC stability and UV-spectrophotometric analyses. Two MFRs were formulated with alcohol. One study demonstrated a 14-day shelf life. One study did not clearly mention the MFR. Alfred-Ugbenbo et al attempted to validate their analysis for a previous study. Finally, only 8 MFRs matched the inclusion criteria, as they were alcohol-free with at least a 30-day shelf life. Some studies offered MFRs with ingredients that were not available at our institution. This MFR was included in the results to illustrate a sample MFR that may be used; However 8 studies were found suitable (Table 1) [16-19].

A UV-spectrophotometric assay to demonstrate acceptable stability (30 days at 4°C or 25°C). The investigators selected alcohol-free syrup (syrup USP) due to the lack of commercially available vehicles in the Ukraine and Nigeria. The microbial growth was within limits during the study. The task force supported the formulation, as it was free from alcohol and ingredients are easily available. UV-spectrophotometric methods lack the needed specificity for quantitation. The authors nevertheless tried to validate their method in a second study (Table 2).

Although favorable stability of 90 days at 4°C or 25°C, the ingredients were not available at our institution [9]. The authors preferred a suspension-based formulation. Potassium sorbate was used as a preservative. Benzoate and parabens are ineffective in alkaline media. Benzoates are active only in the unionized form, while parabens are potentially hydrolyzed to inactive products at a pH above 8. Tween 80 was added to increase the solubility which resulted in no pH variation in the study (pH was 4.5-4.7). With 2% sodium methylcellulose, the pH was maintained at 6, while during the study period remained above 6.5 in all three vehicles. No microbial growth was observed during the 90-day study period. Storage at 25°C demonstrated fewer effects on viscosity as compared to refrigeration.

An attractive MFR with a stability of 60 days, despite the pH being less than 6 during the test period. The study incorporated HPLC design and the end product was stored at 4°C or 25°C. The authors considered safety in neonates and thus eliminated alcohol. Although xanthan gum was not available at our institution, it may be a viable option to procure. Microbiological testing was done and within limits.

Table 1: Literature review of extemporaneously compounded furosemide oral liquid dosage forms.

Citation	Concentration	Vehicle	Shelf life (Temp)	API traceability	Reviewer's comments
Alfred-Ugbenbo et al	5 mg/ml	Simple syrup (USP)	30 days (REF and RT). Glass bottles. Protect from light.	Furosemide (FRU) substance, Ipca Laboratories Ltd. India (batch 5074HRII), Furosemide tablets 40 mg («Arterium»,batch 118840, Ukraine), Furosemide tablets 40 mg («Sanofi», batch 114402, Ukraine).	Used tablet. Standard vehicles were not available justifying the use of simple syrup. Thin-layer chromatography test and UV-spectrophotometric assay. Samples were subjected to stress conditions Microbiology acceptable.
Alfred-Ugbenbo et al	5 mg/ ml	Simple syrup (USP)	-	Same Products used by Alfred-Ugbenbo et al.	Authors Alfred-Ugbenbo et al, attempted to validate the UV-spectroscopic method for determining furosemide in compounded syrups. The author concluded that the assay is accepted and has an accuracy range of 80%-120%.
Ali et al	2 mg/ml	Sugar syrup Inverted sugar syrup (citric acid) 2% Sodium methylcellulose	90 days (REF and RT)	Furosemide standard (gift from Julphar). Product details were not mentioned. Furosemide tablets 40mg ((Hoechst Marion Roussel), batch not mentioned.	Spectrophotometer stability test. Syrups contain glycerol, sorbitol 70%, tween 20, and potassium sorbate (pH 4.5-4.7). Stored in a glass bottle. Protect from light
Geiger et al	10 mg/ml	SyrSpend SF ALK®	14 days (REF)	Furosemide (Lot VG0951; Spectrum Chemicals).	Company compatibility chart. pH>7. No preservatives. HPLC assay.
Ghanekar et al	1 mg/ ml 2 mg /ml	Furosemide injection. Syrpalta (Humco) contains alcohol.	30 days (RT)	Furosemide injection. Product details not mentioned. Study mentions that all chemical and reagents were USP, but product details not mentioned.	HPLC stability test. Sugar and acidity affects stability. Stable in alkaline media. Alcohol stabilizing effects. Used furosemide injection due to pH 8.9 to 9.3. Fungus growth with Syrpalta 2 mg/ ml, despite containing sodium benzoate. Formulation with sorbitol, alcohol (10%-20%), and preservatives (methylparaben and propylparaben). pH should be adjusted
	0.5 mg/ ml 1 mg/ ml	Phosphate buffer Water			
	1 mg/ml	50% Glycerin in water 70% Sorbitol 50% Sorbitol 50% Sorbitol+20% alcohol 50% Sorbitol+10% alcohol 85% Sugar			
Nahata and Pai	1 mg/ml 2mg/ ml	Furosemide injection. Syrpalta® (Humco).	30 days (RT)	Same Products used by Alfred-Ugbenbo et al	Refer Ghanekar et al Contains alcohol.
Shoosanglertwijit et al	2 mg/ ml	Vehicle 1: Xanthan gums 0.25 g, glycerin 10 mL, syrup USP 50 mL, parabens concentrate 1 mL, purified water to 100 ml. Vehicle 2: Sodium Carboxymethylcellulose, glycerin 5 mL, sorbitol solution 20 mL, syrup USP 50 mL, parabens concentrate 1 ml, purified water to 100 ml.	60 days (REF, RT and 45°C) Protect from light. Glass bottle	Furosemide, analytical grade (Sigma-Aldrich, St. Louis, USA), furosemide tablets (FURETIC 40-mg tablet, Siam Pharmaceutical Co, Bangkok, Thailand). Batch not mentioned.	Used tablet. An attempt to avoid ethanol and PEG which are considered toxic, especially to neonates and children. HPLC stability test. Vehicle 1 is similar to Ora-sweet SF but it contains syrup. Vehicle 2 is similar to Ora-plus. PH was below 6 for the entire test. Microbiology acceptable
Sklubalová et al	2 mg/ml	Freshly prepared 7.5% (w/w) of disodium hydrogen phosphate dodecahydrate (DNaHP) Qs water for injection	30 days (RT) protect from light.	Generic product of furosemide was used. Product details were not mentioned.	HPLC stability test. Prepared for neonates. Should be preservative-free. Prepared under aseptic conditions and sterilized using a bacteria retentive filter (0.22 µm) or autoclaved.

Svirskis D et al	2 mg/ml	Ora-blend® Ora-blend SF® SyrSpend SF ALK®	30 days (REF and RT)	Abstract only, details could not be extracted.	HPLC stability test. The test was done with and without pH adjustment. The author mentioned that suspensions remained chemically stable regardless of the pH of the vehicle. Abstract only
Thaweethamcharoen, Tanita, et al	2 mg/ml	Siriraj Hospital formul (Thailand)	360 days (REF) Protect from light	Furosemide powder (Siam Pharmaceutical Co. Ltd., Bangkok), batch not mentioned. Source of tablets or syrup not mentioned.	MFR was not mentioned. UPLC (ultra-performance liquid chromatography) was done. UPLC is the same work as HPLC but under high pressure. The stability previously reported was 30 days.
Trissel LA	10 mg/ml	None (used the commercially available 20 mg/ mL product)	180 days (RT)	Traceable standard not used. Commercially available Furosemide 10 mg/mL (Lasix, Hoechst-Roussel) was used.	Repackaging from the original product. HPLC was done. Use of polypropylene syringes and amber glass bottles.
Trissel LA	1 mg /ml	Syrpalta®	30 days (RT)	Same product as Ghanekar et al	Refer to Ghanekar et al Sorbitol solution plus alcohol.
Zahálka, Lukáš, et al	2 mg/ml	Formula 1: Furosemide. Methylparaben Sodium hydroxide Saccharine sodium Water for injection Formula 2: Furosemide. Methylparaben. Disodium hydrogen phosphate dodecahydrate (DNaHP). Saccharine sodium. Water for injection.	9 months (RT) Glass bottle Protect from light	Furosemide obtained from Fagron, however the details of traceable standards was not mentioned.	The study aimed to find an alcohol-free formula for pediatric patients. HPLC stability test. The author concluded that formula 2 is more palatable and DNaHP is easier to manipulate. Ingredients are not available.

Note: API = Active pharmaceutical ingredient; DNaHP=disodium hydrogen phosphate dodecahydrate; HPLC=high performance liquid chromatography; MFR=master formula record; QS=sufficient quantity; REF=refrigerator; RT=room temperature; SF=sugar free; UV=ultraviolet

Table 2: Citation and reasons for limitations

Citation	Reason for limitation
Ali et al	Tween 80, potassium sorbate, and aspartame are not available at our institution.
Sklubalova Z et al	Disodium hydrogen phosphate dodecahydrate is not available on the formulary.
Trissel LA	Used the commercially available form which was out of stock due to product recall.
Zahálka, Lukas, et al	Ingredients not available at our institution.
Thaweethamcharoen et al	Master formula record was not mentioned.

HPLC tests with a stability of 30 days at 4˚C or 25˚C (with and without pH adjustment). The formulation was free from alcohol and was considered a suitable alternative for neonates. Vehicles are easily available and the MFR was accepted by the task force members [20-23].

Reasons for excluding some studies were due to stability (14 days) presence of alcohol, and lack of ingredients. A stability of 360 days, however, the MFR was not clear and had to be excluded [17].

DISCUSSION

In this review, we considered the stability of compounded furosemide oral liquids suitable for pediatric patients. Copies of commercially registered medicines should be avoided except under very limited conditions. The authors were tasked to compound furosemide oral liquid, due to sudden shortages in supply. Studies with longer stability data were preferred, as this would reduce pharmacy workload, patient visits, and pharmacy costs. One of the limiting factors at our institution was the lack of excipients used in some MFRs. This is due to the lack of suppliers within the Kingdom of Saudi Arabia. Safety was a priority and therefore alcohol-free formulations were preferred. Furosemide is insoluble in water and freely soluble in alkali solutions with a pH above 8. Furosemide injections should maintain a pH of 8.0 to 9.3,

while solutions should be between 7 and 10. Despite favoring an alkali pH, there were no significant differences in stability with or without pH adjustment. Regardless of the destabilizing effects of sugars, promising studies were found using simple syrup USP and sorbitol [18,20]. Some authors cautioned against the use of sugar-sweetened medications for long-term use, as it may cause dental caries[9]. In such cases, a sugar-free form may be preferred. Suspension formulations (sugar-free) were preferred with water-insoluble medicines by some authors, while Alfred-Ugbenbo et al found content uniformity and sedimentation rates within limits. Suspensions have the added advantage of masking a bitter taste [9,18,24].

With any extemporaneously compounded formulation, there is a lack of evidence in regards to long-term safety and efficacy. Our study had several limitations. Factors that were not considered were the effects of gastrointestinal absorption and sugar-sweetened medicines. Several MFRs used ingredients not available at our institution, however purchasing these may be a viable option. Traceable standards or research chemicals of active pharmaceutical ingredient can be purchased from organizations such as the USP, Thermo Fisher or Sigma Aldrich. Some studies did not report the traceable reference standard for furosemide. Using the company-manufactured form of furosemide, as a standard, would be suboptimal as compared to using an actual traceable standard [20,22,24].

Within the Saudi Arabian Market, chemical excipients are subject to importation regulations and standards and as such may not be readily available. Institutions should use a suitable formulation based on their local context and availability of ingredients. This study had found 8 suitable formulations, and only one of them was formulated due to availability of ingredients and costs of procurement. Purchasing unavailable ingredients may be a viable option; however the task force of extemporaneous compounding considered the extra costs as unfeasible (Table 3).

Table 3: Sample Master Formulation Record.

Drug name	Route	Dosage form	Concentration
Furosemide	Oral	Suspension	2 mg/ mL
Formula qty. 80 mL		Shelf life: 30 days (REF or RT)	
Equipment needed: Amber plastic bottle, mortar and pestle, graduated cylinder, stirring rod.			
Ingredients	**QS**	**Quantity**	**Units**
Furosemide 40mg	-	2	Tablets
Ora-Blend® or Ora-Blend SF®	X	80	mL

Directions:

1. Crush tablets and triturate to a fine powder in a mortar and pestle.
2. Levigate with a small amount of vehicle to form a paste.
3. Add remaining vehicle geometrically, mixing well.
4. Pour into graduate cylinder.
5. Rinse mortar with vehicle, QS with vehicle to final volume.
6. Transfer to an amber plastic bottle and label.

Auxiliary labeling/Storage: Shake well; refrigerate or room temperature. Store in an amber plastic bottle.

Note: REF=Refrigerator; QS=Quantum Satis (add sufficient quantity to achieve the desired volume); RT=Room Temperature.

CONCLUSION

Small-scale compounding of oral liquid dosage forms lacks long-term safety and efficacy data. Extemporaneous compounding of furosemide oral liquid is necessary under specific conditions. These include medication shortages or cases where the commercially available products do not meet the clinical needs of patients. Alcohol-free formulations may be safer in the pediatric population. Extemporaneous compounding may be a viable option for improving access to medication. The outcomes of this review found that there are 13 sources of literature supporting small-scale compounding of furosemide oral liquids, while 8 alcohol-free formulations may be appropriate to the local institutional context.

ACKNOWLEDGEMENTS

We declare that this study was conducted by the authors named in this article. All authors read and approved the manuscript.

SOURCES OF FUNDING

There is no any funding received for this performed work.

CONFLICT OF INTEREST

Mohammed Al-Anezi, Imraan Joosub, Zohair Emara and Dr. Eman Youssif declare that they have no conflicts of interest.

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