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A retrospective study of oral and dermatological formulations compounded via dosage form modifications at Kenyatta National Hospital from January 2020 to December 2021

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The current study aimed to elucidate the extent of compounding involving dosage form modifications at Kenyatta National hospital from 2020-2021. A total of 2205 oral formulations, containing one out of thirty-eight active pharmaceutical ingredients, were compounded from commercially available tablets or capsules during the study period. The most frequently compounded oral formulations were furosemide (34.40%), spironolactone (25.72%), and sildenafil (9.40%) suspensions, which also accounted for the highest volumes produced. The study revealed that the total volume of oral formulations compounded was 161.4L, a marked rise from 38.4L compounded in the 2012-2013 period. Oral formulations were all prepared using 40% dextrose as diluent, packaged in amber colored plastic bottles and recommended for storage at 4-8°C. The majority of the formulations (71.29%) were assigned a beyond-use date of 14 days, in compliance to the United States Pharmacopeia (USP)recommendation. A total of 17 dermatological formulations, comprising either single-entity or dual combination of three active pharmaceutical ingredients, were prepared from commercially available powders or tablets during the two-year study period. The dermatologicals were reformulated as either ointments (with emulsifying ointment as diluent) or pastes (with white soft paraffin as base), packaged in white translucent plastic jars and recommended for storage at room temperature. Nifedipine paste accounted for the highest percentage by weight and frequency of the dermatological formulations. About 75.76% of the dermatological formulation were assigned a beyond-use date of 30 days, in compliance with the USP recommendation. The study revealed that extensive compounding, involving dosage form modifications, was carried out during the study period.

Keywords: Compounding, beyond-use date, dosage form modification, oral, dermatological

INTRODUCTION

Pharmacy compounding is the art and science of preparing, packaging and labeling of personalized medications for patients based on a practitioner's prescription. This allows the compounding pharmacist to work with the patient and the prescriber to customize a medication to meet the patient's specific needs.[1] Compounding is often necessary when the dosage form and/or dosage strength available in the market are unsuitable for the particular patient. Other reasons for compounding include patient allergies to an excipient in commercial products, the need to formulate a combination product and rapid decay of formulated product in case of radiopharmaceuticals.

Compounding is wrought with many risks such as calculation errors, labeling errors, dosing errors, mix-ups, physical and microbiological contamination, exposure of personnel to harmful active pharmaceutical ingredients and drug-excipient incompatibility. Thus every compounding process must follow standardized guidelines.[2]

Most of the available oral dosage forms are tablets and capsules, which presents a challenge for pediatric or geriatric patients who have

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difficulties swallowing solids. Additionally, the tablets/capsules are manufactured to cater for adult doses, thus necessitating dose dilution during compounding for pediatric patients. Compounding oral medications for pediatrics/geriatrics often involves dosage form modifications; either crushing a tablet in a mortar and pestle or opening a capsule and then dissolving/suspending powder in a suitable diluent. The major risk with these dosage form modifications is altering the physical, chemical and microbiological stability of the original formulation. Caution must also be exercised as modified-release tablets (e.g. enteric coated tablets and sustained release tablets), should not be crushed.

The choice of compounding diluent, packaging material and storage conditions need to be critically selected, as these factors have a direct bearing on the stability of the resultant formulation. The compounding diluent, which must be compatible with the active pharmaceutical ingredient, may contain excipients such as preservatives, viscosity modifying agents, flocculating agents (suspensions), flavouring agents, sweetening agents, and buffers. The beyond-use date of these oral compounded formulations is assigned as per United States Pharmacopeia (USP)[2] recommendation of 14 days, or longer after extensive stability studies have been carried out.

Compounding involving dosage modifications of essential oral drugs is widely practiced in Kenya but only one published study elucidated the extent, nature, stability of oral compounded medications in Kenyatta National Hospital during the period 2012-2013.[3] No similar study prior or after the 2012-2013 period was found from a literature search.

Topical dosage form modifications may include incorporation of a crushed tablet into a suitable base to change the administration route of various prescription dermatological agents, for example sirolimus.[4] The choice of compounding base, packaging material and storage conditions must be rational. The beyond-use date of these topical compounded formulations is assigned as per USP [2] recommendation of 30 days. There is a paucity of data on topical dosage form modifications locally. The goal of this study was to determine the extent and nature of extemporaneous preparation, involving dosage form modifications, of oral and dermatological products in Kenyatta National Hospital during the 24-month period from January 2020 to December 2021.

METHODOLOGY

Study site

This study was carried out in the Kenyatta National Hospital (KNH) Manufacturing Unit where oral and dermatological products are extemporaneously prepared. KNH is a Level 6 national and referral hospital, handling special cohorts of patients including pediatrics and geriatrics.

Study design

The study was a retrospective study that was conducted by collecting data from the compounding logs for the period of January 2020 -December 2021.The data was entered into a Microsoft Excel spreadsheet and the following information was extracted: Date of preparation, name of Active Pharmaceutical Ingredient (API), strength, dosage form, excipients, diluent (or base for ointments and creams), volume/weight, beyond use date, packaging and storage conditions. Incomplete and illegible records were excluded from the study.

Ethical approval

The study involved access to compounding logs which are part of patients' medical records. Ethical approval to conduct the study was granted by the KNH/UoN ERC (Ethics Research Committee) under approval number UP92/02/2022.

Data analysis

The data was analysed using Microsoft Excel (Microsoft Corporation, Redmond, WA, USA) 2013. The results were presented as pie charts for display of volumes and frequency of formulations.

RESULTS AND DISCUSSION

The study investigated compounding, involving dosage form modifications, to formulate oral suspensions as well as dermatological ointments and pastes. Oral formulations were compounded from commercially available tablets or capsules, while dermatological formulations were compounded from commercially available powders or tablets.

Oral formulations

A total of 2205 oral liquid formulations were compounded over the two-year study period. Each formulation incorporated one of 38 active pharmaceutical ingredients (API). The APIs included: acetazolamide, acyclovir, allopurinol, amitriptyline, benzhexol, captopril, carvedilol, cetirizine, cholestyramine, ciprofloxacin, clindamycin, clonazepam, desmopressin, digoxin, enalapril, folic acid, furosemide, gabapentin, hydrochlorothiazide, hydralazine, hydroxyurea, labetalol, levetiracetam, levofloxacin, levothyroxine, nifedipine, nitrofurantoin, phenobarbital, phenytoin, propranolol, pyridoxine, sildenafil, sodium bicarbonate, spironolactone, tranexamic acid, ursodeoxycholic acid, valganciclovir and warfarin.

The oral liquid dosage forms were all reformulated as suspensions. The formulations were prepared using 40% w/v dextrose as diluent, carboxymethyl cellulose as viscosity modifying/suspending agent with methyl paraben and propyl paraben as preservatives. The choice of dextrose as diluent, enhanced palatability of the formulation by masking the bitter taste of the APIs. The compounded formulations were packaged in amber colored bottles, ideal for light sensitive drugs, with a snug-fitting white lid. The recommended storage temperature for all oral compounded formulations is 4-8°C which is the standard refrigerator temperature range.

Volumes of oral formulations compounded

The total volume of oral compounded formulations during the two-year study period was 161.36L. This is a four-fold increase from the 2012-2013 study period in which the total volume compounded was 38.4L.[3] The formulations with the highest percentage volumes compounded were furosemide (35.23%), spironolactone (27.04%), sildenafil (11.49%), enalapril (4.58%), levetiracetam (3.73%) and ursodeoxycholic acid (3.16%). The total volume of the above six drugs is 137.52L. This comprises 85.23% of the total volume compounded. The remaining percentage accounted for the remaining 32 drugs. Some of these drugs were compounded in very low volumes of below 80 ml, because each formulation was tailored for an individual patient some of whom were neonates with low dosing requirements. They include: amitriptyline (73 ml), captopril (31 ml), cetirizine (62 ml), folic acid (65 ml), hypertonic saline (63 ml), levofloxacin (70 ml) and valganciclovir (51 ml).

Frequency of compounding of oral formulations

The most frequently compounded APIs were furosemide (34.40%), spironolactone (25.72%), sildenafil (9.40%) and enalapril (7.69%), which accounted for 77.21% frequency of the compounded medications.

It was noted that the oral formulations were compounded in multiple strengths, dependent on the weight of the pediatric patient and indications. For instance, furosemide suspension was compounded in 21 different strengths, spironolactone suspension in 33 different strengths, and sildenafil suspension in 41 different strengths. This observation highlights the complexity of weight-dosing in pediatric patients. It was also noted that the formulation strengths were given in varying ratios, namely dose/1 ml; dose/1.5 ml; dose/2 ml; dose/2.5 ml; dose/3.5 ml; dose/5 ml increasing the chances of errors while compounding, dispensing. It is recommended that the dosage strengths are standardized.

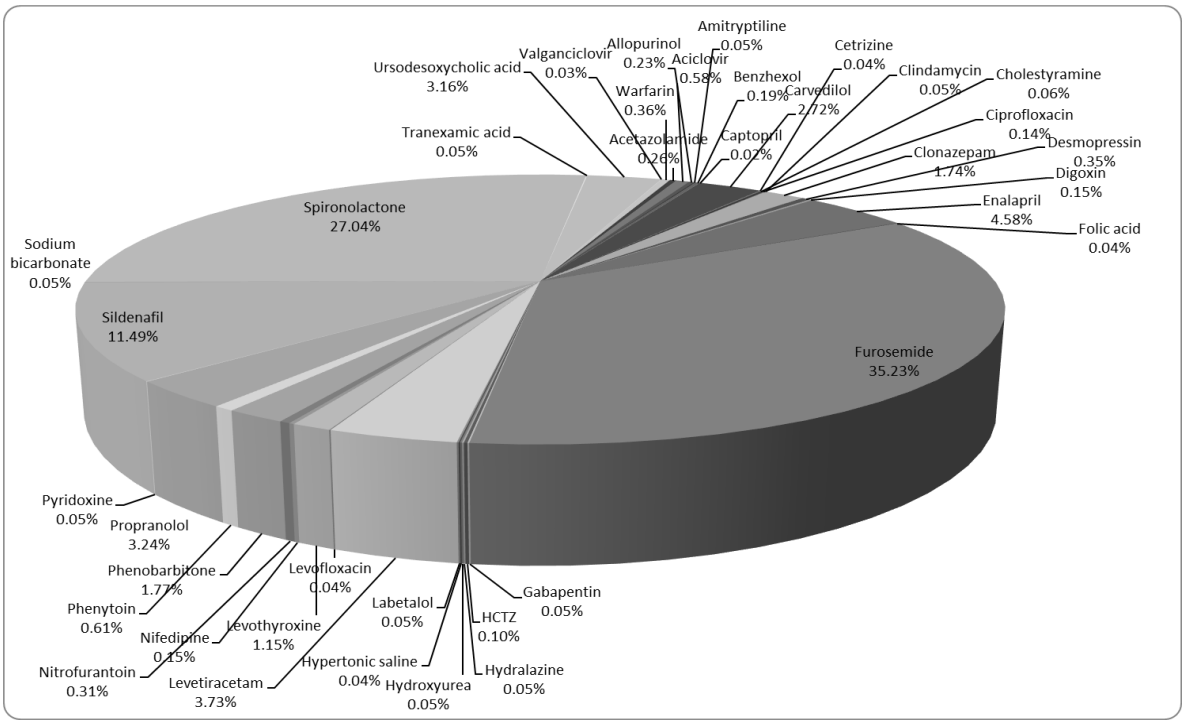

Figure 1: Percentage volume of oral formulations compounded at Kenyatta National Hospital in the year 2020-2021

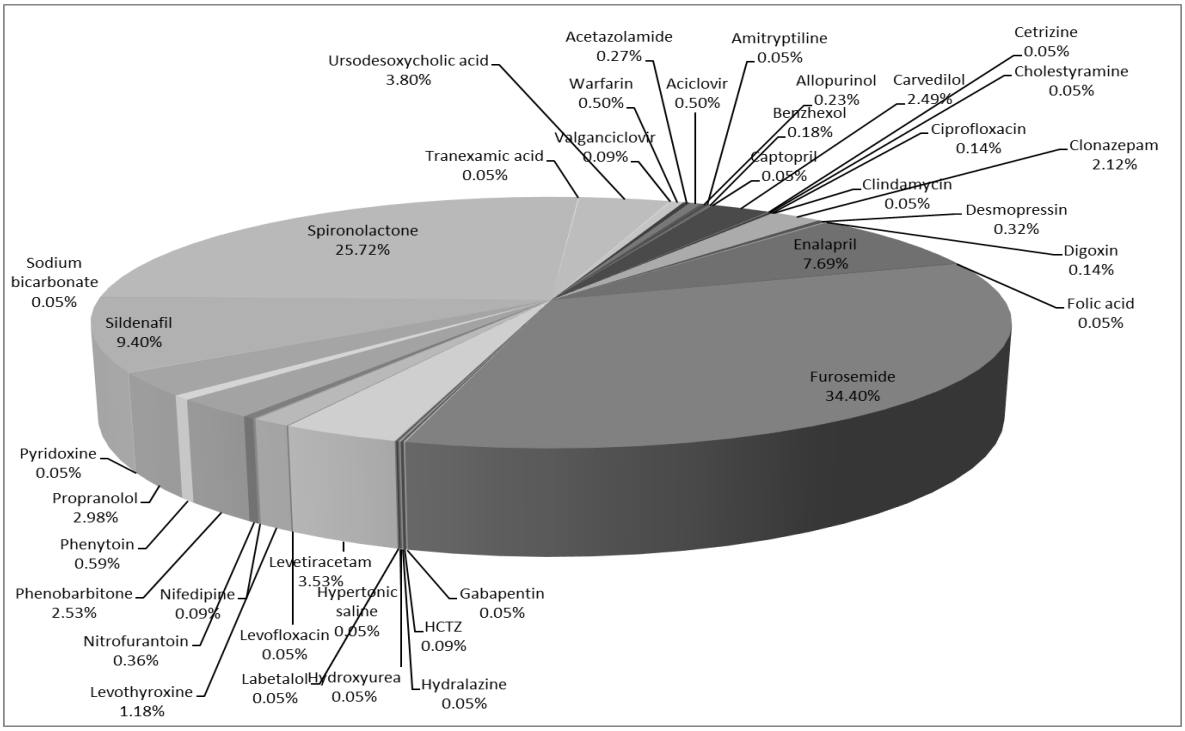

Figure 2: Percentage frequency of oral formulations compounded at Kenyatta National Hospital in the year 2020-2021

Beyond use dates assigned for the oral formulations ranged from 5 days to 17 days. However, the majority of the formulations (71.29%) were assigned beyond-use dates of 14 days, in accordance with USP recommendation. Some formulations were assigned beyond-use dates of 13 days or 15 days indicating some likely misnumbering of the USP 14-day guideline.[2]

Most compounded formulations contained cardiovascular drugs (85.08%) namely acetazolamide, captopril, carvedilol, digoxin, enalapril, furosemide, hydrochlorothiazide, hydralazine, labetalol, nifedipine, propranolol, sildenafil and spironolactone. Acetazolamide is used for many conditions including metabolic alkalosis in pediatric intensive care, certain kinds of seizures and to eliminate excess fluid. Captopril and enalapril are used in pediatrics in the management of heart failure in situations where there is no structural heart disease, with left ventricular systolic dysfunction such as dilated cardiomyopathy while sildenafil is a phosphodiesterase-5 inhibitor used for the management of pulmonary arterial hypertension in pediatrics. Loop diuretics such as furosemide, are recommended for patients with heart failure and symptoms of congestion. Patients who are not responsive to furosemide can be put on hydrochlorothiazide. Spironolactone therapy is used in children with chronic systolic heart failure. Beta blockers such as labetalol, propranolol and carvedilol can be used in pediatric left ventricular systolic dysfunction. Hydralazine is used for the management of hypertension and heart failure in pediatrics. Management of pediatric cardiovascular conditions is quite challenging as most medicines particularly off-label medicines [5], are not available in age-appropriate formulations/dosages often necessitating compounding. Other than cardiovascular drugs, the rest of the formulations comprised central nervous system drugs (8.57%), bile acid sequestrants (3.22%), while the remaining percentage comprised of anti-infectives, supplements, anticoagulants and supplements.

The compounding of oral formulations, involving dosage form modifications, markedly increased in terms of frequency, volume and the active pharmaceutical ingredients relative to the study carried out in 2012 -2013 which found 392 oral liquid formulations totaling up to 38.4L in volume and comprising either of 19 active pharmaceutical ingredients.[3] The current study period which coincided with the COVID-19 pandemic saw drugs like benzhexol, ciprofloxacin, clindamycin, levofloxacin, desmopressin, cetrizine and ursodeoxycholic acid, among others, being added to the compounding list. Cetrizine, clindamycin and levofloxacin suspensions are commercially manufactured and available in the local market. However, due to the repurposing of drugs, drug shortages, the increased demand of antibiotics and cough medicines during the pandemic, it was necessary to compound these drugs.

Dermatological formulations

A total of 17 dermatological formulations with a total weight of 1.04 kg were compounded over the two-year study period, indicating preponderance of oral formulations among compounded products. Only those formulations where tablets were crushed or powders added to the base were reported. Those formulations compounded by simply blending commercially available creams, ointments, gels and/or bases were excluded from the study. Each formulation contained either single-entity or dual combination of three active pharmaceutical ingredients namely betamethasone, salicylic acid and nifedipine.

Nifedipine paste was formulated from crushed nifedipine tablets with white soft paraffin as base. Betamethasone-salicylic acid ointment was formulated from salicylic acid powder with betamethasone ointment as the base. All dermatological formulations were packaged in plastic, translucent jars with snug-fitting lids and recommended for storage at room temperature.

The formulations were compounded in either one (betamethasone-salicylic acid ointment) or two strengths (nifedipine paste). Nifedipine paste and accounted for the highest percentage weight (72.12%) and percentage frequency (88.24%) of the compounded formulations respectively.

The majority of the dermatological formulations were assigned a beyond use date of 30 days in line

with USP recommendations.[2] Nifedipine paste is intended for rectal application for the treatment of hemorrhoids and anal fissures, while betamethasone-salicylic acid ointment exerts both anti-inflammatory and keratolytic action on topical application.

The current study elucidated compounding of topical formulations, involving dosage form modifications, thus may serve as a baseline as no prior studies were found on literature survey. Notably, the 2012-2013 study only focused on oral medications.

CONCLUSION

Compounding involving dosage form modifications, particularly for oral medications, was extensively carried out at Kenyatta National Hospital during the study period. There was a marked increase in the volume, frequency and active pharmaceutical ingredients compounded relative to 2012-2013 period, indicating a higher demand for the previously compounded formulations as well as emergence of new compounded formulations.

This trend observed emphasizes the emerging importance of compounding in patient care. There is need to invest resources to continually optimize compounding practices and products. Furthermore, use of the active pharmaceutical ingredient powders for compounding, as opposed to dosage form modifications should be explored. Extensive stability studies would optimize compounded products allowing for compounding and dispensing of larger quantities, without the limitation of the arbitrary two-week or thirty days beyond use date for oral and topical formulations respectively. The study also provides product developers with insights into which products are needed in the market.

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REFERENCES

(1) Kochanowaska-Karamyan, A.J. Pharmaceutical Compounding: The Oldest, Most Symbolic, and Still Vital Part of Pharmacy. *Int. J. Pharm. Comp*. **2016**, 20(5), 367-374.

(2) United States Pharmacopeial Convention. USP General Chapter <795> Pharmaceutical Compounding- Nonsterile Preparations in USP 34 – NF 29; United States Pharmacopeial Convention: Rockville, MD, USA, 2020.

(3) Bilakhia, N.A.; Tirop, L.J.; Menge, T.B.; Kuria, K.A.M. A Retrospective Study of Oral Medications Compounded for Pediatric patients at Kenyatta National Hospital. *East Cent. Afr. J. Pharm. Sci*.**2014**, 17 (3), 64–69.

(4) Brichta, L.;Carver, J.G.; DeKlotz, C.M.C. Topical sirolimus: Difference between Compounded Preparations and Commercial Oral Solution. *Ped. Derm*. **2021**, 38, 967-969.

(5) Kimland, E.; Odlind, V. Off-label Drug Use in Pediatric Patients. *Clin. Pharmacol. Ther*. **2012**,91, 796–801.