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RESEARCH PAPER

ASSESSMENT OF THE PHYSCIO-CHEMICAL AND MICROBIAL QUALITY OF SELECTED EXTEMPORANEOUS PAEDIATRIC ORAL FORMULATIONS FREQUENTLY PREPARED AT KOMFO ANOKYE TEACHING HOSPITAL IN KUMASI

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ABSTRACT
The Komfo Anokye Teaching Hospital (KATH) pharmacy prepares paediatric formulations of unavailable dosage forms on daily basis for children with a variety of acute and chronic diseases. This study assessed the physical and microbiological quality, and chemical stability of extemporaneous oral paediatric formulations prepared in this facility. The study team surveyed the hospital for unavailable formulations which were requested and prepared extemporaneously in the hospital's pharmacy. Stability studies were then conducted on the six (6) most frequently prepared paediatric suspension formulations namely; acetazolamide, spironolactone. propranolol, furosemide, phenobarbitone and lamivudine. These were prepared in accordance with KATH approved formulation procedures. HPLC and the agar diffusion methods were employed in the analysis. The formulated suspensions of spironolactone and furosemide were microbiologically and chemically stable up to 30 days. Lamivudine suspension was stable both chemically and microbiologically up to 60 days. The acetazolamide suspension was not stable up to a 30 days' mark. Phenobarbitone and propranolol suspensions were highly unstable even within 30 days and therefore, might require refrigeration to maintain their stability. The results showed that the formulated suspensions had sufficient microbial integrity and a range of active content stability, which suggested suitability for use as follows; lamivudine suspension up to 60 days, spironolactone and furosemide suspensions up to 30 days; acetazolamide, phenobarbitone and propranolol suspensions possibly up to 2 weeks, after preparation.

Keywords: *Paediatric, extemporaneous formulations, microbial integrity, content stability*

INTRODUCTION

Drug therapy plays a vital role in disease management for paediatric populations having a variety of acute and chronic diseases. Out of the many drugs approved and marketed for adults, only about one fourth are specifically indicated for use in paediatric populations (Breitkreutz, 2008). Drugs that are not specifi-

cally authorized for use in infants and children, and even a lot of those authorized are often unavailable in suitable paediatric dosage forms (Yir-Erong *et al.,* 2018: Sinha and Cranswick. 2007). For instance, drugs such as phenobarbitone, aminophylline and spironolactone which are authorized (by FDA) for paediatric use are not available in the appropriate dosage forms (Australian government, 2008; Marriot *et al.,* 2010). As such, compounding paediatric dosage forms of these drugs with the appropriate excipients remains a significant portion of the Pharmacist's daily functions in paediatric settings or units (Breitkreutz. 2008; Ceci *et al.,* 2006). It is therefore essential to determine the stability of various drugs at clinically important concentrations and safe practical storage conditions.

There are significant challenges associated with drug treatment options available for paediatric populations. Most children struggle to swallow tablets and capsules, while a lot more have acute innate resistance for injections due to pain and the fear of needles. which leads to significant patient noncompliance (Yir-Erong *et al.,* 2018). Although most paediatric oral medications come in the form of liquids which are more easily swallowed, these require the need for masking of bitter taste and unpleasant smell of some active ingredients. Current approaches using high sugar concentrations and sweeteners may present dental, obesity and type 2 diabetes concerns. The WHO model formulary for children provides independent prescriber information on dosage and treatment guidance for medicines based on the WHO model list of essential medicines for paediatrics (WHO. 2007: Boateng. 2017). Some of the desirable features that are essential and need to be taken into consideration when designing paediatric dosage forms include: convenient, reliable administration and preferably ready-to-use formulations; minimal manipulations by healthcare professionals, parents or caregivers; dose and dose volume/weight adjusted to the intended age-group: acceptable and palatable dosage form with minimum dosing frequency, minimal impact on lifestyle and minimum nontoxic excipients: transportable and low bulk/weight easy to produce and stable in a variety of climates, affordable and commercially viable (PIC/S, 2008; Australian Government, 2008; Yir-Erong *et al.,* 2018). Ideally, paediatric oral dosage formulations must be easy to prepare and administer. The formulation must have the appropriate drug concentration and volume for accurate administration. The taste should be palatable for compliance and the formulation should be stable up to the expiry date (Giam and McLachlan. 2008). In extemporaneous compounding. tablets and capsules of the drugs. are used to prepare suspensions. These modifications of adult dosage forms for paediatric purposes are usually done for immediate use, otherwise proof of stability of the reformulated medication should be available. This is necessary because manufacturers provide stability data for only their original products and very few pharmacy units are equipped with the capacity to conduct microbiological quality assurance and chemical stability studies on extemporaneous products using standard laboratory methods (Barnes, 2007).

For over four decades now the Komfo Anokye Teaching Hospital (KATH) in Kumasi, Ghana, has been thriving to meet some of the medication needs of neonates, infants and children who are brought to the hospital. The KATH Pharmacy prepares extemporaneous paediatric formulations from adult dosage forms such as tablets, capsules and injections to meet the medication needs of these children. KATH as a referral hospital in the Ashanti Region of Ghana, serves the whole of the northern parts of the country. Infants and children diagnosed with chronic disease conditions and on long term medication with these formulations have to come weekly. fortnightly or monthly for refills due to formulation stability concerns. Although some stability reports are cited and used for the formulations, there is currently no documented evidence on stability of these paediatric dosage formulations prepared at KATH. As more infants and children are being diagnosed with diseases that are known in adult life without the appropriate dosage forms of medications, there is the need to carry out studies on the formulations to ascertain the stability, efficacy and safety of these preparations to guarantee their continuous usage.

This study therefore sought to survey the types

of oral paediatric formulations extemporaneously prepared at KATH and to select the most frequently requested, for physical and chemical stability and microbiological quality analysis. Realization of an appreciably long term stability of these products could lead to a reduced frequency of hospital visits of parents for their wards' medication refills.

MATERIALS AND METHODS

Survey and selection of formulations for the study

The KATH Child Health-Directorate (established in 1983) is a referral Centre for neonates, infants and children from the Northern and sometimes the Western parts of Ghana, aside catering for the Ashanti Region and training of clinical students (medical, dental, pharmacy and nursing). On a yearly basis the directorate provides various forms of services to nearly 12,000in-patients and 21,000 outpatients (KATH, 2017).

Drug therapy plays a vital role in the management of diseases of these paediatric populations. However, many of the drugs prescribed for these patients are not available in paediatric dosage forms. Paediatric dosage forms are therefore extemporaneously compounded at the KATH Pharmacy for these patients. From our survey in January to June 2017, the KATH pharmacy drug production unit received requests and prepared various quantities of paediatric formulations from adult dosage forms, totalling 1078 units of products (Table 1). The six (6) most frequently prepared formulations (Table 2), constituting 83.2% of all the paediatric oral dosage forms prepared within the period were selected for this study.

Materials

Pharmaceutical additives used in the formulation of the suspensions

Methylcellulose and carboxymethylcellulose (CMC) as suspending agents have widely been reported to be suitable and compatible with most drugs (Barnes, 2007; Marriot *et al.,* 2010). As such. CMC has been the main suspending agent employed in the KA TH pharmacy formulations. Aspartame and sodium benzoate are also used as sweetener and preservative, respectively; while sunset yellow serves as a colourant. Purified water usually served as the vehicle and 50 ml clear amber plastic bottles with closures were used for packaging.

Reference active pharmaceutical ingredients

The active pharmaceutical ingredients (APIs) used as standards were obtained from Ernest Chemists Ltd, Ghana; except Lamivudine which was obtained from Global Pharma Health Fund (GPHF).

Materials for microbiological analysis

All the microbiological growth media used were obtained from Oxoid Cambridge, UK. These included Nutrient agar, Sabouraud agar, MacKonkey agar and Bismuth Sulphite agar. All other reagents and solvents used were of analytical and HPLC grades.

Working environment

The extemporaneous compounding of the products was done in the KATH pharmacy aseptic preparation room.

Methods

Preparation of the paediatric suspensions

The suspensions were prepared using a modified form of the USP-NF (2018) method for formulating paediatric oral dosage forms from adult dosage forms with a mortar and pestle.

Formula

Active ingredient (i.e. from the required number of tablets)

Carboxymethylcellulose (CMC, low viscosity)	0.24%
Sodium Benzoate	0.20%
Aspartame	0.132%
Purified water to	qs

General procedure

The required number of tablets for 1 L of suspension of the appropriate drug were crushed and triturated into a fine powder using a porcelain mortar and pestle. The sodium benzoate (2.0g) and aspartame (l.32g) were separately and accurately added with further trituration into a smooth fine mix. The low viscosity grade

Table 1: Paediatric formulations prepared at KATH Pharmacy from January to June 2017

SN	FORMULATED SUSPENSION	JAN	FEB	MARCH	APRIL	MAY	JUNE	TOTAL	%
1	**Acetazolamide**	3	7	2	**12**	**14**	**10**	**48**	**4.45**
2	Acyclovir		3	3	2	1		9	0.83
3	**Spironolactone**	**59**	**43**	**51**	**68**	**76**	**65**	**362**	**33.58**
4	Allopurinol			1	2	1		4	0.37
5	Amlodipine					2	**1**	3	0.28
6	Artane				2			2	0.19
7	Atenolol				1	1		2	0.19
8	Azathiopine	1						1	0.09
9	Azithromycin		1					1	0.09
10	Buscopan				3			3	0.28
11	Ciprofloxacin	5	2	6	4	3	1	21	1.95
12	Clindamycin	2	4		1			7	0.65
13	Clonazepam	1		2		4		7	0.65
14	Dexamethasone						1	1	0.09
15	Deoxycholic acid				1	2	1	4	0.37
16	Digoxin	1	1	1	1	1		5	0.46
17	Enalapril	5	7	5	5	5	3	30	2.78
18	Fluconazole		1	1	1			3	0.28
19	**Frusemide**	**67**	**52**	**60**	**70**	**54**	71	**374**	**34.69**
20	Haloperidol				3			3	0.28
21	Isoniazid					1		1	0.09
22	Itraconazole					1		1	0.09
23	**Lamivudine**	6	4	8	2	5	4	**29**	**2.69**
24	Levetracetam		1			1		2	0.19
25	Lisinopril			1	1	1	1	4	0.37
26	Loperamide			1				1	0.09
27	Losartan					1		1	0.09
28	Methyldopa						1	1	0.09
29	Nitrofurantoin	2	1	1	2		5	11	1.02
30	Ofloxacin	6						6	0.56
31	Omeprazole		4	1	7	8	2	22	2.04
32	Penicillin V				1		1	2	0.19
33	**Phenobarbitone**	**18**	1	**10**	9	**12**	11	**61**	**5.66**
34	Phenytoin						1	1	0.09
35	Prednisolone	2	1			2	3	8	0.74
36	**Propranolol**	1	4	5	5	1	7	**23**	**2.13**
37	Pyridoxine					1		1	0.09
38	Sildenafil	1	5	3	2		1	12	1.11
39	Sodium Valporate						1	1	0.09
	TOTAL							**1078**	**100**

Table 2: The six most frequently prepared oral paediatric drug formulations at KATH selected for the study

Paediatric suspensions compounded	Indications of use at KATH	Paediatric dose regimen	Adult dosage forms commonly used
Acetazolamide	Diuretic/reduction of fluid in the body	5mg/kg/6-12hours	Acetazolamide 250*mg* tablets (Ernest Chemist Ltd. Ghana)
Furosemide	Diuretic/reduction of fluid in the body	1 mg/kg/12hours	Furosemide 40mg tablets (Bristol Lab. Ltd. UK)
Spironolactone	K^+ sparing diuretic	1-3mg/kg/day	Spironolactone 50mg tablets (Ernest Chemist Ltd, Ghana)
Propranolol	Beta blocker for hypertension	0.5-1mg/kg/day (not >8mg/kg/day)	Propranolol 40mg tablets (Ernest Chemist Ltd, Ghana)
Phenobarbitone	Anticonvulsant.	10mg/kg/day	Phenobarbitone 60mg tablets (Kinapharma Ltd, Ghana)
Lamivudine	Anti-HIV	4mg/kgll2hours (8mg/kg/day)	Lamivudine 150mg tablets (Cipla, India)

CMC (2.4g) was thoroughly mixed with 500 ml of purified water into a uniform syrup-like solution with the aid of a magnetic stirrer, after which the content of the mortar was carefully transferred into it. Enough purified water was added with further stirring and the product made up to 1L **(**Table 2). The pH of each formulated suspension was determined upon preparation **(**Table 3). The products were then packaged in 50 ml portions into clear, amber plastic bottles, sealed with closures and labelled appropriately.

Storage and analysis of formulated suspensions

The suspensions were stored at room temperature (27 ± 3°C). Samples were taken at time intervals of 0, 30, 60, 90 and 120 days for physical and chemical stability, and microbiological quality analysis. Samples that showed evidence of instability or deterioration at any point were not analysed further.

Physical stability evaluation

The organoleptic properties of the suspensions were assessed over the storage period by observing for changes in product colour, odour and flavour.

Spectrophotometric assay of formulations

High performance liquid chromatography (HPLC) was used to analyse the suspensions to determine the percentage content of the active pharmaceutical ingredient present; immediately after formulation and at the end of the specified storage periods under the set out conditions (USP-NF, 2018). The specific analytical conditions employed per product were as outlined in Table 3.

Microbiological quality analysis

The microbiological quality of the suspensions was assessed using the method stated in the British Pharmacopeia (2018) with slight modifications. Generally, 20 ml quantities of molten Nutrient and Sabouraud agars (at 50°C) were aseptically poured into sterile petri dishes and 1.0 ml aliquots of the suspensions were transferred at time intervals of 0, 30, 60, 90 and 120 days, into the plates.

After thorough mixing of the contents, the

Table 3: HPLC analytical test conditions for the formulated suspensions

Suspension	Specific analytical conditions Column	Temp (℃)	Wave-length (λ}{nm)	Injection volume (µl)	Flow rate (ml/min)	Mobile phase
Acetazolamide 5mg/ml (pH 6.20)	Zorbax 5B-C18 (3.9x300 mm) 5µ	28	254	20	2	Sodium nitrate :water :acetonitrile (95:2:3)
Spironolactone 1 mg/ml (pH 6.88)	Agilent Pep-C18 (3.9x300 mm)5µ	28	230	20	2	Methanol: water :acetonitrile (70:15:15)
Furosemide 1 mg/ml (pH 5.30)	Zorbax 5B-C18 (3.9x300 mm) 5µ	28	230	20	2	Water: acetonitrile: acetic acid (81:18:1)
Lamivudine 10mg/ml (pH 6.10)	Zorbax 5B-C18 (3.9x300 mm) 5µ	35	277	20	1	Methanol: Ammonium acetate (95:5)
Phenobarbitone 3mg/ml (pH 5.90)	Zorbax 5B-C18 (3.9x300 mm) 5µ	60	235	5	1	Water :acetonitrile (70:30)
Propranolol 1mg/ml (pH 5.80)	Pheno mene-rC8 (4.6x150 mm) 5µ	28	290	20	1.5	Methanol: acetoni-trile :sodium dodecyl sulphate (36:36:28)

plates were allowed to set and incubated (Nutrient agarat 37℃ for 36 hand Sabouraud agar at 25℃ for 5 days). Triplicate experiments were performed on each suspension and the number of colonies appearing on the plates were counted and used to determine the mean counts for the suspensions. The presence of *Escherichia coli* and S*almonella* species were also assessed by cultivating 1.0 ml quantities of the various suspensions on MacConkey and Bismuth Sulphite agars, respectively.

RESULTS AND DISCUSSION

The KATH Child Health Directorate is a major referral centre for neonates, infants and children. Paediatric outpatients with chronic health conditions usually visit the hospital every four months for review and those on drug treatment of which the appropriate paediatric dosage forms are not available in the market even visit more frequently (monthly and bi-weekly) for medication refills; which are compounded in the KATH pharmacy (Table 1). The six most frequently compounded paediatric oral suspensions were; Spironolactone, furosemide, Phenobarbitone, acetazolamide, lamivudine and propranolol. These formed about 83% of the total paediatric dosage forms prepared and dispensed within the period (Table 2).

Acetazolamide. furosemide and spironolactone are diuretics used in the management of congenital cardiovascular anomalies in neonates, infants, and children. Lamivudine. an antiretroviral agent is used in the management of HIV infection. Phenobarbitone is used as an anticonvulsant, whilst the propranolol (a beta-blocker) is used to treat tremors, angina and hypertension, and heart rhythmic disorders (Porter, 2011). These drugs are therefore used in specialized care. However, the total dosage requirements of these medications in paediatric disease management are small and demand is relatively low, so manufacturers do not find such child specific formulations economically viable to put on the market.

These selected specialized care drugs with chemical structures as shown in Fig. 1 were

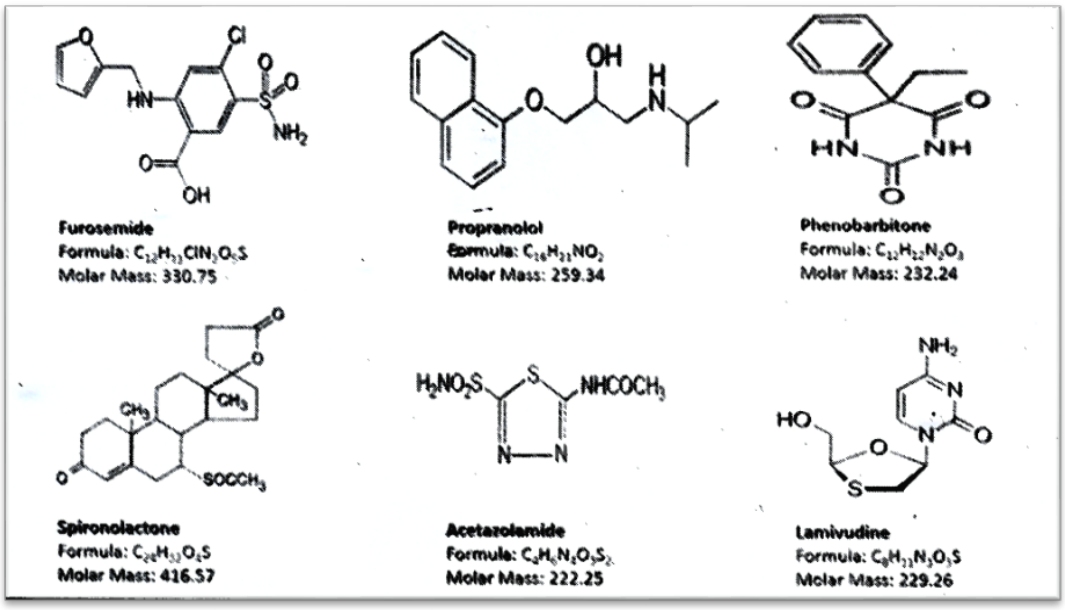


Fig. 1: Chemical structures and formulae of the selected drugs

investigated for physical and chemical stability, and microbiological quality in order to ascertain their efficacy and safety to justify their continuous formulation and provide indications of safe duration of use.

Physical stability

The suspensions of the selected drugs showed no changes in colour, odour and flavour during the period of the stability studies.

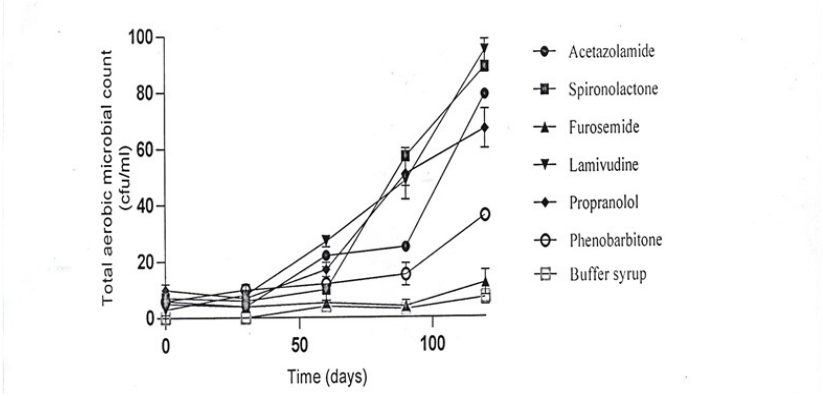
Microbial quality assessment

Both the USP-NF (2018) and the BP (2018) states the acceptance criteria of total aerobic microbial count (TAMC) and total yeast/mould count (TYMC) of non-sterile pharmaceutical dosage forms to be $\leq 2.0x10^2$ CFU/ml and $\leq 2.0x10^1$ CFU/ml, respectively. The microbial counts of the suspensions were all within the official acceptance limits throughout the 120 days of storage (Fig. 2). Also, *E. coli* and *Salmonella* species were not detected in any of the suspensions.

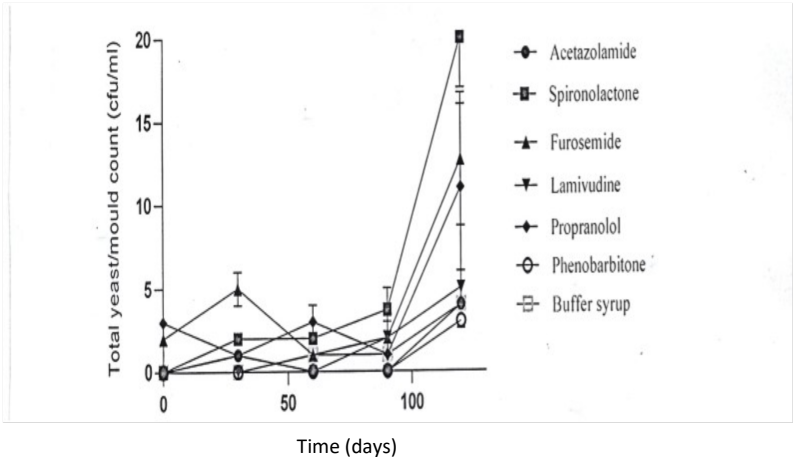
Sodium benzoate was used as the preservative in these suspensions. The effectiveness of sodium benzoate as a preservative increase with decreasing pH. This is because the ratio of undissociated benzoic acid to the ionized form increases as the pH decreases. This probably explains why the sodium benzoate was quite more effective in all the formulations with pH values lower than and up to about 6.00; than in those such as spironolactone suspension with pH values close to 7.00 (Table 3).

Sodium benzoate is a microbiostatic agent. Its action is by the absorption of benzoic acid into the cells of microorganism (Hodges, 2007). If the intracellular pH gets to about 5 or lower, the anaerobic fermentation of glucose through phosphofructokinase decreases drastically, resulting in the inhibition of growth and survival of microorganisms that cause instability in pharmaceutical products. It is also clear that the use of sodium benzoate in the preservation of these suspensions is partly economic, as majority of the patients cannot afford relatively more expensive products resulting from the use of expensive alternative excipients.

In the nut shell, the 0.2% sodium benzoate was effective in preserving and ensuring the microbial safety of the suspensions for use, more



(a) TAMC-Acceptance criteria for non-sterile dosage forms is ≤ $2.0xl0^2$; $n = 3$ (BP, 2018)



(b) TYMC-Acceptance criteria for non-sterile dosage forms is ≤ $2.0xl0^1$; $n = 3$ (BP, 2018)

Fig. 2 (a & b): Microbiological load of the formulated suspensions

especially up to 90 days after formulation and storage at room temperature.

Content of active ingredient

No pharmaceutical product is stable indefinitely, which is why all drug formulations have expiry dates. Obviously, microbial content or growth is not the only cause of drug instability. The instability of pharmaceutical products may be as a result of drug and or excipient degradation. The degradation may be exacerbated by poor formulation process, packaging and inappropriate storage conditions. Light, temperature and humidity may also influence chemical degradation of pharmaceutical products. Therefore. the appropriate packaging and storage conditions must carefully be selected to reduce degradation so as to improve on the stability of the product. Instability of pharmaceutical products results in reduction or loss of active drug content.

The HPLC analysis of the suspensions generally indicated a gradual reduction in the active constituents on storage. However, the loss of active constituent was more rapid in some formulations than others **(**Fig. 3). The acceptable criteria for content of active constituents for most of the formulated suspensions is 90 - 110%, when stored at room temperature (lP, 2018). From the results of the study. the formulated lamivudine suspension had active content of 93%, (hence within the acceptable criteria) even after 60 days of storage. The content however dropped to 83% (well below the accepted range) by day 90. The active contents of spironolactone (95%) and furosemide (93%) suspensions were within the acceptable range for up to 30 days, but those of acetazolamide (69%), propranolol (17%), and phenobarbitone (54%) were far below the acceptable limits within this same period.

The results suggest that lamivudine suspension compounded in KATH pharmacy is safe and effective for use within a period of 60 days of preparation, while the spironolactone and furosemide suspensions may be acceptable within 30 days. Suspensions of acetazolamide, propranolol and phenobarbitone will have to be used within much shorter periods. probably 2 weeks after preparation and may even require refrigeration to maintain their integrity and remain within specifications.

To the best of our knowledge, this seems to be the first report of stability studies of extemporaneously prepared oral lamivudine suspension. as there appears to be no available data in the literature to support it. The acceptance criteria of spironolactone suspension is 90 -110% active content at a storage condition of 2 - 8°C (Shakir and El-gied, *2015).* In this study, the storage was at room temperature (27±3°C) and the content was within acceptable range up to 30 days. This is supported by Nahata *et al.* (2004) who reported of spironolactone oral suspension formulated from *25mg* tablets methylcellulose (0.3%) and simple syrup (40%) being stable in content for 91days at room temperature. Also in that study, oral furosemide liquid prepared from an injection formulation with *syrpalta* (oral syrup vehicle) as a base and stored at room temperature was stable for 30 days; which also lends support to the results of this study.

However, an acetazolamide oral suspension formulated using 250mg tablets, syrup (30 %), methylcellulose (0.3%), Veegum (1 %) and

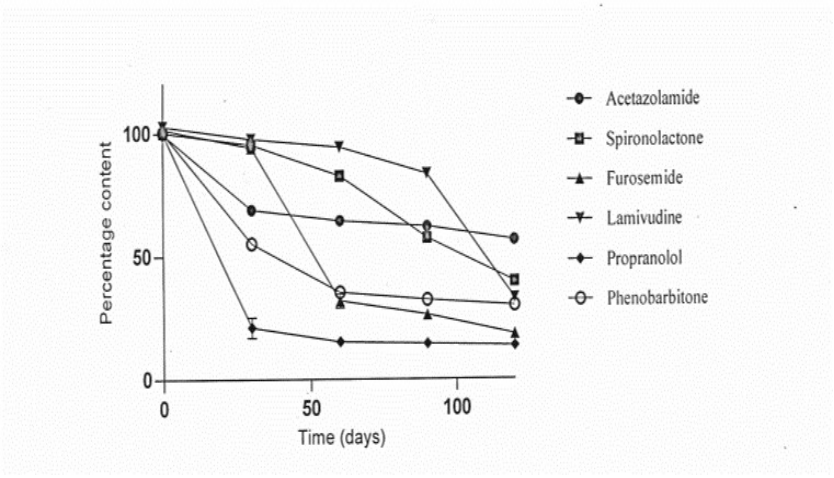


Fig. 3: Content of active ingredient in the suspensions on storage

parabens concentrate was stable for 79 days. This does not support our findings, though different and much superior excipients were employed in the formulation in that study. Therefore, by probably modifying the excipients used, the method of preparation and storage condition, the stability of the acetazolamide suspension formulation could be enhanced. Similarly, it has been reported that propranolol suspension formulated from tablets, required stabilization with 1 % citric acid and refrigeration to remain stable for 84 days; whilst phenobarbitone oral suspension formulated with the powdered API, 20% glycerine and 30% sorbitol. required refrigeration to remain stable for 30 days (Nahata *et al,.*2004; Wong, 2007).

These reports amply support the instabilities observed with the extemporaneously prepared suspensions of acetazolamide, propranolol and phenobarbitone in this study, and emphasises the need for these to be used well before 30 days after preparation, and more importantly the need for refrigeration (which is often not available in rural populations) of these products even within these short periods.

It is evident from these results that the excipients and procedures used in the preparation of extemporaneous paediatric formulations from adult dosage forms at KATH may be adequate for some of the products, but a good number may need to be reviewed towards improving the chemical stability of the active constituents. There should therefore be a continuous study and evaluation of the stability of these preparations, which should be well documented. It is necessary for continuous education of parents and care givers of infants and children who are given these preparations on their proper storage, especially refrigeration where possible. how to detect instability of these products, when to discontinue usage, and to report any changes observed during usage of these preparations.

It is crucial to collaborate with other institutions and all stakeholders involved in paediatric formulations, especially preparations from adult dosage forms, to exchange and improve on the knowledge and experiences to enhance paediatric formulations efficacy and efficiency for improved therapeutic outcomes.

CONCLUSION

From this study, the formulated lamivudine suspension had sufficient microbial integrity with an active content stability up to 60 days, hence suitable for use up to 60 days following preparation. Suspensions of spironolactone and furosemide were microbiologically safe, chemically stable, appropriate and convenient for use up to 30 days. Acetazolamide, phenobarbitone and propranolol suspensions had good microbial integrity but low active ingredient content within 30 days, and therefore can possibly be used only immediately or within 2 weeks after preparation. Even in the latter case refrigeration, which is often lacking in rural settings; would be required to keep these suspensions within specifications.

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