Sridharan K, Jain SK. Do drugs really expire beyond the expiry date? evaluation of expired (30 years from the manufacturing date) acetaminophen suspension and captopril tablet preparations. Pharmacy Practice 2024 Jan-Mar;22(1):2906.
https://doi.org/10.18549/PharmPract.2024.1.2906

Original Research

Do drugs really expire beyond the expiry date? evaluation of expired (30 years from the manufacturing date) acetaminophen suspension and captopril tablet preparations

Kannan Sridharan, Satyendra Kumar Jain

Received (first version): 14-Jun-2023 Accepted: 11-Jul-2023 Published online: 09-Mar-2024

Abstract

Background: Medicinal products are not supposed to be used beyond their expiry date. A few studies indicate that expired medicinal products still retain active pharmaceutical ingredients (API) and hence, efficacy. There is a dearth of literature evaluating the medicinal products that have expired for several decades and particularly, with liquid dosage formulations. **Objective:** To evaluate the quantities of API and degradation products in the expired acetaminophen suspension and captopril tablets that expired around 30 years ago. **Methods:** Unused acetaminophen suspension with the expiry date October 1994, and captopril tablets with the expiry date January 1992 were evaluated. Quantification of active ingredients (acetaminophen in the suspension and captopril in the tablets) and degradation products (4-aminophenol and 4'-Chloroacetanilide in the suspension, and captopril disulphide in the tablets) was carried out using high-performance liquid chromatography adhering to United States Pharmacopoeia (USP) standards. A dissolution test was done for captopril tablets as per US Pharmacopoeia to determine in vitro bioavailability of the active ingredient. The quantities of active ingredients were considered acceptable if they fell within 90 to 110% of the standard preparations. The quantity of degradation products was evaluated according to the following USP limits: captopril disulphide (not more than 3%), 4-aminophenol (not more than 0.1%) and 4'-chlorocetanilide (not more than 10 parts per million). The limit for Dissolution of Captopril was NLT 80%(Q) dissolved in 20 minutes. **Results:** We evaluated the quantity of active ingredients and key degradation products in the expired acetaminophen suspension and captopril tablets. Active ingredients in the expired acetaminophen suspension and captopril tablets were 97.21 and 96.12%, respectively. Captopril tablets meet the requirement of Dissolution test as per US Pharmacopoeia with average value of 104.84%. Regarding degradation products for acetaminophen, only 4-aminophenol was detected and was within the acceptable limit. However, the quantity of captopril disulphide exceeded by 19.3% compared to the USFDA recommended limits. Methyl paraben was also present at 93.7% of stated claim in the acetaminophen suspension. **Conclusion:** We observed acceptable quantities of active ingredients in the expired acetaminophen suspension and captopril tablets even after 30 years past their expiry date. The degradation products were observed to be present within the specified limits in the acetaminophen suspension but exceeded by 19.3% in the captopril tablet. The pharmaceutical companies shall consider extending the shelf life of medicinal products and guidelines from the concerned regulatory agencies on this regard is urgently needed.

Keywords: expired medicines; paracetamol; acetaminophen; captopril

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INTRODUCTION

Expiry date of drugs ensure that the drug's potency (and consequently the effect) is maintained until that timeframe when stored properly.[1] Manufacturers put an estimated shelf-life for drugs, and it is usually 2 to 3 years from the manufacturing date as it is hardly profitable to use drugs beyond that timeframe.[2] In the United States, ciprofloxacin, a commonly stockpiled antibiotic for responding to an anthrax attack, with a manufacturer-assigned shelf life of 3 years, was investigated under the shelf-life extension program and after testing, it was recommended that an average of 10 years can be added to the shelf life of ciprofloxacin, for a total shelf life of 13 years.[3] Using drugs past their expiry date has been shown to reduce the financial burden of procuring new drugs and the US saved around 23 million USD in the financial year – 1997.[4] It is surprising that FDA regulations do not require determination of how long medications remain potent after that, allowing manufacturers to arbitrarily establish expiration dates without determining actual long-term drug stability.[5] The accumulation of pharmaceutical waste imposes ecological, economic, and social/ethical burdens as an opportunity for using expired drugs has been missed.[6] Analysis of donations of the medicines to the voluntary organizations revealed that the median times to expiry when shipment by the organizations were 550 days; about 30% of shipment items had a year or less of shelf-life, and about 6% had less than 100 days of shelf-life.[7] Further, medicine donations to low- and middle-income countries have been observed to cross their expiry dates.[8] It is an ethical dilemma in such cases on whether to use or not to use such expired drugs in situations where many people are affected by disaster and needing medicines and only the expired drugs are available. A study from New Zealand revealed that only one-fourth of the public returned the expired medicines to the pharmacy; while another study from the region (Saudi Arabia) revealed this to an extent of only 5%.[9,10] Hence, there is a risk of either accidental consumption or intentional use of expired medicine by consumers. Interestingly, even the estimates

Kannan SRIDHARAN*. Professor, Department of Pharmacology & Therapeutics, College of Medicine and Medical Sciences, Arabian Gulf University, Manama, Kingdom of Bahrain. skannandr@gmail.com
Satyendra Kumar JAIN. Advisor, Drug Quality Assurance Laboratory, Ministry of Health, Manama, Kingdom of Bahrain.

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are not different amongst nursing and pharmacy students in proper disposal of expired medicines.[11] It is also not uncommon to find expired medicines in hospital set-ups as a study from the primary health care centers reported to an extent of 36%.[12] Zilker et al in a systematic review have concluded that it is reasonable to extend the expiry dates of the drugs beyond five years.[13] The guidelines recommend that the active pharmaceutical ingredient should be present between 95% and 105% of its labeled value according to ICH Q1A(R2) guideline.[14]

A few studies have explored the potency of expired drugs from dissolution tests. Regarding the toxicity of the degradation products in the expired drugs, it has been observed that such products from a drug belonging to analgesic class (diclofenac) resulted in varying toxicities.[15] Only one report has been published relating the occurrence of Fanconi syndrome with consumption of degraded tetracycline almost five decades ago.[16] However, it is currently unknown whether this is applicable in the contemporary world given the advances in pharmaceutical manufacturing technologies.

There is clearly a lack of adequate literature evaluating the potencies and effects of drugs that have expired several decades ago. Furthermore, amongst the available fewer studies, there is hardly any that has explored the potency of oral liquid preparations. The present study is intended to evaluate acetaminophen syrup in addition to captopril tablets. Considering the above gaps in the evidence, we carried out the present study with the primary objective of evaluating the *in vitro* bioequivalence of the expired medicinal products of oral liquid dosage form of acetaminophen and oral solid dosage form of captopril. Additionally, we also tried to identify the presence of degradation products from the expired medicinal formulations.

METHODS

Study ethics

We obtained approval from the Institutional Ethics Committee before initiating the study. We adhered to the latest Declaration of Helsinki guidelines.

Study site

The analyses of the active pharmaceutical ingredients in the expired medicinal products were carried out in the Drug Quality Assurance Laboratory, under the Ministry of Health, Kingdom of Bahrain that handles around 500 pharmaceutical samples for drug testing annually.

Details of expired medicinal products and reference standards

Liquid preparation of acetaminophen (Figure 1) from the Wellcome Foundation Ltd. (Calpol® suspension) with the batch number A 8370; manufactured date October 1991; expiry date October 1994; and each 5 ml of the syrup contains 120 mg acetaminophen with 5 mg methylparaben was used in the present study. Tablet Capoten® 25 (Figure 2) containing 25 mg captopril manufactured by Squibb with the batch number 8A0141; manufactured date January 1988; and expiry date January 1992 was also used in the present study.

Figure 1. Expired acetaminophen suspension

Figure 2. Expired captopril tablets

Regarding acetaminophen, the following compounds were evaluated as degradation products as per United States Pharmacopeia: USP Acetaminophen Related Compound J RS N-(4-Chlorophenyl) acetamide (p-chloroacetanilide) (C_8H_8ClNO, MW-169.61) and USP 4-Aminophenol RS (C_6H_7NO, MW- 109.13 [18, 19]. For captopril tablets, USP Captopril Disulfide RS [L-Proline, 1,1'- [dithiobis(2-methyl-l-oxo-3, 1- propanediyl)] bis-[S-(R*,R*)]-($C_{18}H_{28}N_2O_6S_2$ MW-432.55) was evaluated as the degradation product. The reference standards used in the present study were purchased from Sigma-Aldrich that were according to the United States Pharmacopeia and were as follows: Acetaminophen (Lot number: R16510), captopril (Lot number: R069U0), acetaminophen related compound J (LRAC9456), acetaminophen related compound K (LRAD1744), captopril disulphide (Lot number: R14420) and methylparaben (EP standard batch 5).

Acetaminophen and related degradation products

Waters® HPLC (PCM/515) was used with Rheodyne injector and Waters® UV 486 detector at 245 nm for determination of Paracetamol,4- Aminophenol & 4- chloroacetanilide. We used

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Zorbax SB® columns [C8 columns (150 x 4.6 mm) with 5 µm particle size, (P. No. 883975-906) at 35°C. Isocratic pump mode was used. A mobile phase as follows: 250 ml methanol; 1.15 gm Tetrabutylammonium hydroxide (40%) solution; 375 ml of 0.05M sodium dihydrogen orthophosphate; and 375 ml of 0.05M disodium hydrogen orthophosphate in water. The following retention times were observed for each of the compounds: acetaminophen (3.8 minutes), 4-aminophenol (2.5 minutes), methyl paraben (32.8 minutes) and 4'-chlorocetanilide (43.5 minutes).

Captopril and captopril disulphide

Waters® HPLC (PCM/515) was used with Rheodyne injector and Waters® UV 486 detector at 220 nm. We used Water's Symmetry C18 column (250 x 4.6 mm) with 5-µm particle size P. NO. WAT 054275 at 25°C]. Isocratic pump mode was used. A mobile phase consisting of 550 ml of HPLC Methanol and 450 ml of water containing 0.50 ml of Phosphoric acid was used. The following retention times were observed for each of the compounds captopril (4.1 minutes), captopril disulphide (7.19 minutes).

In vitro content analysis, dissolution tests, and degradation products

In vitro analyses of acetaminophen, 4-aminophenol, and 4'-chlorocetanilide was carried out according to the recommendations by the British Pharmacopoeia, while United States Pharmacopoeia was adhered to for the assessment of captopril and captopril disulphide.

For the assay of paracetamol, weighed quantities of the expired medicinal product (1 ml of acetaminophen suspension diluted with 175 ml mobile phase and sonicated for 5 minutes, then diluted to 200 ml with mobile phase and reference standard (25 mg) diluted with mobile phase to a final concentration of 0.024 mg/ml). The standard and sample were injected (50 µl) after filtration with 0.2-micron pore size Millipore syringe filters.

Regarding 4- aminophenol, 0.00012% w/v of the reference standard and acetaminophen reference standard were used. Similarly, for 4'-chlorocetanilide, 0.0000012% w/v of the reference standard was used.

All dilutions were done in Mobile phase using Class A certified volumetric glassware.

For the estimation of methyl paraben, the reference standard (16 mg) was diluted mobile phase to achieve a final solution containing 0.048 mg/ml. Acetaminophen suspension (5 ml) was diluted with mobile phase in 100 ml volumetric flask and both the reference standard and suspension were injected (50 µl) after filtration with 0.2-micron pore size Millipore syringe filters .

Captopril was assayed with four expired captopril tablets (25 mg each) dissolved in 80 ml mobile phase and made up to volume of 100 ml in volumetric flask and the reference standard (20 mg) dissolved in 15 ml diluent and made up to a volume of 20 ml to have concentration of 1 mg/ ml. The final solutions were filtered using 0.2-micron pore size Millipore syringe filters before injection.

Captopril disulphide was assayed diluting the reference standard in mobile phase to achieve a concentration of 10 µg/ ml. regarding the expired medicinal product, 2 tablets (25 mg each) were diluted with 25 ml mobile phase to have a final concentration of 2 mg/ ml of captopril. The final solutions were filtered using 0.2-micron pore size Millipore syringe filters.

Dissolution test for captopril tablets

Dissolution test for Captopril tablets was done as per USP using 900 ml 0.01N Hydrochloric acid as the medium (deaerated to minimize exposure of Captopril to air and analyzed the samples immediately. Medium was maintained at a temperature of 37 ±0.5°C.

USP Apparatus was 1 (Basket) at 50 RPM was used. One tablet was introduced to each of 6 vessels and apparatus was operated as per above stated conditions for 20 minutes. 20 ml samples were withdrawn from each vessel as per standard practice from midway between top of liquid media and basket and at least 1 cm away from vessel wall. Reference Standard was made up in dissolution medium to contain about 0.014 mg /ml. Test solution was filtered using 0.20-micron millex filters and diluted with dissolution media to a concentration like standard dilution. Content of captopril was estimated by UV-Visible spectrophotometer @ 205 nm.

Microbiological examination of the acetaminophen suspension was carried out as per microbial limit test in United States Pharmacopoeia standards.[17]

Statistical analysis

Area under the peak was used to identify the quantity of standard and test compounds. The analyses were repeated three times and the average value of the area under the peak was estimated. The percentage of the labeled amount of the test compounds (present in the expired medicinal preparation) were evaluated as follows:

(Ru /Rs) x (Cs/Cu) x 100

Ru = peak response of test compound from the sample solution (expired preparation).

Rs = peak response of reference compounds from the standard solution.

Cs = concentration of reference compounds from the standard solution (mg/mL)

Cu =nominal concentration of test compound from the sample solution (mg/mL).

The quantity of active ingredients (acetaminophen and captopril) in the expired medicinal products were considered acceptable if they fell within 90 to 110% of the standard preparations.[18] Dissolution test meets the requirement if each unit is more than (Q +5%) The quantity of degradation products was evaluated according to the following USP limits: captopril disulphide (not more than 3%),[19] 4-aminophenol (not more

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than 0.1%) and 4'-chlorocetanilide (not more than 10 parts per million).[20]

RESULTS

Active pharmaceutical ingredients in the expired medicinal products

The mean-area under the peak for the acetaminophen reference standard was observed to be 5440907 compared to 5043726 for the same compound from the expired acetaminophen suspension (Figures 3 and 4). The product label of Calpol® suspension claims 120 mg/5 ml and the estimated quantity (in 5 ml) in the expired medicinal product was 116.653 mg (97.21% of the claimed quantity) (Electronic Supplementary Material – Sheet 1).

The mean-area under the peak for the captopril reference standard was observed to be 10235134 compared to 9902741 for the same compound from the expired captopril tablets (Figures 5 and 6). The product label of Capoten 25® claims 25 mg per tablet and the estimated quantity in the expired medicinal product was 24.03 mg (96.12% of the claimed quantity) (Electronic Supplementary Material – Sheet 2).

Dissolution of captopril tablets

The captopril tablets released between 96.70 to 110.86% (Average of six tablets -104.84%) of contents in 20 minutes. Regarding the dissolution of captopril tablets, USP limits are that each of six tablets release NLT 85 % (Q+5%) of contents in 20 minutes S1 stage.

Degradation products in the expired medicinal products

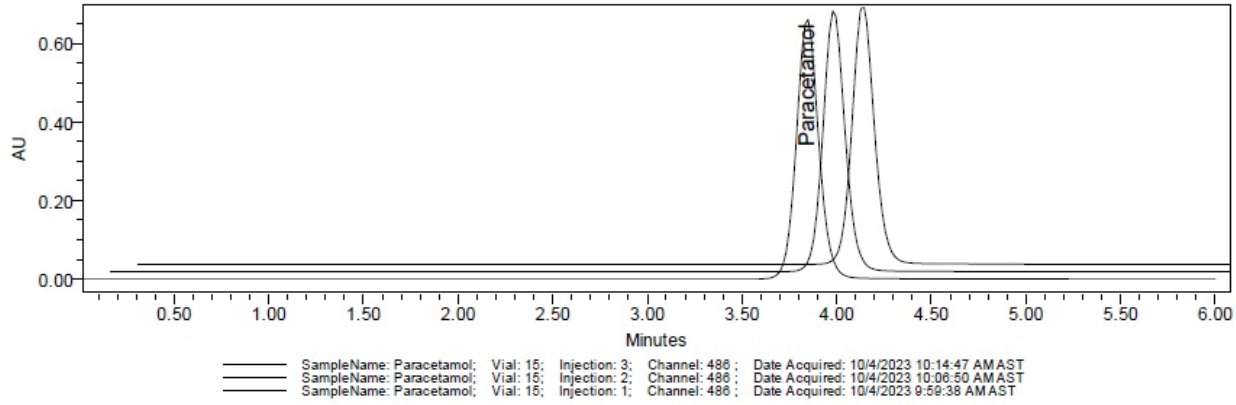
The mean-area under the peak for 4-aminophenol reference standard was observed to be 112852 compared to 39252 for the same compound from the expired acetaminophen suspension (Figures 7 and 8). The quantity of 4-aminophenol in the expired suspension was observed to be 0.0433 mg/5 ml contributing to 0.0361% (Electronic Supplementary Material – Sheet 1). 4'-chloroacetanilide was not detected in the expired medicinal product.

The mean-area under the peak for the captopril disulphide reference standard was observed to be 168875 compared to 1244215 for the same compound from the expired captopril tablets (Figures 9 and 10). The quantity of captopril disulphide in the expired tablets was observed to be 0.913 mg contributing to 3.58% (Electronic Supplementary Material – Sheet 2).

Methyl paraben in the expired acetaminophen suspension

The mean-area under the peak for the methyl paraben reference standard was observed to be 11064667 compared to 10581474 for the same compound from the expired acetaminophen suspension. The product specification of Calpol® suspension claims 5 mg/5 ml and the estimated quantity (in 5 ml) in the expired medicinal product was 4.685 mg (93.7% of the claimed quantity) (Electronic Supplementary Material – Sheet 1).

Further, the expired acetaminophen suspension did not reveal any microbial growth (Aerobic and anaerobic microorganisms) were detected in the microbial limit test. A pH of 4.07 was observed for the suspension.



Component Summary Table
Name: Paracetamol

	SampleName	Inj	Vial	Name	RT	Area	Height (µV)
1	Paracetamol	1	15	Paracetamol	3.847	5434912	662401
2	Paracetamol	2	15	Paracetamol	3.839	5440520	664718
3	Paracetamol	3	15	Paracetamol	3.845	5447290	661179
Mean						5440907	
Std. Dev.						6198	
% RSD						0.1	

Figure 3. Chromatogram of acetaminophen reference standard

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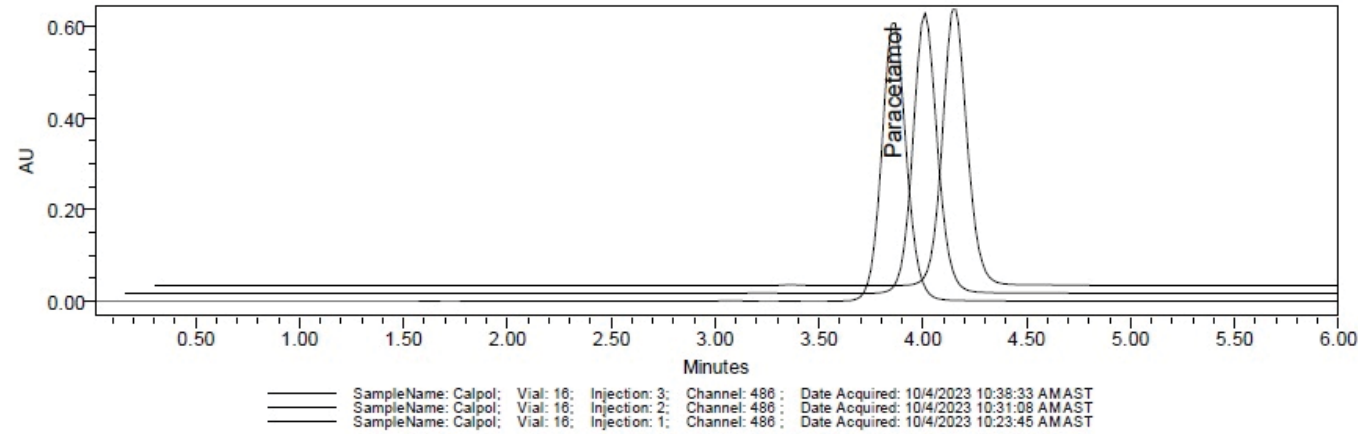
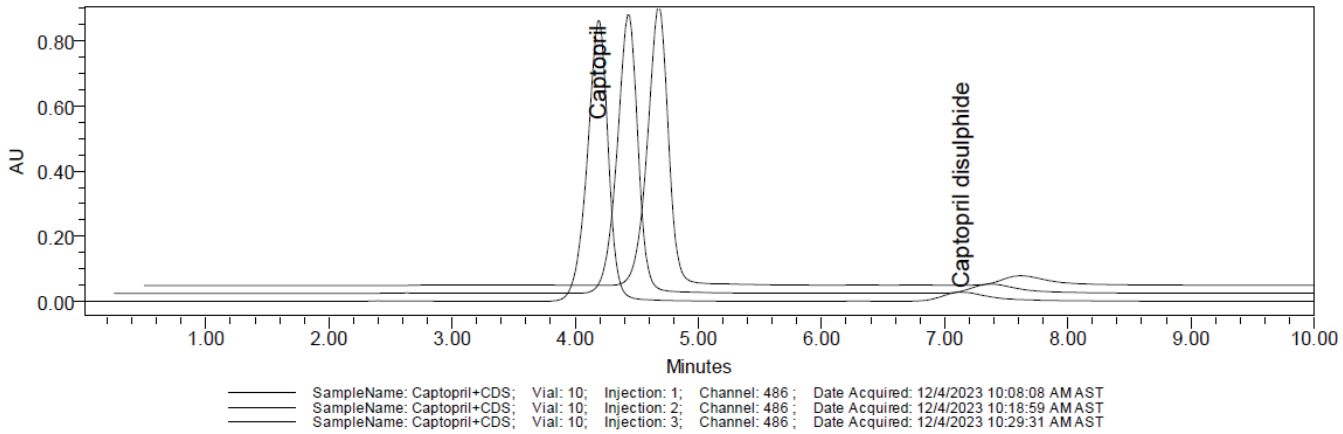


Component Summary Table
Name: Paracetamol

	SampleName	Inj	Vial	Name	RT	Area	Height (µV)
1	Calpol	1	16	Paracetamol	3.864	5042742	611485
2	Calpol	2	16	Paracetamol	3.866	5042522	610476
3	Calpol	3	16	Paracetamol	3.860	5045915	610967
Mean						5043726	
Std. Dev.						1899	
% RSD						0.0	

Figure 4. Chromatogram of the active ingredient from the expired acetaminophen suspension



Component Summary Table
Name: Captopril

	SampleName	Inj	Vial	Name	RT	Area	Height (µV)
1	Captopril+CDS	1	10	Captopril	4.190	10276486	863439
2	Captopril+CDS	2	10	Captopril	4.191	10195971	858133
3	Captopril+CDS	3	10	Captopril	4.196	10232946	860225
Mean						10235134	
Std. Dev.						40302	
% RSD						0.4	

Figure 5. Chromatogram of captopril reference standard

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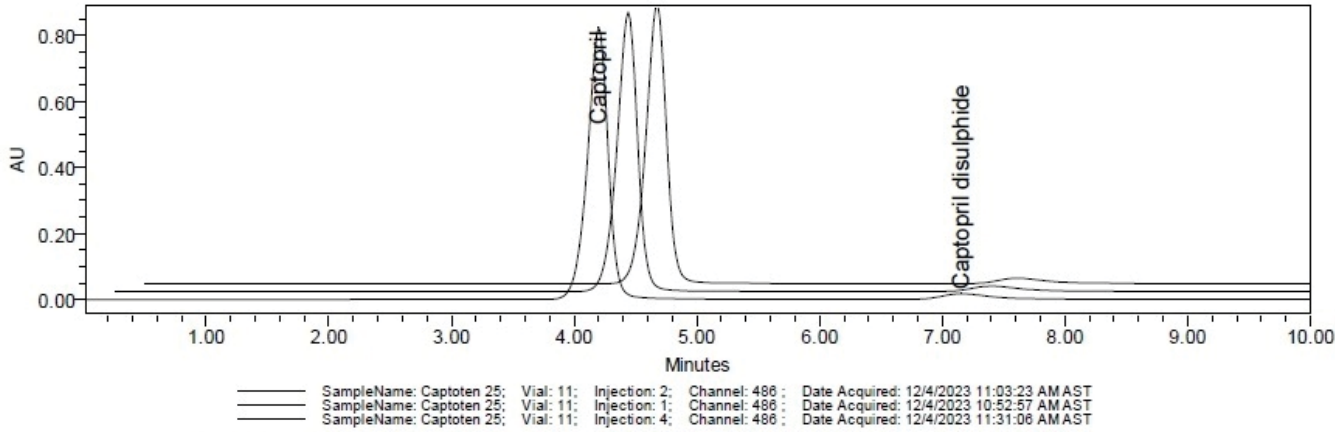
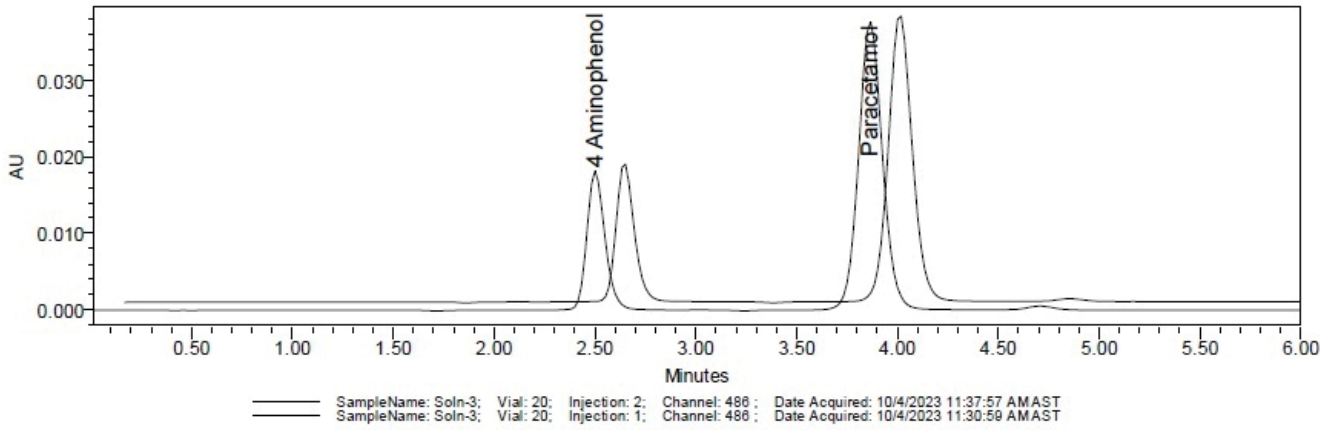


Component Summary Table
Name: Captopril

	SampleName	Inj	Vial	Name	RT	Area	Height (µV)
1	Captoten 25	1	11	Captopril	4.199	9999905	845621
2	Captoten 25	2	11	Captopril	4.200	9784527	823314
3	Captoten 25	4	11	Captopril	4.193	9923790	846266
Mean						9902741	
Std. Dev.						109221	
% RSD						1.1	

Figure 6. Chromatogram of captopril from the expired tablet



Component Summary Table
Name: 4 Aminophenol

	SampleName	Inj	Vial	Name	RT	Area	RT Ratio	Height (µV)
1	Soln-3	1	20	4 Aminophenol	2.495	112931	0.646	17915
2	Soln-3	2	20	4 Aminophenol	2.502	112772	0.647	18032
Mean						112852		
Std. Dev.						112		
% RSD						0.1		

Figure 7. Chromatogram of 4-aminophenol from the reference standard

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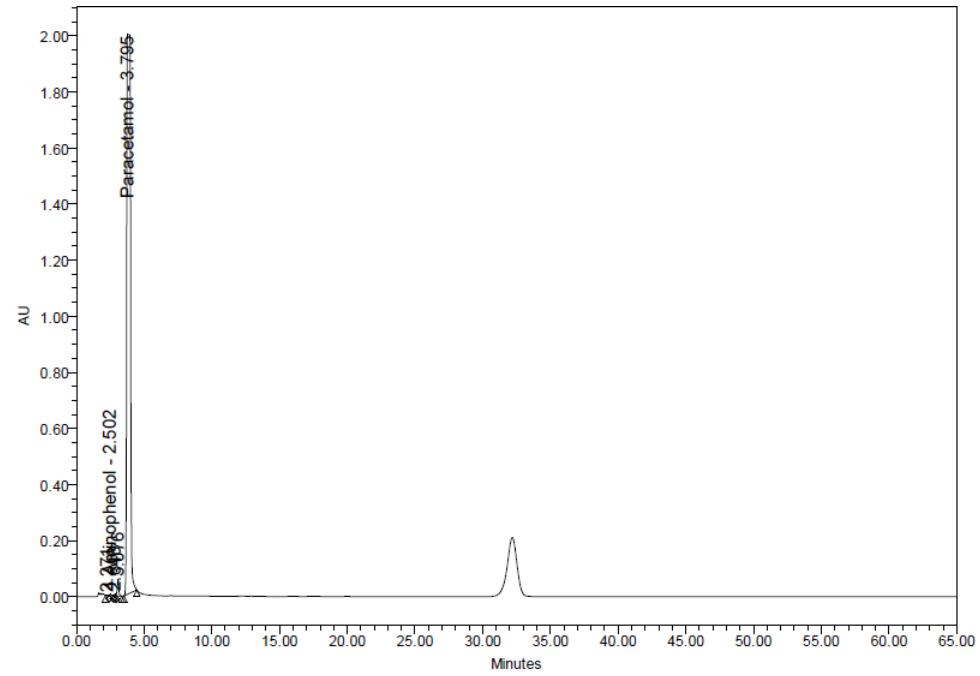
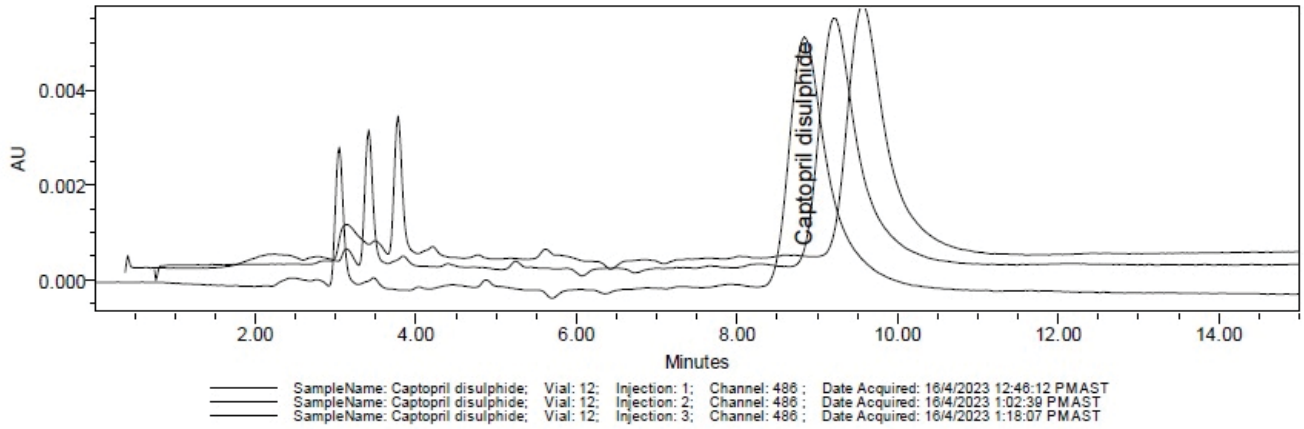


	Peak Name	RT	Area	% Area
1	4 Aminophenol	2.502	39252	0.10
2	Paracetamol	3.795	38473508	98.64
Sum			38512759.8	

Figure 8. Chromatogram of 4-aminophenol from the expired acetaminophen suspension



Component Summary Table
Name: Captopril disulphide

	SampleName	Inj	Vial	Name	RT	Area	Height (µV)
1	Captopril disulphide	1	12	Captopril disulphide	8.840	169317	5194
2	Captopril disulphide	2	12	Captopril disulphide	8.848	167614	5153
3	Captopril disulphide	3	12	Captopril disulphide	8.834	169695	5222
Mean						168875	
Std. Dev.						1109	
% RSD						0.7	

Figure 9. Chromatogram of captopril disulphide reference standard

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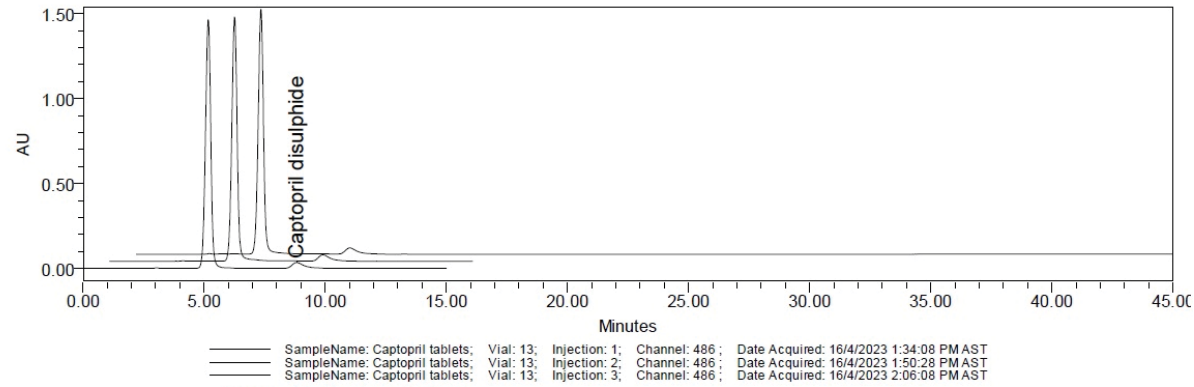

Component Summary Table
Name: Captopril disulphide

	SampleName	Inj	Vial	Name	RT	Area	Height (µV)
1	Captopril tablets	1	13	Captopril disulphide	8.825	1182590	34062
2	Captopril tablets	2	13	Captopril disulphide	8.822	1279651	37427
3	Captopril tablets	3	13	Captopril disulphide	8.845	1270403	36563
Mean						1244215	
Std. Dev.						53568	
% RSD						4.3	

Figure 10. Chromatogram of captopril disulphide from the expired captopril tablets

DISCUSSION

Key findings of the present study

We evaluated the quantity of active ingredients and key degradation products in the expired acetaminophen suspension and captopril tablets with the expiry dated October 1994 and January 1992, respectively. Active ingredients in the expired acetaminophen suspension and captopril tablets were 97.21 and 96.12%, respectively. Regarding the degradation products for acetaminophen, only 4-aminophenol was detected and was within the acceptable limit. However, the quantity of captopril disulphide exceeded by 19.3% compared to the USFDA recommended limits. Methyl paraben was also present at 93.7% of stated claim in the acetaminophen suspension.

Comparison with the existing studies

There are very few studies that have quantified the active ingredients and impurities in medicinal preparations that have expired beyond 30 years. Zilker *et al*[21]evaluated the active ingredients of epinephrine, etilefrine, synephrine, caffeine and procaine, caffeine and sodium salicylate, dipyridamole, furosemide, and metamizole in ampoules that expired 40 years ago and observed that only five out of nine had contents within the specified limits. Similarly, Cantrell *et al*[5] have evaluated oral tablets and capsules that expired 28 to 40 years before the analysis and observed that 12 out of 14 compounds were present in the defined limits. In the present study, we have evaluated the presence of active ingredients in an expired liquid preparation (suspension) used in the pediatric population. Pediatric liquid dosage formulations are usually flavored and contain sweeteners for enhancing the taste for improving the compliance to therapy. Liquid, non-sterile medicinal products are susceptible to microbial contamination. The results of the present study are encouraging wherein no microbial growth was detected as well as the pH of the expired suspension was low. Further, methyl paraben has anti-microbial properties[22] and was also observed to be present within the specified limits. Regarding the expired captopril tablets, we observed that the key degradation product was present at 19% more than the specified limit. It is most probable that at the time of manufacturing this tablet, there were no regulations specifying the maximum quantities of degradation product.

Our results recommend extending the shelf life of the medicinal products by the pharmaceutical companies considering the economic burden resulting from disposing the expired but still retaining potency/efficacy. Tufts Medical Center disposes expired medicines worth 200,000 USD annually.[23] The expiry dates usually range between two to five years and are chosen arbitrarily based on the stability data submitted by the pharmaceutical company.[24] Until now, there has been no regulation requiring the pharmaceutical companies to continue assessing the stability of the medicinal preparations beyond their duration of expiry. It is high time that the Drug regulatory authorities insist periodic (annual) evaluation of stability of medicinal products including their impurities throughout the lifespan of the drugs. This may pave way for revising the expiry dates of medicinal products resulting in the reduction of hospital expenses.

Strengths and limitations

The present study has evaluated medicinal products that expired around 3 decades ago. Particularly, we have evaluated

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the suspension formulation which has not been explored before. Further, the quantification of compounds has been carried out in a dedicated national drug testing laboratory in the Kingdom. However, the study is limited in not evaluating the *in vitro*/*in vivo* bioequivalence as well as evaluating their therapeutic and adverse effects.

CONCLUSION

We observed acceptable quantities of active ingredients in the expired acetaminophen suspension and captopril tablets even after 30 years past their expiry date. The degradation products were observed to be present within the specified limits in the acetaminophen suspension but exceeded by 19.3% of accepted limit in the captopril tablet. The pharmaceutical companies shall consider extending the shelf life of medicinal products and guidelines from the concerned regulatory agencies on this regard is urgently needed.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by the Institutional Ethics Committee of CMMS, Arabian Gulf University with the approval number E 24-PI-5/22. No human being was recruited in the study and so consent is not applicable.

CONSENT FOR PUBLICATION

No human being was recruited in the study and so consent is not applicable.

COMPETING INTEREST

None.

FUNDING

The study was funded by the intra-mural grant from CMMS, Arabian Gulf University with the grant number G-03-AGU-5-22.

ACKNOWLEDGEMENTS

We thank the Ministry of Health, Kingdom of Bahrain, for providing permission to utilize their Drug Testing Laboratory for the present study. We also thank Ms. Sumaiya Husain, for her initial liaison with the Ministry of Health.

AUTHORS' CONTRIBUTIONS

KS: Conceived the study, provided the expired medicinal products, wrote the original draft, and was involved in the revisions and final approval of the manuscript; SKJ: Carried out drug testing and data analysis, and data interpretation, and was involved in the revisions and final approval of the manuscript.

AVAILABILITY OF DATA AND MATERIALS

The chromatograms are provided in the manuscript and the data analysis is provided as the Electronic Supplementary Material.

References

1. Title 21 CFR 211.166(a) and (b). Current good manufacturing practice in manufacturing for finished pharmaceuticals and expiration dating. 2012.
2. FDA tests let military use expired drugs. Available at: https://www.thepharmaletter.com/article/fda-tests-let-military-use-expired-drugs (Accessed on 20 Dec 2021).
3. Extending the shelf life of critical "war reserves" medical materiel using the FDA/DoD Shelf Life Extension Program. March 31, 2005.
4. Garamone J. Program extends drug shelf-life. American Forces Press Service March 29, 2000.
5. Cantrell L, Suchard JR, Wu A, et al. Stability of active ingredients in long-expired prescription medications. Arch Intern Med. 2012;172(21):1685-7.
6. Alnahas F, Yeboah P, Fliedel L, et al. Expired Medication: Societal, Regulatory and Ethical Aspects of a Wasted Opportunity. Int J Environ Res Public Health. 2020;17(3):787.
7. Reich MR, Wagner AK, McLaughlin TJ, et al. Pharmaceutical donations by the USA: an assessment of relevance and time-to-expiry. Bull World Health Organ. 1999;77(8):675-80.
8. van der Heide B, Schouten E. Assortment of drugs causes more problems than it solves. BMJ. 1995;311:684.
9. Braund R, Peake BM, Shieffelbien L. Disposal practices for unused medications in New Zealand. Environment International 2009;35:952-955.
10. Wajid S, Siddiqui NA, Mothana RA, et al. Prevalence and Practice of Unused and Expired Medicine-A Community-Based Study among Saudi Adults in Riyadh, Saudi Arabia. Biomed Res Int. 2020;2020:6539251. https://doi.org/10.1155/2020/6539251
11. Bashatah A, Wajid S. Knowledge and Disposal Practice of Leftover and Expired Medicine: A Cross-Sectional Study from Nursing and Pharmacy Students' Perspectives. Int J Environ Res Public Health. 2020; 17(6): 2068. https://doi.org/10.3390/ijerph17062068
12. Ebrahim AJ, Teni FS, Yimenu DK. Unused and Expired Medications: Are They a Threat? A Facility-Based Cross-Sectional Study. J Prim Care Community Health. 2019;10:2150132719847857. https://doi.org/10.1177/2150132719847857
13. Zilker M, Sörgel F, Holzgrabe U. A systematic review of the stability of finished pharmaceutical products and drug substances

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beyond their labeled expiry dates. J Pharm Biomed Anal. 2019;166:222-235. https://doi.org/10.1016/j.jpba.2019.01.016
14. ICH harmonised tripartite guideline stability testing of new drug substances and products Q1a(R2). Available at: https://database.ich.org/sites/default/files/Q1A%28R2%29%20Guideline.pdf (Accessed on 28 Dec 2021).
15. Gaudiano MC, Valvo L, Bertocchi P, et al. RP-HPLC study of the degradation of diclofenac and piroxicam in the presence of hydroxyl radicals. J Pharm Biomed Anal. 2003;32:151-158. https://doi.org/10.1016/s0731-7085(03)00058-x
16. Frimpter GW, Timpanelli AE, Eisenmenger WJ, et al. Reversible "Fanconi syndrome" caused by degraded tetracycline. JAMA. 1963;184:111-113.
17. Microbiological examination of nonsterile products: microbial enumeration tests. Available at: https://www.usp.org/sites/default/files/usp/document/harmonization/gen-method/q05b_pf_ira_34_6_2008.pdf (Accessed on May 10, 2023).
18. USFDA guidance for industry. Investigating out-of-specification (OOS) test results for pharmaceutical production. Available at: https://www.fda.gov/media/71001/download (Accessed on May 10, 2023).
19. Captopril tablets. Available at: https://file.wuxuwang.com/yaopinbz/USP42-NF37/USP42-NF37_594.pdf (Accessed on May 10, 2023).
20. OTC medicine monograph: Paracetamol for oral use. Therapeutic Goods Administration. Available at: https://www.tga.gov.au/resources/publication/publications/otc-medicine-monograph-paracetamol-oral-use (Accessed on May 10, 2023).
21. Zilker M, Sörgel F, Holzgrabe U. A stability-study of expired ampoules manufactured more than 40 years ago. J Pharm Biomed Anal. 2018;150:318-326. https://doi.org/10.1016/j.jpba.2017.12.019
22. Soni MG, Taylor SL, Greenberg NA, et al. Evaluation of the health aspects of methyl paraben: a review of the published literature. Food Chem Toxicol. 2002;40(10):1335-73. https://doi.org/10.1016/s0278-6915(02)00107-2
23. Diven DG, Bartenstein DW, Carroll DR. Extending shelf life just makes sense. Mayo Clin Proc. 2015;90:1471-74. https://doi.org/10.1016/j.mayocp.2015.08.007
24. Courtney B, Easton J, Inglesby TV, et al. Maximizing state and local medical countermeasure stockpile investments through the Shelf-Life Extension Program. Biosecur Bioterror. 2009;7(1):101-107. https://doi.org/10.1089/bsp.2009.0011

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