Nigerian Journal of Pharmaceutical Sciences
Vol. 20, No1, 2021, ISSN: 0189-823X
All Rights Reserved

POTENCY EVALUATION OF EXPIRED MORPHINE SULPHATE INJECTIONS

[1]*Abdullahi, S. T., [1]Yusuf A., [1]Njinga, N. S., [1]Eniayewu, O. I., [1]Bamidele, O. D., [2]Amali M. O., Ayanniyi, R. O. and Bakare-Odunola M. T

[1]Department of Pharmaceutics and Industrial Pharmacy, Faculty of Pharmaceutical Sciences, University of Ilorin, Ilorin, Nigeria.
[2]Department of Pharmaceutics, Faculty of Pharmacy, Obafemi Awolowo University, Ile-Ife, Osun, Nigeria.
[3]Department of Pharmacology, Faculty of Pharmacy, Obafemi Awolowo University, Ile-Ife, Osun, Nigeria.
[4]Department of Pharmacology and Toxicology, Faculty of Pharmaceutical Sciences, University of Ilorin, Ilorin, Nigeria.
***Author for correspondence**: *abdullahi.st@unilorin.edu.ng*; +2348035883569

ABSTRACT

Expired drugs have not necessarily lost their potency and efficacy as expiration dates are only assurances that the labeled potency will last at least until that time. Clinical situations may arise in which expired medicines might be considered owing to lack of viable alternatives or financial concerns. Moreover, limited studies have reported potency of pharmaceuticals beyond their labeled expiration dates. This study determined the potencies of expired morphine sulphate (10 mg and 15 mg) injections using British Pharmaceutical Codex specific absorptivity [E (1%, 1 cm)] values of 41 [at wavelength of maximum absorbance (λ_{max}) of 285 nm] in water and 70 [at λ_{max} of 298 nm] in 0.1N NaOH and compared with that of unexpired morphine hydrochloride (10 mg) injection. With the exception of expired morphine 15 mg injection, both the unexpired and expired 10 mg injections exceeded the United State Pharmaceutical Codex maximum acceptance limit of 110.0% (acceptance criteria of 90.0% – 110.0%). Although the percent contents of expired morphine 15 mg injections were significantly different from those of unexpired morphine 10 mg injections [mean percent content difference (95% confidence interval): 13.98% (11.05, 16.92) using water and 13.02% (8.95, 17.08) using 0.1N NaOH], expired morphine 10 mg injections were not significantly different from the unexpired morphine 10 mg injections [2.68% (-0.56, 5.92) using water and 7.33% (-3.40, 18.06) using 0.1N NaOH as assay solvents]. This study corroborates a previous report and indicates that expired morphine injections, if properly stored, can be extended past their expiration dates. While it is always best to use unexpired medication, expired morphine injections could be considered when it becomes the sole available option.

Keywords: expiration dates, expired medicines, assay, morphine injection, potency evaluation

INTRODUCTION

It is used in the management of moderate to severe pain resistant to the non-narcotics (Murphy and Barrett, 2019).

Morphine is the most commonly used opioid for severe cancer-related pain and remains the gold standard for management of moderate to severe cancer pain. (Schug, *et al*., 1990; Pharo and Zhou, 2005; Plante and VanItallie, 2010).

Other clinical conditions that benefit significantly by medicating with morphine include management of palliative/end-of-life care, and vaso-occlusive pain during sickle cell crisis (Murphy and Barrett, 2019). Although there is no proven superiority of morphine as compared with other available opioids, it is widely used off-label for almost any condition that causes pain and is also the most cost-effective analgesic (Hanks *et al*., 2001; Mandalà *et al*., 2006).

The chemical formula of morphine was deduced in 1847 to be $C_{17}H_{19}NO_3$ (Blakemore and White 2002). The molar mass of morphine is 285.34 g/mol (National Center for Biotechnology Information, 2020). It is chemically designated by the International Union of Pure and Applied Chemistry (IUPAC) as (4R,4aR,7S,7aR,12bS)-3-methyl-2,4,4a,7,7a,13-hexahydro-1H-4,12-methanobenzofuro[3,2-e]isoquinoline-7,9-diol and with the Chemical Abstract Service (CAS) registry number, 57-27-2 (Ben Haddou *et al*., 2014; National Center for Biotechnology Information, 2020). It is usually administered as the sulphate, although the hydrochloride and the tartrate are used in similar doses (National Center for Biotechnology Information, 2020). The morphine sulphate (2:1) salt pentahydrate (Figure 1) is a white crystalline powder, soluble in water, with a melting point of 255 °C and a boiling point of 190 ° C (National Center for Biotechnology Information, 2020). Preservative-free morphine sulphate injection USP is a sterile, nonpyrogenic solution of morphine sulphate in water for injection (United States Pharmacopeial Convention, 2012). For 0.5 mg or 1 mg presentation, each mL contains morphine sulphate USP (pentahydrate) 0.5 mg or 1 mg, respectively, and sodium chloride 9 mg in water for injection.

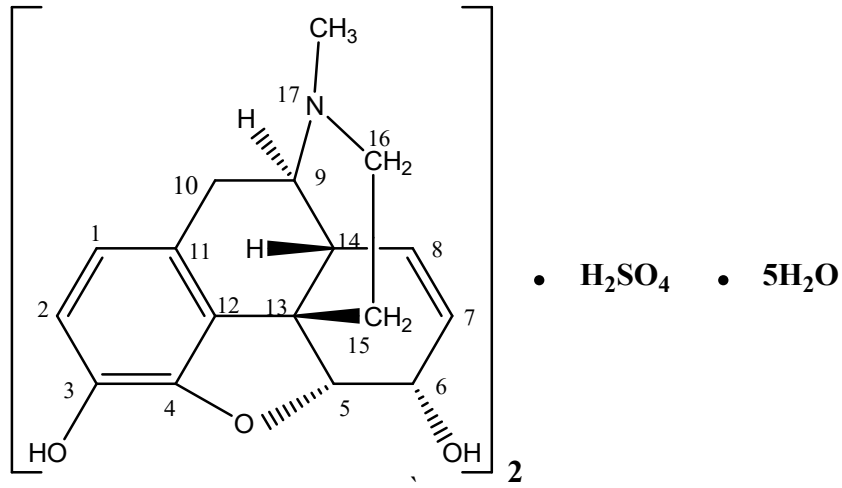

Figure 1: Structure of morphine sulphate pentahydrate

Morphine is a pharmaceutically important alkaloid of the benzylisoquinoline type with two additional ring closures (Facchini and Bird, 1998). Specifically, the basic structure of morphine is that of a phenanthrene nucleus, with the methylated nitrogen in a heterocyclic ring structure (White *et al*., 1997). Morphine has a rigid pentacyclic structure consisting of a benzene ring, two partially unsaturated cyclohexane rings, a piperidine ring and a tetrahydrofuran ring (Blakemore and White, 2002). The phenanthrene ring system has little conformational flexibility. Morphine also has two hydroxyl functional groups: a C3-phenolic OH (pK_a 9.9) and a C6-allylic OH, an ether linkage between C4 and C5, unsaturation between C7 and C8, a basic tertiary amine function at position 17, and 5

centers of chirality (C5, C6, C9, C13 and C14) enabling morphine to exhibit a high degree of stereoselectivity of analgesic action (Benyhe *et al*., 2015).

Morphine can be analyzed qualitatively and quantitatively by ultraviolet spectrophotometry (Ehrlich-Rogozinsky and Cheronis 1963). Qualitative analysis involves determination of the wavelength of maximum absorbance (λ_{max}) in defined solvent medium. The λ_{max} of morphine in water and 0.1N NaOH, are 285 nm and 298 nm respectively (BPC, 2018). Quantitative assay of morphine involves determining the percentage (%) content of morphine in a pharmaceutical formulation from either the specific absorbance value or extrapolation from the standard calibration curve (Jadhav *et al*., 2012). Only a limited number of studies (Lyon *et al*., 2006; Cantrell *et al*., 2012) have reported on the potency of medicines beyond their expiration dates as this field is only recently being investigated. This study determined the potency levels of expired morphine sulphate injections and compared them with those of unexpired morphine hydrochloride injections.

MATERIALS AND METHODS

Chemical Reagents

Two brands of morphine injection, Morfina® (brand of morphine hydrochloride 10 mg/mL) manufactured by Laboratorios Serra Pamies, Spain, and Verve® (brands of morphine sulphate 10 mg/mL and 15 mg/mL) products of Verve Human Care Laboratories, India were obtained from reputable Pharmacy outlets in Ilorin metropolis. Some of the reagents used include sodium hydroxide (BDH) analar powder and distilled water. Glassware apparatus includes 100 mL volumetric flasks, calibrated pipettes (1mL, 5mL, 10 mL and 25mL), beakers and funnels.

Instruments Used

Analytical weighing balance (PA214) by Ohaus, USA; GS-UV61PC double beam spectrophotometer serial No: UQC1212006 by General Scientific Hong Kong Limited**.** Water distiller - model Basic/PH4 Pure-Hit Still.

Preparation of Assay Solvent

A 0.1N NaOH solution was prepared by weighing 4g of NaOH pellet and dissolving it in a 1L volumetric flask containing about 500 mL distilled water and making it up to mark with distilled water.

Identification tests

Expired and unexpired morphine injection samples were collected and analyzed between May 15 and June 15, 2019. Approximately 0.010% w/v unexpired morphine hydrochloride [molecular formula: molar mass; $C_{17}H_{19}NO_3.HCl.3H_2O$: 375.84] solution in water was prepared and scanned in the UV range of 350 to 200 nm to obtain the λ_{max} which was compared with British Pharmaceutical Codex (BPC, 2018) specification of exhibiting a maximum at 285 nm ± 1. Similarly, 0.010% w/v and 0.015%w/v solutions of expired morphine sulphate [$(C_{17}H_{19}NO_3)_2.H_2SO_4.5H_2O$; 758.83] in water were prepared and scanned. The obtained spectra were compared with the BPC specifications. The UV absorption spectra of the solutions of the morphine injections in 0.1N NaOH as assay solvent were also obtained and the λ_{max} values were compared with the BPC specification of exhibiting a maximum at 298 nm ± 1.

Assay of Morphine Injection

Quantities of the morphine injection equivalent to 10 mg and 15mg were dissolved in 100 mL volumetric flask containing about 20 mL of distilled water or 0.1N NaOH. The solutions were made up to 100 mL with distilled water and with 0.1N NaOH. The test solutions were prepared in triplicate and absorbances of the resulting solutions were determined at their respective λ_{max}. The percentage contents of active morphine of the parenteral preparations were calculated using the BPC (2018) E (1%, 1

cm) specifications of 41 for water and 70 for 0.1N NaOH.

Statistical Analysis

Results were presented as mean (% relative standard deviation). Statistical comparison was done using one-way Analysis of Variance (ANOVA) and Independent Samples Test. Differences in the potencies between products were expressed as mean difference (95% confidence interval) Statistical significance was expressed as P-values < 0.05 or the 95% confidence interval excluding 0. All results were analyzed using SPSS 20.0 software.

RESULTS

Descriptive Characteristics of Samples

The baseline characteristics of the study products are summarized in Table 1. The unexpired morphine 10 mg injection (Morfina®), from Laboratorios Serra Pamies, Spain served as control in the absence of morphine analytical reference standard. The expired morphine 10 mg and 15 mg injections (Verve®) were manufactured by Verve Human Care Laboratories, India with expiration date of 12/2018. Both brands were manufactured in 2017, but while Morfina® had a shelf life of three years, the shelf-life of Verve® was two years.

Table 1: Characteristics of the Analyzed Morphine Injections

Brands	Strength (mg/mL)	Batches	Manufacturer location	Manufactured dates	Expiry dates	Active ingredient
Morfina	10	7070	Spain	04/2017	03/2020	Morphine hydrochloride
Verve	10	EN031702	India	01/2017	12/2018	Morphine sulphate IP
Verve	15	EN041703	India	01/2017	12/2018	Morphine sulphate IP

Abbreviation: IP: - International Pharmacopoeia

Qualitative Analysis

Identification of the three products was carried out by comparison of λ_{max} of spectra of their samples in water and in 0.1N NaOH in accordance with BPC (2018) specifications and values of 284 nm and 298 nm were obtained respectively. Additionally, Figures 2B and 2C show that spectra of the expired morphine 10 mg and 15 mg injections in water respectively compared with that of the unexpired morphine 10 mg injection (Figure 2A). Similarly, Figures 3B and 3C absorption spectra of the expired morphine injections in 0.1N NaOH also compared with the spectrum of unexpired injection (Figure 3A). Thus, indicative of morphine as the active pharmaceutical ingredient in of the three products.

Quantitative Analysis

Table 2 shows differences in the potencies of the three products in water compared with in 0.1N NaOH [mean difference (95% confidence interval): unexpired morphine 10 mg injection: 8.01% (6.44, 9.57); expired morphine 10 mg injection: 12.66% (4.42, 20.89) and expired morphine 15 mg injection 7.99% (4.66, 11.33)].

Table 1: Characteristics of the Analyzed Morphine Injections

Brands	Strength (mg/mL)	Batches	Manufacturer location	Manufactured dates	Expiry dates	Active ingredient
Morfina	10	7070	Spain	04/2017	03/2020	Morphine hydrochloride
Verve	10	EN031702	India	01/2017	12/2018	Morphine sulphate IP
Verve	15	EN041703	India	01/2017	12/2018	Morphine sulphate IP

Abbreviation: IP: - International Pharmacopoeia

Table 2: Comparison of Potency of the Different Products in Water and 0.1N NaOH

Product	Potency [% content (% RSD)]		Mean difference (95% CI)	P-value
Assay solvent:	H_2O	0.1N NaOH		
Unexpired 10 mg	128.29 (1.17)	120.29 (0.00)	8.01 (6.44, 9.57)	< 0.001
Expired 10 mg	125.61 (2.19)	112.95 (3.84)	12.66 (4.42, 20.89)	0.013
Expired 15 mg	114.31 (2.50)	106.32 (2.16)	7.99 (4.66, 11.33)	< 0.001
P-value	< 0.001	< 0.001		

Abbreviations: RSD: -relative standard deviation; CI: - confidence interval; H_2O: - water; NaOH: - sodium hydroxide

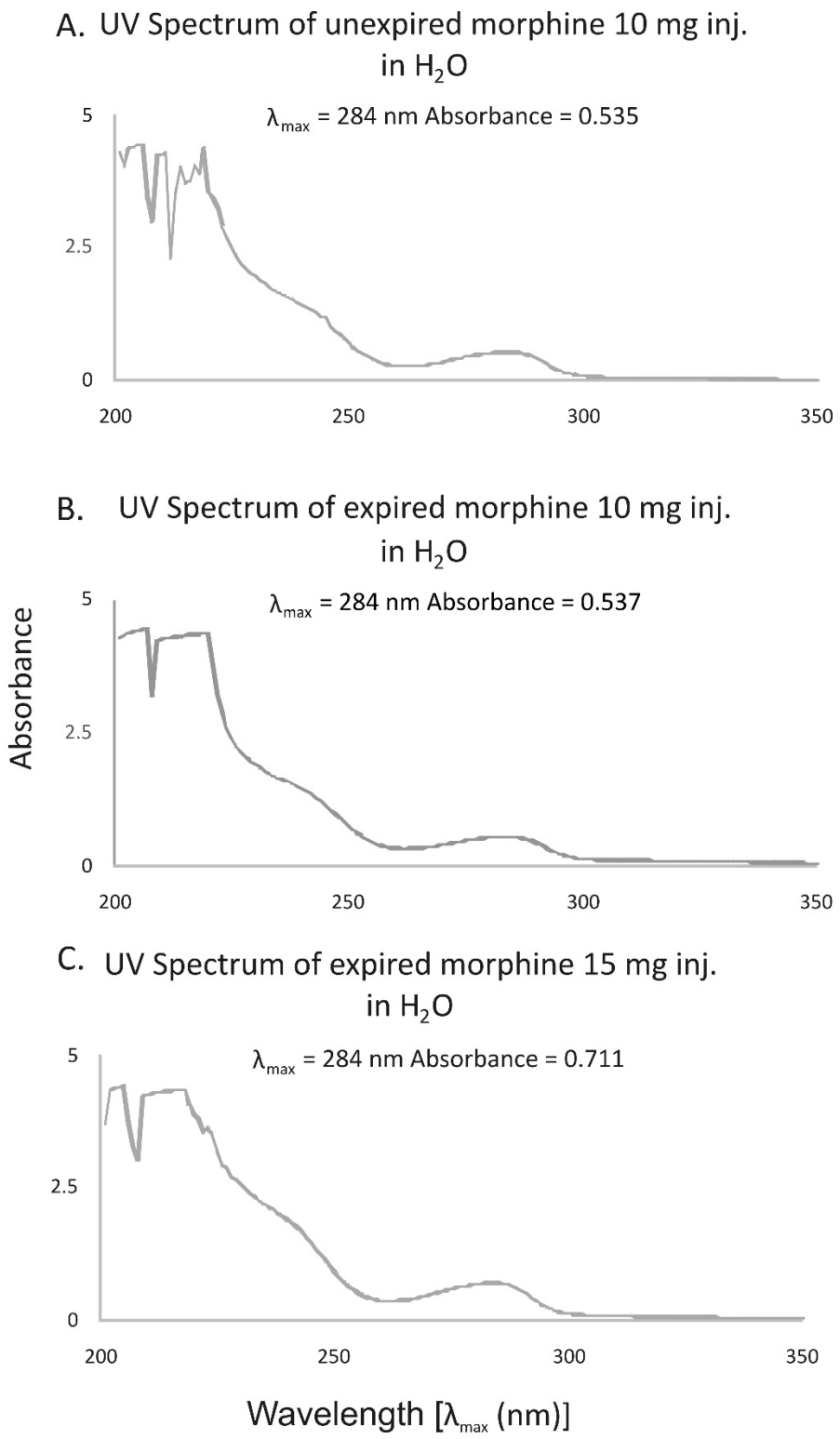

Figure 2: Comparison of unexpired morphine 10 mg injection spectrum (A) with expired morphine 10 mg (B) and 15 mg (C) injection spectra using H_2O as assay solvent

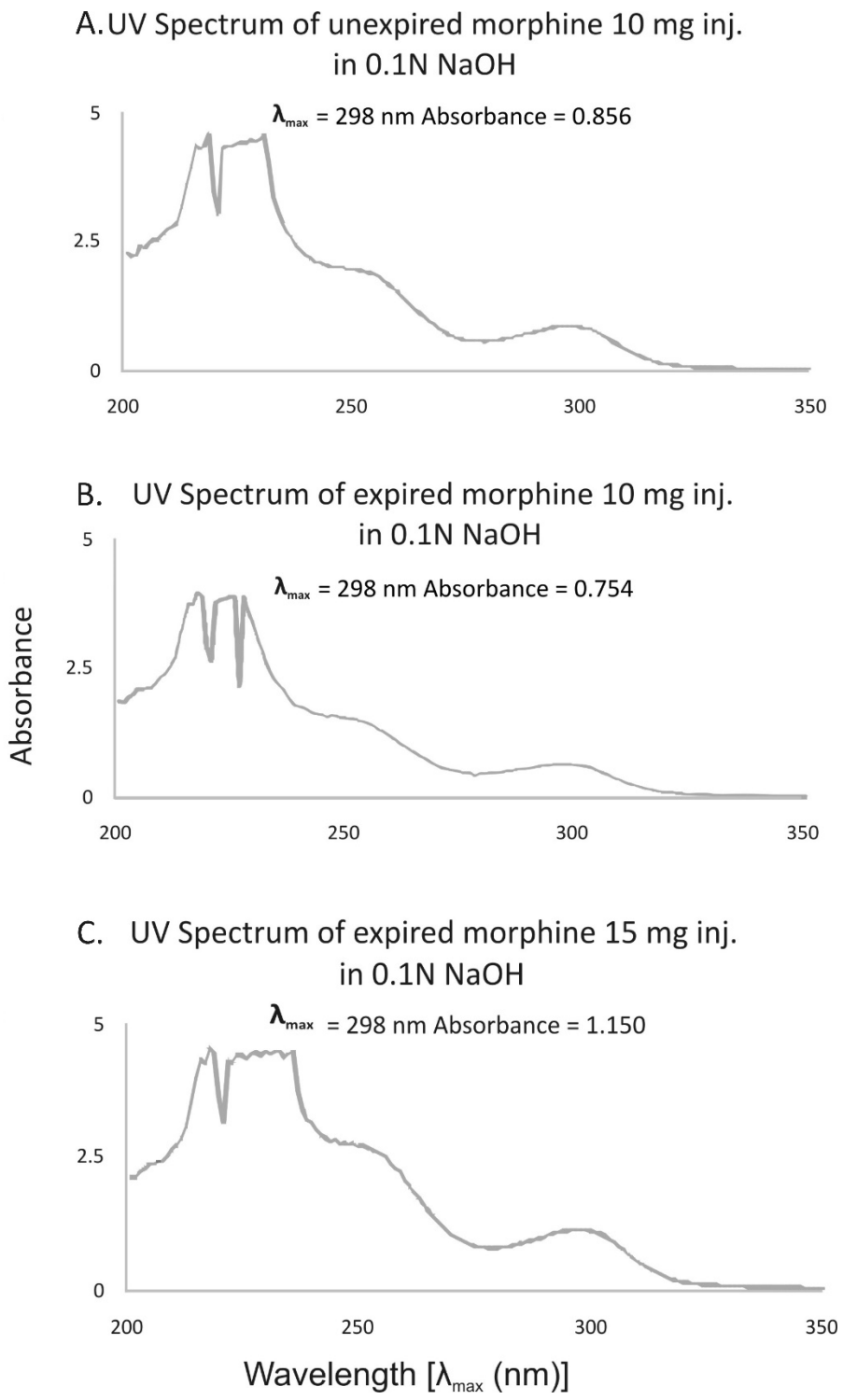

Figure 3: Comparison of unexpired morphine 10 mg injection spectrum (A) with expired morphine 10 mg (B) and 15 mg (C) injection spectra using 0.1N NaOH as assay solvent.

DISCUSSION

Comparison of potencies between the three products with water as the assay solvent showed significant difference ($P < 0.001$) although post-hoc analysis revealed that the significant differences were only between unexpired morphine 10 mg injection versus expired morphine 15 mg injection [13.98% (11.05, 16.92)] and between expired morphine 10 mg injection versus expired morphine 15 mg injection [11.30% (6.57, 16.03)]. Expired morphine 10 mg injection was not significantly different from the unexpired morphine 10 mg injection [2.68% (-0.56, 5.92)].

Similarly, the potencies of the three products were different ($P < 0.001$) using 0.1N NaOH as assay solvent. However post-hoc analysis indicated that the significant difference was only between unexpired morphine 10 mg injection versus expired morphine 15 mg injection [13.02% (8.95, 17.08)]. Expired morphine 10 mg injection versus unexpired morphine 10 mg injection [7.33% (-3.40, 18.06)]; as well as expired morphine 10 mg injection versus the 15 mg injection [5.68% (-2.36, 13.73)] were not significantly different.

The analyzed expired morphine sulphate 10mg and 15mg injections were found to have > 90% of labeled amounts of active ingredient which is the recognized minimum acceptable potency within their shelf-life (United States Pharmacopeial Convention, 2012). A drug's shelf-life is defined by the period of time its pharmaceutical potency is > 90% (Kommanaboyina and Rhodes, 1999). The chemical nature of a drug within its shelf-life is expected to remain stable and not contaminated or degraded into byproducts (Culbertson, 2011). The mean potencies of both the unexpired and expired morphine injections using water as the assay solvent were significantly higher when compared with those using 0.1N NaOH. Using the lower assay values of the 0.1N NaOH, the potency of both the unexpired (120%) and the expired (113%) morphine 10 mg injections exceeded the United State Pharmaceutical Codex acceptance criteria of 90.0% – 110.0%. However, expired morphine 15 mg injection with potency of 106% was within the USP limit. The comparisons of relative potency of expired 10 mg and 15 mg injections to the unexpired 10 mg injection were 94% and 88% respectively.

Result of this study shows that both the 10 mg and 15 mg morphine sulphate injections retained a significant amount of their original potency approximately half a year after the labelled expiration date as their % contents of active morphine were above the lower permissible limit of 90% according to USP criteria. These results corroborate a previous study which reported that expired morphine sulphate injection, like many other drug products, may have extended shelf lives beyond their expiration date (Shelf-Life Extension Program [SLEP], 2018). The SLEP undertaken by the FDA for the Department of Defense in which morphine sulphate injection was one of the over 122 different drug products that were assessed and found to be potent, provides the best evidence that some drugs can outlive their expiration dates. The American Medical Association (2001) and Anon (2015) have also shown that many medications were still potent decades beyond their expiration dates. Expiration dates are the final days that the manufacturer guarantees the full potency and safety of medications (Gikonyo *et al*., 2019). However, the actual shelf life of a drug may be much longer than the assigned expiration date as stability studies have shown (Lyon *et al*., 2006: Jasinska *et al*., 2009). Thus, labeled expiration dates may not really imply points at which medications are no longer effective or have become

unsafe to use. Solid's dosage forms such as tablets, and capsules appear to be most stable past their expiration dates compared to liquid dosage forms such as suspensions and emulsions (Simons *et al*., 2000; Gikonyo *et al*., 2019). Most liquid dosage forms, unlike solid pharmaceuticals, usually maintain a shelf-life that is very comparable to their given dates of expiration (Lougheed *et al*., 1983). The ability of a drug to have an extended shelf life is not only greatly dependent upon the individual drug or actual active pharmaceutical ingredient. The production batch, presence of preservatives, and storage conditions are also very important factors (Culbertson, 2011). Expired medications that contain preservatives, such as ophthalmic (eye) drops, may be unsafe after expiration date due to outdated preservatives which may allow bacterial growth in the solution (Anon, 2015). Proper storage of medications may help to extend their potency. When stored under optimal conditions, many drugs retain 90% of their potency for up to five years beyond the labeled expiration date (Abramowicz, 2002). The morphine injections in the present study are without preservatives and are probably stored under optimum storage conditions as shown by the percentage content retained past their expiry date, and therefore, may be good to use.

The most important implication of this study is that while it is always best to use unexpired medication, expired medicine should only be considered when it becomes the sole available option especially in clinical situations (owing to lack of viable alternatives or financial concerns) where the benefits of usage of the expired medication outweighs doing nothing at all. However, it is important that the current potency or stability of the expired medicine be experimentally ascertained before use, rather than extrapolating from results of previous studies.

A major limitation of this study was the lack of morphine reference standard for the assay as we had to resolve to the use of the specific absorbance value as well as comparison of results with that of an unexpired product to serve as control. Secondly, the opportunistic nature of the study, as it was warranted due to scarcity of parenteral morphine preparations in Nigeria as at the time of this study. This necessitated the small-scale pilot nature of the study. In addition, studies have shown that shelf-life can greatly vary depending on the brands (due to the different excipients/chemically inactive ingredients) or the individual drug lot (resulting from minor inconsistencies between batch productions) (Borgheini, 2003; Lyon, *et al*., 2006). Hence, incorporation of different brands and batches of expired morphine injections into the study would have provided greater insight.

CONCLUSION

In conclusion, study results suggest that morphine sulphate injection retains its potency and may be stable beyond its expiry date if stored within the recommended storage conditions. Thus, possibility of considering the use of this product when clinical situations warrant exist, provided its potency and stability levels at the time of usage are established.

References

Abramowicz, M. (ed). (2002), Drugs past their expiration date. *Med. Lett. Drugs Ther*. 44(W114B):93–94.

American Medical Association (2001). "Pharmaceutical Expiration Dates." Report 1 of theCouncil on Scientific Affairs (A-01). Retrieved July 30, 2020 from https://www.documentcloud.org/documents/3671873-CSA-Rep-1-Pharmaceutical-Expiration-Dates-a-01.html

Anon (2015). Drugs past their expiration date. *Med. Lett. Drugs Ther*. 57(1483):164-165.

Ben Haddou, T., Béni, S., Hosztafi, S., Malfacini, D., Calo, G., Schmidhammer, H. and Spetea, M. (2014). Pharmacological investigations of N-substituent variation in morphine and oxymorphone: opioid receptor binding, signaling and antinociceptive activity. *PloS One*, 9(6), e99231.

Benyhe, S.; Zádor, F. and Ötvös, F (2015). Biochemistry of Opioid (Morphine) Receptors: Binding, Structure and Molecular Modelling. *Acta Biol. Szeged*. 59 (1), 17–37.

Blakemore, P. R. and White, J. D. (2002). Morphine, the Proteus of organic molecules. *Chem Commun (Camb).* (11), 1159–1168.

Borgheini, G. (2003). The bioequivalence and therapeutic efficacy of generic versus brand-name psychoactive drugs. *Clin. Ther.* 25(6), 1578-1592.

British Pharmaceutical Codex (BPC, 2018). The Stationery Office, London.

Cantrell, L., Suchard, J. R., Wu, A. and Gerona, R. R. (2012). Stability of active ingredients in long-expired prescription medications. *Arch. Intern. Med*. 172(21), 1685–1687.

Culbertson, N. T. (2011). What can be done with expired pharmaceuticals? A review of literature as it pertains to special operations forces medics. *J Spec Oper Med.* 11(2), 1–6.

Ehrlich-Rogozinsky S. and Cheronis N.D. (1963). The identification and determination of morphine. *Microchem. J.* 7 (3): 336-356.

Facchini, P.J. and Bird, D.A. (1998). Developmental regulation of benzylisoquinoline alkaloid biosynthesis in opium poppy plants and tissue cultures. *In Vitro Cell. Dev. Biol. Plant* 34, 69–79.

Gikonyo, D., Gikonyo, A., Luvayo, D. and Ponoth, P. (2019). Drug expiry debate: the myth and the reality. *Afr. Health Sci.* 19(3), 2737–2739.

Hanks, G. W., Conno, F., Cherny, N., Hanna, M., Kalso, E., McQuay, H. J., Mercadante, S., Meynadier, J., Poulain, P., Ripamonti, C., Radbruch, L., Casas, J. R., Sawe, J., Twycross, R. G., Ventafridda, V. and Expert Working Group of the Research Network of the European Association for Palliative Care (2001). Morphine and alternative opioids in cancer pain: the EAPC recommendations. *Br. J. Cancer* 84(5), 587–593.

Jadhav, K., Dhamecha, D., Tate, A., Tambe, H. and Patil, M. B. (2011). Application of UV spectrophotometric method for easy and rapid estimation of lafutidine in bulk and pharmaceutical formulation. *Pharm. Methods* 2(4), 264–267.

Jasinska, M., Karwowski, B., Orszulak-Mickalak, D. and Kurczewska U. (2009). Stability studies of expired tablets of metoprolol tartrate and propranolol hydrochloride. Part 1. Content determination. *Drug Res*. *66*(6), 697-701.

Kommanaboyina, B. and Rhodes, C.T. (1999). Effects of temperature excursions on mean kinetic temperature and shelf life. *Drug Dev Ind Pharm*. 25(12), 1301-1306.

Lougheed, W.D., Albisser, A.M., Martindale, M.H., Chow, J.C. and Clement, J.R. (1983). Physical stability of insulin formulations. *Diabetes 32*(5), 424-432.

Lyon, R., Taylor, J., Porter, D., Prasanna, H. and Hussain, A. (2006). Stability profiles of drug products extended beyond labeled expiration dates. *J. Pharm. Sci*. 95(7), 1549-1560.

Mandalà, M., Moro, C., Labianca, R., Cremonesi, M. and Barni, S. (2006). Optimizing use of opiates in the management of cancer pain. *Ther Clin Risk Manag*. 2(4), 447–453.

Murphy, P.B. and Barrett, M.J. (2019). Morphine. In: StatPearls. StatPearls Publishing, Treasure Island (FL); 2019.

National Center for Biotechnology Information (2020). PubChem Compound Summary for CID 5288826, Morphine. Retrieved September 4, 2020 from https://pubchem.ncbi.nlm.nih.gov/compound/Morphine.

Okpala, I. and Tawil, A. (2002). Management of pain in sickle-cell disease. *J. R. Soc. Med*. 95(9), 456–458.

Pathan, H. and Williams, J. (2012). Basic opioid pharmacology: an update. *Br. J. Pain* 6(1), 11-16.

Pharo, G. H. and Zhou, L. (2005). Pharmacologic management of cancer pain. *J Am Osteopath Assoc.* 105(11 Suppl 5), S21–S28.

Plante, G. E. and VanItallie, T. B. (2010). Opioids for cancer pain: the challenge of optimizing treatment. *Metab. Clin. Exp.* 59 Suppl 1, S47–S52.

Schmitz, R. (1985). Friedrich Wilhelm Sertürner and the discovery of morphine. *Pharm Hist.* 27(2), 61–74.

Schug, S. A., Zech, D. and Dörr, U. (1990). Cancer pain management according to WHO analgesic guidelines. *J. Pain Symptom Manag.* *5*(1), 27–32.

Shelf-Life Extension Program (2018) Database. The Department of Defense/Food and Drug Administration Shelf-Life Extension Program (SLEP). Retrieved November 24, 2020 from https://slep.dmsbfda.army.mil/portal/page/portal/SLEP_PAGE_GRP/SLEP_HOME

Simons, F. E., Gu, X. and Simons, K. J. (2000). Outdated EpiPen and EpiPen Jr autoinjectors: past their prime? *J. Allergy Clin. Immunol.* 105(5), 1025–1030.

United States Pharmacopeial Convention 2012: Morphine Sulphate injection Revision Bulletin. Retrieved October 30, 2020 from https://www.uspnf.com/sites/default/files/usp_pdf/EN/USPNF/2012-11-30_morphine_sulfate_injection_rb_text.pdf

White, J. D., Hrnciar, P. and Stappenbeck, F. (1997). Asymmetric synthesis of (+)-morphine. The phenanthrene route revisited. *J. Org. Chem.* 62, 5250–5251.