THE Pharmaceutical Journal of Kenya

PJK

Vol. 28 No. 1/2024

ISSN 2411-6386

FEATURE ARTICLE:

Evaluation of Cross-linked Methylcellulose and cross-linked Acacia gum as suspending agents in Ibuprofen oral suspension

OFFICIAL JOURNAL OF THE PHARMACEUTICAL SOCIETY OF KENYA

PUBLISHED BY:

Pharmaceutical Society of Kenya
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The Pharmaceutical Society of Kenya (PSK) is a representative organization that was formed enabling Pharmacists' to employ their professional expertise in the care of patients.

Established in 1964, PSK has its roots in the Pharmaceutical Society of East Africa, which was registered in 1950. Since its formation, PSK continues to promote a common standard for professional conduct and code of ethics for its members, as well as advocate for the welfare of Pharmacists.

EDITORIAL

Challenges in the pharmaceutical supply chain in Kenya

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Editor-in-Chief and Chair of the Editorial Board, Pharmaceutical Journal of Kenya

Delivery of medicine as a strategic product is crucial in any healthcare system. Over the years pharmaceutical supply chains have grown so complex because of involvement of many stakeholders like drug manufacturers, wholesalers, distributors, governments, hospitals, customers, information service providers and regulatory agencies. Pharmaceutical companies are subject to many risks that can interrupt the quantity and quality of supply of medicine and their delivery to the right place and time (1, 2). The Sessional Paper No. 4 of 2012 on the Kenya National Pharmaceutical Policy (3) provides for better management and delivery of pharmaceutical services through relevant reforms; strengthened national medicines supply chain, regulation and quality control; better developed and managed pharmaceutical human resources; and enhanced collaborations.

Supply chain management is the amalgamation of key business processes to generate value for customers and stakeholders [2, 4]. The Council of Supply Chain Management Professionals defines supply chain management as the planning and management of all activities involved in sourcing, procurement, conversion and all logistics activities [5]. There are a variety of aspects to evaluate in supply chain [6]. These include eliminating bottlenecks; balancing between material cost and transportation; optimizing manufacturing flow; maintaining the right mix and location of factories and warehouses; vehicle routing analysis; and dynamic programming. The efficient use of capacities, inventories, and labours are major components of supply chain optimization [6]. Pharmaceutical supply chain should deliver medicines in the right quantity and quality; to the right place and customers; at the right time; at optimum cost; and still make profits for the stockholders [2].

The various supply chain external and internal stakeholders drive, facilitate, or inspect the process of sustainable supply chain management practices. The supply chain is complicated by the fact that it is responsible for the distribution of prescription drugs, over-the-counter (OTC) medicines, branded drugs, generics, as well as biologics, all having different handling needs and operational objectives [7]. Other organizations that come in to increase the complexity include insurance companies, healthcare management organizations, and Group Purchasing Organizations (GPO's).

The main barriers to quality Pharmaceutical Supply Chain include counterfeiting, adverse drug reactions, and issues related to supply chain operations. Barriers to quality manufacturing may include mixing incorrect input raw materials, or cross contamination when more than one drug is manufactured in one facility, or improper labelling of the final product. Other barriers include retailer's issues like improper temperature controls and handling; transportation issues caused by mishandling, improper temperature controls, and use of improper shipping mode; storage and warehousing issues like improper temperature controls, improper handling and mixing products with raw materials. Finally, raw material suppliers' issues such as poorly prepared raw material, raw material with high impurity levels and mislabeling of raw material shipments can also form major barriers [2, 8]. Pharmaceutical Supply Chain gets more complex because of challenges such as lack of coordination, poor inventory management, inadequate demand information, human resource dependency, on-shelf expiration, warehouse management, temperature control and shipment visibility. New and expensive medicines are continuously developed to overcome drug dependency, resistance, and to alleviate human suffering from difficult-to-treat diseases. Bringing such drugs to new markets like Kenya is a major challenge as registration is largely a costly and lengthy process [9].

Notably, there is lack of quality assurance for antimicrobial susceptibility data, hence lack of anti-microbial Resistance data and poor implementation of prudent anti-microbial utilization in public health. In addition, there are cases of unqualified personnel administering medicines to animals and operating small unlicensed retail outlets for agricultural products and veterinary medicines. In Kenya, there is countrywide uncontrolled access and over the counter (OTC) dispensing of antimicrobials; and often this occurs in open markets to the general public. Consequently, overuse and misuse of antimicrobials is prevalent. Misuse, sale of counterfeits, substandard drugs and smuggling of drugs all make it difficult to control access to antimicrobials with optimal usefulness.

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A comparative study of the dissolution profiles of selected Diclofenac Sodium Tablets available in Nairobi County, Kenya

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Abstract

Introduction: Diclofenac sodium is a widely used cyclooxygenase inhibitor for anti-inflammatory, analgesic and antipyretic activities in the treatment of osteoarthritis and joint pains. The drug has a high permeability and low solubility, thus falls under Class II in the BCS classification. Generic drugs are becoming widely used in the local market due to their affordability and therefore the need to have published reports on their comparative dissolution and bioequivalence studies to show conformance to prescribed standards of quality, safety and efficacy.

Objective: The objective of this study was to compare the dissolution profiles of diclofenac sodium 100mg tablets from different generic brands available in the market with the innovator product, Voltaren Retard® 100mg tablet.

Methods: Samples of the innovator and three generic brands of diclofenac sodium tablets 100 mg were analysed using United States Pharmacopeia specifications and single-point dissolution specifications. The similarity factor, f2, and difference factor, f1 were then determined.

Results: The innovator and two generic brands met the USP specifications for dissolution of diclofenac sodium tablets. However, only one brand complied with the requirements for similarity factor between the innovator and generic product while two other brands failed to comply.

Conclusion: The study shows that most generic diclofenac tablets in Kenya do not meet similarity requirements with the original brand. Monitoring is crucial for safety and effectiveness of generic diclofenac 100mg tablets.

Key words: *Diclofenac sodium, extended release, innovator, generic .*

Introduction

Diclofenac sodium is an NSAID that is widely used to manage joint pain, osteoarthritis, and rheumatoid arthritis by inhibiting cyclooxygenase, an enzyme responsible for the synthesis of prostaglandins, which are associated with inflammation and pain [1]. The Biopharmaceutics Classification System classifies diclofenac sodium as a class II drug due to its low solubility (17.8 mg/L) and high permeability (log P of 4.4), which may limit its absorption because of its weak acidic nature and low lipophilicity, particularly at lower pH levels [2, 3]. Diclofenac sodium tablets are available in immediate-release and extended-release formulations, each with different dosing schedules. Due to gastrotoxicity, all diclofenac sodium oral formulations are enteric-coated [4, 5]. The delayed release and extended-release tablets should not be dispensed interchangeably as overlapping product strengths may occur [4, 5, 6]. For instance, diclofenac sodium tablets approved by the FDA include Voltaren® delayed- release tablets (25mg, 50mg) and Voltaren XR® extended-release tablets (100mg) [7].

Recently, the acceptance of generic drug products as a cost-saving measure in healthcare has increased. Generic products are intended to be interchangeable with innovator products, satisfying the same standards of quality, efficacy, safety, and clinical interchangeability [8, 9, 10]. However, there are no published reports of comparative dissolution or bioequivalence studies on generic diclofenac oral formulations in the Kenyan market [11]. The aim of this study was to determine whether three different brands of 100mg diclofenac sodium extended-release tablets have equivalent pharmaceutical properties to the innovator product Voltaren Retard® 100mg tablet through comparative dissolution testing.

Methodology

Sampling

Samples of the innovator and three generic brands of diclofenac sodium tablets 100 mg were collected from pharmacy outlets in Nairobi central business district. A sample size of 120 tablets (30 tablets per brand) was obtained on 23rd April 2020. The batch number, manufacture and expiry dates, physical appearance, list of excipients, and manufacturer name were recorded. The three generic brands were selected based on an initial survey on the most frequently purchased brands [4]. All tablet brands were light pink/orange, biconvex, and blister packed in strips of ten.

Determination of uniformity of weight

The weight variation of each brand was evaluated by selecting twenty tablets randomly from each brand and weighing them on an analytical top-loading balance. Twenty tablets were selected randomly from each brand and weighed on an analytical top-loading balance. The weight

variation of each brand was determined using the average weight of the 20 tablets and the standard deviation for each brand determined according to the British Pharmacopeia.

Determination of hardness of tablets

Tablet hardness was determined by means of diametrical compression using a tablet hardness tester as per the British Pharmacopeia.

Dissolution and Disintegration Test of extended release Diclofenac Sodium Tablets

The disintegration test and dissolution test were carried out in accordance to the United States Pharmacopeia [2]. A comparative in-vitro dissolution study was conducted using USP Type II apparatus and following the US Pharmacopeia procedure. Dissolution media of 0.1N HCl for 2 hours and phosphate buffer pH 6.8 for 10 hours were used at 37±0.5°C and 50 rotations per minute. Samples were taken at specific time intervals, filtered, diluted, and the absorbance measured at 276 nm using a UV spectrophotometer. The percentage of drug released at each time point was calculated, and similarity factor (f2) and difference factor (f1) were determined using standard mathematical equations.

Results

Hardness, weight variation, diameters, thickness and disintegration

Table 1 shows a comparison of physicochemical properties of three different brands of extended release diclofenac sodium against the innovator brand.

Table 1. Physical Properties of Selected Brands of Diclofenac Sodium 100mg Extended Release Tablets

Brand	Hardness (kp)	Diameter (cm)	Thickness (cm)	Average tablet weight (mg) and Weight variation (%)	DT in 0.1N HCL	DT in Phosphate buffer (pH 6.8)
A	17.4	0.91	0.42	303.1,1.31	No disintegration after 120min	76min
B	>20	0.94	0.33	255, 1.36	No disintegration after 120min	46min
C	12.4	0.91	0.39	285.9, 1.38	No disintegration after 120min	77min
D	15.7	0.95	0.43	333.9,1.4	No disintegration after 120min	11min

Note: Values are expressed as mean ± standard deviation (n=20). Brand A refers to the innovator product, while brands B, C and D refer to the generic products. DT= Disintegration Time.

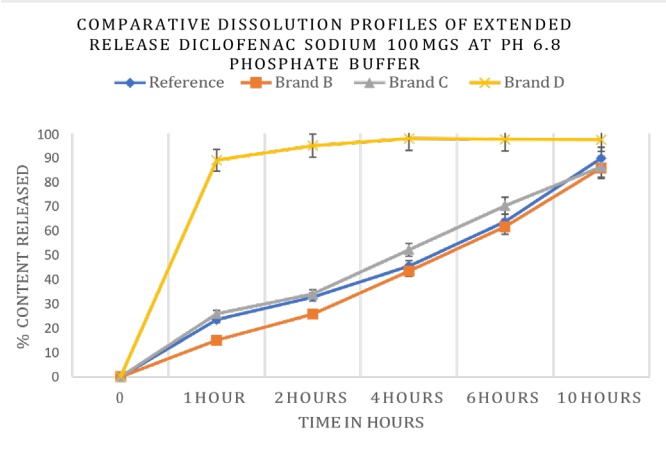
Dissolution profiles

Table 2 provides the dissolution data for the generic and reference extended-release diclofenac sodium 100 mg tablets in pH 6.8 buffer.

Table 2. Display of intricate data regarding how the generic (B, C and D) and the reference(A) extended release diclofenac sodium 100mg tablets dissolve in a pH 6.8 buffer solution.

% Content Released					
Brand					
Time in Hours	A-Reference	B	C	D	USP Specifications
1	23.48±	15.02±	25.95±	88.94±	not more than 28%
2	32.78±	25.78±	34.00 ±	94.92±	between 20% and 40%
4	45.48±	43.45±	52.18±	97.91±	between 35% and 60%
6	63.7±	61.67±	70.28±	97.58±	between 50% and 80%
10	89.79±	85.78±	86.24±	97.39±	not less than 65%

Graph 1 shows the comparison of percentage content released against dissolution time points 0, 1,2,4,6 and 10 hours of generic and innovator brands of extended release of diclofenac sodium 100mgs tablets.



Graph 1. Comparison dissolution profiles of extended release diclofenac sodium 100mg at pH 6.8 phosphate buffer.

Calculation of comparative dissolution profile fit factors (f1 and f2)

The US FDA guidelines were used to calculate the fit factors, namely the difference factor f1 and the similarity factor f2, using Brand A as the reference. The results are presented in Table 3. For the dissolution profiles to be considered similar, the f1 values should be close to 0 (0 to 15) and the f2 values should be close to 100 (50-100).

The f1 value was calculated using the formula:

$$F1 = \{[\Sigma\ t=1\ n\ |Rt-Tt|] / [\Sigma\ t=1\ n\ R]\}*100$$

where n is the number of time points, Rt is the dissolution value of the reference brand at time t, and Tt is the dissolution value of the test brand at time t.

The f2 value was calculated using the formula:

$$F2 = 50 \times \log \{[1+ (1/n)\ t=1\ n\ (Rt - Tt)2]-0.5 \times 100\}$$

where n is the number of time points, Rt is the dissolution value of the reference brand at time t, and Tt is the dissolution value of the test brand at time t.

Table 3. Results of the f1 and f2 calculations for the different generic brands relative to Brand A.

	Brand B	Brand C	Brand D
f1 values	4.46	3.94	-8.46
f2 values	48.35	50.99	34.5

Discussion

All the four brands passed the test for weight uniformity, an important predictor of tablet quality and efficient manufacture procedures. The intra-brand deviations in weight variation were below the permissible ±5% value for each individual tablet in accordance with USP limits for tablets weighing above 250 milligrams [4]. The difference in tablet mean weight across the four brands indicates the use of different excipients in formulation. The diameter and thickness values of the four tablet brands were comparable with a mean deviation below ±5% as per BP specifications of tablets of 12.55mm or less diameter. The consistency of tablet diameter and thickness in either generic or innovator brands is not necessary, but may optimize consumer acceptability when offered an alternative brand [12]. A crushing strength of 4-15kp is recommended for tablets as per the BP 2010, specifications. Only brand C tablets had values within the acceptable limits. These high hardness values observed may be attributable to choose/concentration/in cooperation method of binding agent, high compression forces or tablet coating [13]. Hardness is an important determinant in tablet resistance to chipping, breakage under storage, transportation and handling. However, excessive hardness of tablets increases disintegration time, decreases the release of the drug as well as promotes tablet capping on attrition [14-16].

The USP specifies that enteric coated tablets should remain intact for 2 hours in simulated gastric media (0.1N HCl) and thereafter disintegrate within 1 hour in simulated intestinal media (pH 6.8 phosphate buffer) [16]. All tablet brands complied with this specification, in the simulated gastric media, indicating the tablet coatings resisted dissolution at gastric pH. However, only tablets of Brand B and D complied with disintegration specifications in the simulated intestinal media. Tablet of Brand A and C took slightly longer than an hour to disintegrate. It is noteworthy that there was no association observed between the disintegration time and the hardness of the tablets.

The reference brand A and generic brands B and C met the dissolution specifications recommended by the US Pharmacopeia (USP) for extended-release diclofenac sodium tablets. However, brand D did not comply with the USP specifications at any time point, with 88.94% of the API dissolving within the first hour. This indicates that brand D is not an extended-release tablet and does not demonstrate sustained release properties.

Since about 95% of the drug was released within the first 2 hours, it is unlikely to remain available in the body for extended periods, especially considering the drug's relatively short half-life of approximately 2 hours, during which it is metabolized and eliminated through the liver and kidney. If brand D were administered as an extended-release tablet, the immediate release pattern observed would likely result in therapeutic failure. The different extended drug release rates observed with brands A, B, and C may be attributed to the varying types, sources, and concentrations of polymers used as release-controlling agents, such as HPMCP and sodium carboxymethyl cellulose. These polymers exhibit different degrees of water penetration, swelling, and matrix erosion, which can influence the drug release rate [12,13,16]. Additionally, different strategies, such as osmotic pumps, polymeric matrices or coatings, may have been used in the formulation of extended-release tablets.

Only one batch, batch C, of the three tested generic products met the similarity factor requirements between the innovator and the generic batch with a value of 50.99. However, both batch B (48.35) and batch D (34.5) failed to meet the specifications set by the US FDA guidelines [10]. This indicates a compliance rate of 33% for the tested generic products. The demonstration of overall profile similarity is essential as it predicts the comparability to and interchangeability with the reference product. That only one product subjected to experimental dissolution profile testing was similar to the innovator product raises valid concerns on the therapeutic results obtained when the different generic products in the market are used.

All the products met the specifications for the difference factor f1 as per the US FDA guidelines except Brand D (-8.46). Brand D also failed to comply with USP specifications for the dissolution of diclofenac sodium extended release tablets, displaying immediate drug release. Brand D which has similar dosage strength, appearance, packaging to Brands A, B, C and was sold interchangeably highlights a medication prescribing/dispensing concern.

Conclusion

The dissolution profiles of the extended release diclofenac sodium 100mg tablets were found to have significant differences. Out of the brands tested, only one generic brand met the specifications for both difference and similarity factors when compared to the innovator product, while three brands were compliant with the USP dissolution specifications. Additionally, one of the brands demonstrated a drug release pattern that is characteristic of delayed release tablets.

Acknowledgments

The authors would like to thank the School of Pharmacy's Department of Pharmaceutics and Pharmacy Practice and the Drug Analysis and Research Unit (D.A.R.U) at the University of Nairobi for providing the research facilities required for this study. Their contribution is gratefully acknowledged.

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Evaluation of Cross-linked Methylcellulose and cross-linked Acacia gum as suspending agents in Ibuprofen oral suspension

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Abstract

The existing pharmaceutical oral suspensions in commerce are marred with inadequacies such as poor: redispersibility, sedimentation rate, degree of flocculation, stability, and inadequate dosing. A moderate polymer with superior properties than the parent polymer for more stable and accurate dosing of medicated oral suspension was designed.

Methylcellulose (MC), and Acacia gum (AG) were cross-linked separately using citric acid. The products were characterized by Fourier transforms infrared radiation (FTIR), swelling index, viscosity, and pH. The ibuprofen suspensions were prepared by using crosslinked MC (c-MC), crosslinked AG (c-AG), pure MC, and pure AG as suspending agents at concentrations of 1, 2, and 3% w/v (batches A1-3, B1-3, C1-3, and D1-3) respectively. They were evaluated for sedimentation volume, pH stability, viscosity, particle size, drug release, and stability.

The results of the study indicate that increasing the concentration of crosslinked polymer powder in suspensions improved physical stability. Formulation B3 contained 3.0% MC and was found to be extremely viscous, inability to flocculate, and had zero flow characteristics. Both A3 and C3 showed satisfactory physical stability (in terms of pH and viscosity); and were redispersed by shaking 6 and 4 times respectively. The degree of flocculation for B3 (MC) was 0.0 and redispersibility was impossible and therefore implies that there was no room for sedimentation of drug particles. Sedimentation rate, viscosity, degree of flocculation, redispersibility, and T90% for A3 were 0.86 cm3/day, 155.5 + 2.5 mPaS, 3.3.3, 6, and 45 min.; for C3 the results were 0.86 cm3/day, 174.1+0.5 mPaS, 3.3 + 0.1, 4 and 25 min respectively.

Among the formulated suspensions batches A3 and C3 containing 3 % c-MC and c-AG respectively showed better sedimentation rate, redipersibility, degree of flocculation, as well as better physical stability (pH) and in vitro drug release profile compared to other formulated suspensions (MC and AG). Both A3 and C3 formulations meet the characteristics of an ideal pharmaceutical suspension.

Key Words: *Ibuprofen, suspension, cross-linked polymer, acacia gum, methylcellulose.*

Introduction

A pharmaceutical suspension is a dispersible system and is thermodynamically unstable; it is necessary to introduce a stabilizer or suspending agent in the formulation to reduce the rate of settling and permitting easy redispersibility of any settled particulates by increasing the consistency of the suspending medium [1,2].

Pharmaceutical suspensions are dispersions of insoluble active pharmaceutical ingredients (API) in an aqueous or non-aqueous continuous phase. When dispersing APIs in suitable liquids the following must be taken into consideration: sedimentation, caking, flocculation, and particle growth [3]. Caking in a pharmaceutical suspension can be minimized with the production of flocculated systems. A flocculated suspension contains the active drug dispersed throughout a liquid medium. Minute particles of the drug associate themselves with one or more excipients to form an agglomerated mass which is referred to as a floccule. Other excipients act to suspend the snowflake-like floccules in water [4]. The viscosity of a suspension is affected by flocculation. Polymers or gums (e.g. tragracanth, bentonite, alginate, xanthan gum, carboxymethylcellulose sodium, etc.) have been widely used as suspending agents, to increase the viscosity of suspensions and therefore decrease the sedimentation rate of suspended particles [4].

Ibuprofen is classified as a non-steroidal anti-inflammatory drug, it is useful pharmacologically for the treatment of inflammation, dysmenorrhea, migraines, osteoarthritis, and rheumatoid arthritis. Ibuprofen formulations are available commercially as tablets in different doses such as 100 mg, 200 mg, and 400 mg. Other formulations include: 200 mg capsules; 100 mg chewable tablets, and 100 mg/5 ml oral suspension (liquid). Suspending agents may be inorganic materials, synthetic compounds, or polysaccharides. Natural gums or synthetic polymers have been widely used as tablet binders, emulgents, thickeners in cosmetics, and suspensions as film-forming agents and transitional colloids [5, 6].

A flocculated suspension is one in which solid particles are loosely aggregated to form a network structure called floccules. Floccules are light and fluffy and are held together

by a weak Vander Waals force of attraction. Aggregation could be attained by the inclusion of flocculating agents into the system. These types of suspensions will readily sediment. Flocculated suspensions possess better physical stability but less bioavailability as compared to deflocculated suspensions due to the dissolution of floccules.

Factors dictating the stability of suspensions include nanoparticle concentrations, dispersants, viscosity of base liquids, and pH value [7].

The overall objective of this study was to prepare and characterize novel crosslinked polymers from methylcellulose and acacia gum respectively using citric acid as a crosslinking agent and to investigate their suspending properties in terms of stability in ibuprofen suspensions.

Methodology

Data Analysis and Statistics

Ibuprofen (IBF) (Pvt. Limited, Hyderabad, India), Sorbitol, Tween 80, Citric acid (Biopac, CA, USA), Sodium benzoate, Methylcellulose (MC) (A4M, Methocel, Dow, USA) and Acacia gum (AG) (Loba Chemie, Pvt. Ltd. Mumbai) and other chemicals and reagents (of analytical grade) were used in the study.

A special method used in research by Demitri [8] was adopted. Methylcellulose (MC) 1.5 g was slowly dispersed in 50 ml distilled water at 80°C with constant stirring for 1h. Sorbitol (S) was added as a plasticizer at 0.25% concentration. Thereafter, citric acid (CA) was added to the mixture at 5(p/pMC) concentration as a crosslinked agent (in the solutions). Samples without citric acid were prepared and used as control. In all cases, a total of 100 ml volume was made up with cold distilled water. The products were dried in an oven until a constant weight was attained and then stored at 20°C and 65% relative humidity in a desiccator. The same processes were performed for acacia gum (in an equal ratio 1:1).

Physico-chemical characterization of the drug-polymer mixtures

Fourier Transform Infrared (FT-IR) Spectroscopy

FT-IR spectra of the crosslinked polymers, drug, and drug-excipients blend were investigated on an FT-IR spectrophotometer (Shimazdu, 8400S, and Shimazdu Corporation) in the frequency range between 4000 and 5000 cm-1 [9].

Determination of swelling index

A 500 mg of crosslinked methylcellulose was weighed and transferred into a petri dish, followed by the addition of 10 ml distilled water. The mixture was stirred and was allowed to stand for an hour. The remaining water in the Petri dish was removed after 1 hour, and the weight increase of the crosslinked methylcellulose was measured. For methylcellulose, crosslinked acacia, and acacia the same process was used.

$$Swelling\ Index\ \%\ (SI) = (W2 - W1/W1) \times 100 \text{ ---------- (1)}$$

W1 and W2 represent the weight of compact at time '0' weight of compact t at time 't' respectively.

Preparation of Ibuprofen suspensions

The quantity of MC (Table 1) was added to 2/3 (65 ml) of water and stirred with low shear forces until no lumps were visible. The suspension was allowed to stand for 10 minutes. Then it was stirred for 15 minutes with high shear forces. The mixture was allowed to stand for another 10 minutes. Thereafter, Ibuprofen, Sorbitol, Flavours, and Tween 80 were added with low shear forces, after which sodium benzoate was added with low shear forces. Finally, the mixture obtained was transferred into a 100 ml measuring cylinder and the volume was made up with distilled water and then stirred vigorously for 2 minutes. The entire procedures were repeated for other batches having crosslinked MC, AG, and cross-linked AG respectively as suspending agents. All formulations are shown in Table 1.

Table 1. Formulation design for various concentrations of primary and crosslinked polymers with their additives.

Ingredients	A1	A2	A3	B1	B2	B3	C1	C2	C3	D1	D2	D3	Function
tbuprofen (g)	2	2	2	2	2	2	2	2	2	2	2	2	Anti-inflammatory
Crosslinked	1	2	3										Suspending agent
MC (g)				1	2	3							Suspending agent
Crosslinked AG (g)							1	2	3				Suspending agent
Acacia (g)										1	2	3	Suspending agent
Simple syrup (ml)	10			10			10	10	10	10	10	10	Flavourant
Sodium benzoate (g)	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	Preservative
Tween 80 (g)	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	Stabilizer/ wetting agent
Glycerin (ml)	10	10	10	10	10	10	10	10	10	10	10	10	Sweetener/ viscosity enhancer
Purified water (ml) to:	100	100	100	100	100	100	100	100	100	100	100	100	

Key: MC- Methylcellulose; AG- Acacia gum

Evaluation of suspension

Sedimentation volume

Sedimentation volume (F) is the ratio of the final volume of sediment (V_u) to the original volume of sediment (V_o) before settling. Fifty milliliters (50ml) of each of the suspension batches were transferred to 50ml measuring cylinders and the volume of sediment formed was noted every 24 hr for 7 days.

The sedimentation volume F(%), was calculated using the formula:

$$F = 100\ Vu/\ Vo \quad \text{---------- (2)}$$

Viscosity measurement

The viscosity of each of the samples was determined at 25°C using the Brookfield Synchro-lectic viscometer, model LVF (Brookfield Laboratories, Massachusetts) at 30 revolutions/min (Spindle ≠ 4).

Particle size measurement of Ibuprofen suspension

The Ibuprofen particle size range in the suspensions was measured by optical microscopy using a trinocular microscope at 100x (10×10) magnification. The size of 100 particles was measured and the average particle size was determined.

Ibuprofen assay

The absorbance of known concentrations of IBF was measured in a UV/Vis spectrophotometer Shimadzu UV 2401 PC, (Shimadzu Company, Japan) at 221 nm after appropriate dilution and treatment of samples. A standard curve of ibuprofen was prepared in the range from 5 to 30 µg/ml. A blank formulation was included by preparing a solution of sucrose (1%), glycerine (1%), and sorbitol (1%) in water as control.

Drug release

The drug release studies were carried out according to a modified United States Pharmacopeia (USP) dissolution apparatus (Erweka, Germany) equipped with a paddle. Tests were performed in 900 mL of 0.01 N phosphate buffer pH 7.2, at 37±0.1°C at a paddle rotation speed of 50 rpm. A cellophane membrane containing 5.00 ml of solution or suspension was placed inside the vessel at time zero. Drug release from the cellophane membrane into the aqueous medium took place. After 15 min., 5 ml solution was withdrawn and the sink condition was maintained. Samples were withdrawn after time intervals of 30, 45, 60, 75, 90, 105, 120 and 135 min. The sample solutions were further diluted with 0.1 N HCL and absorbance was measured in a double beam UV-spectrophotometer (Schimadzu, UV-2401PC, Japan) at the maximum wavelength (max) of 264 nm. Each dissolution study was performed in triplicate.

Results

Transparent and flexible flakes of polymers were obtained for all citric acid crosslinked MC and AG. (Table 2).

Table 2. Physical characteristics of primary and crosslinked polymers.

Excipient/Material	Color	Texture
Crosslinked MC	Light brown	Crystalline
MC	White	Powdery
Crosslinked AG	Brown	Crystalline
AG	Cream	Powdery

The powder characteristics of both primary and crosslinked polymers are shown in Table 3.

Table 3. Powder characteristics of primary and crosslinked polymers

Materials	Weight of powder (g)	Bulk volume (cm^3)	Tapped volume (cm^3)	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Flow rate (gs^{-1})	Angle of repose (°)	Car's index (%)	Hauser ratio
Crosslinked									
MC	10.28	14.0	11.0	0.734	0.735	1.96	27.01	21.43	1.27
MC	10.28	18.5	13.0	0.556	0.791	0.52	38.66	29.73	1.42
Crosslinked									
AG	10.10	13.5	10.0	0.748	1.010	1.84	29.24	25.93	1.35
AG	10.10	14.5	11.5	0.697	0.878	2.53	27.41	20.76	1.26

Table 4 features the swelling index characteristics of both primary and crosslinked polymers.

Table 4. The swelling index (SI) of the suspending agent in water after 1 hour.

Suspending Agent	Initial Weight (g) W_I	Final Weight (g) W_F	SI = $[W_F - W_I]/W_I$	Percentage Increase (%)
MC	0.5	8.02	15.04	1504
c-MC	0.5	3.70	6.40	640
AG	0.5	0	0.00	0
c-AG	0.5	3.55	3.55	610

pH determination

The pH value for batch A (c-MC) and C (c-AG) showed a more constant value compared to the batches of suspension that were not crosslinked (batch B and D) (Table 5). The average pH for all preparations ranged between 6.5 and 7 throughout the experimental period.

Table 5. pH profile for all batches of suspensions

Batch	Day 3	Day 4	Day 6	Day 10	Day 22	Day 27	Day 35
A1	6.80	6.83	6.76	6.89	6.68	6.68	6.61
A2	6.80	6.80	6.65	6.86	6.66	6.63	6.53
A3	6.80	6.77	6.85	6.80	6.65	6.62	6.53
B1	8.76	6.99	6.98	7.0	6.95	6.88	6.85
B2	8.1	7.04	7.03	7.04	6.96	6.94	6.92
B3	8.9	7.08	7.09	7.08	7.02	7.01	7.00
C1	6.70	6.61	6.40	6.68	6.44	6.44	6.37
C2	6.68	6.52	6.42	6.39	6.34	6.35	6.24
C3	6.72	6.52	6.48	6.44	6.32	6.34	6.21
D1	7.25	6.97	6.96	6.95	6.82	6.80	6.76
D2	7.12	6.88	6.85	6.81	6.78	6.75	6.69
D3	8.55	6.94	6.73	6.86	6.67	6.65	6.55

Viscosity of suspension

Evaluation of the viscosity of all suspension formulations revealed a declined trend with an increase in rpm as seen in Figure 1a and Figure 1b

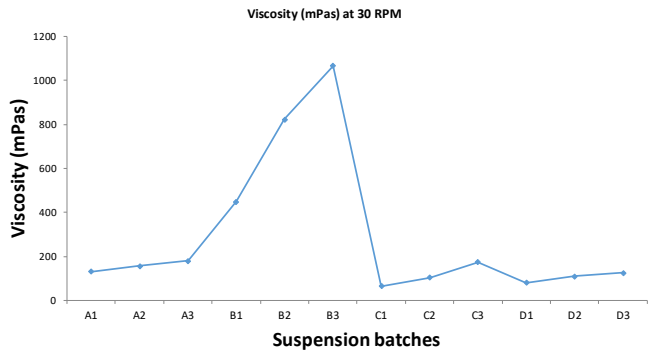

Figure 1a. Viscosity for all batches of suspension at 30 RPM

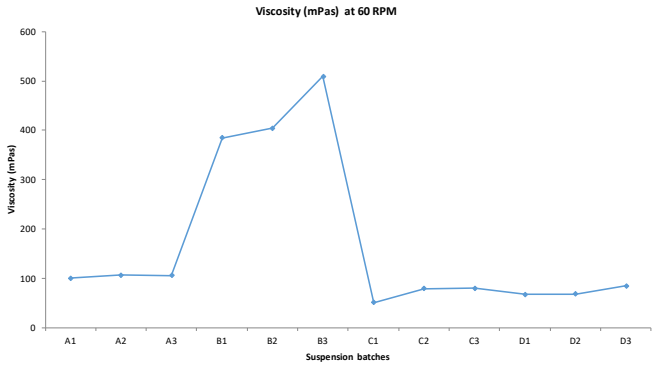

Figure 1b. Viscosity for all batches of Suspension at 60 Rpm

Physical property

The physical properties of the suspending agent used were found to have changed after cross-linking. Methylcellulose changed from white to light brown and the texture from powder to crystalline. Acacia gum was transformed from cream to reddish brown and the texture from powder to crystalline.

Micrometric property

Methylcellulose was found to have a bulk density of 0.556, tapped density (0.791), angle of repose (38.66), carr's index (29.73%), Hausner ratio (1.42) and flow rate of 0.52.

Crosslink methylcellulose was found to have a bulk density of 0.734, tapped density (0.735), angle of repose (27.01), carr's index (21.43%) Hausner ratio (1.27), and flow rate of 1.96.

Acacia gum was found to have a bulk density of 0.697, tapped density (0.878), angle of repose (27.41), carr's index (20.76%), Hausner ratio (1.26) and flow rate of 2.53

Crosslink Acacia gum was found to have a bulk density of 0.748, tapped density (1.010), angle of repose (29.24), carr's index (25.93%), Hausner ratio (1.35) and flow rate of 1.84.

Swelling index

The swelling index for methylcellulose, crosslink methylcellulose, and crosslink acacia gum was found to be 1504%, 640%, and 610% respectively at the end of 1 hour. On observation, the swelling index increased over time. Acacia gum had no swelling index.

Particle size of Ibuprofen suspension

Ibuprofen suspension particle diameter ranged between 12 – 28 µm and an average pH of 6.5.

Sedimentation volume

The sedimentation volumes of all formulated batches of ibuprofen suspensions measured over 35 days were as shown in Figure 2. The rate of particle sedimentation per day determined the sedimentation volume daily as observed over 35 days.

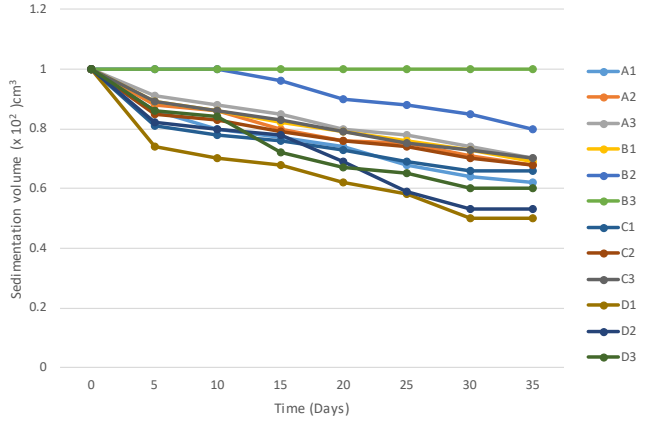

Figure 2. Sedimentation volume of various batches of suspension

KEY

A1 – A3	Crosslinked Methyl Cellulose (c-MC)
B1- B3	Methyl Cellulose (MC)
C1- C3	Crosslinked Acacia Gum (c-AG)
D1-D3	Acacia Gum (AG)

Degree of flocculation (β)

Figure 3 shows the results of the degree of flocculation as calculated using Equation 3 below.

$$\beta = F/F\infty \quad \text{----------(3)}$$

$$\beta = (Vu/Vo)\ \text{flocculated}/(Vu/Vo)\ \text{deflocculated}$$

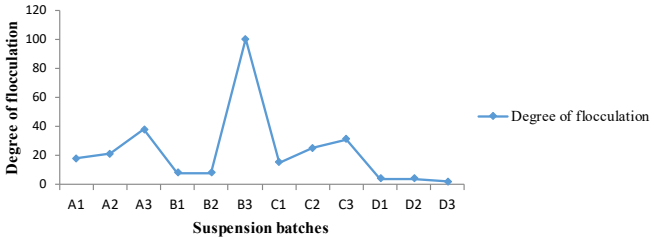

Figure 3. Degree of flocculation for suspension batches

Figure 4 shows the result of the redispersibility of various batches of ibuprofen suspensions. Batches A1-A3 and C1-C3 containing crosslinked polymers were dispersible with fewer shakes ranging from 3-6, whereas MC needed a higher number of shear stress ranging from 13 -23 for B1 and B2, but B3 exhibited total resistance to shear stress and became impossible to redistribute suspended particles.

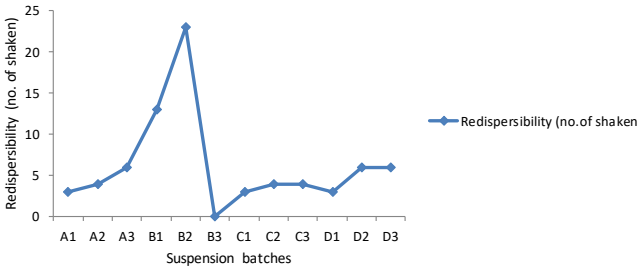

Figure 4. Redispersibility of suspension batches

Evaluation of sedimentation rate

The sedimentation rates were determined for four series of batches as shown in Table 8. The viscosities of the B series (MC polymers as suspending agent) are at the highest level followed by the A series (containing c-MC). The C series (c-AG) showed improved viscosity over the D series (AG as suspending agents).

Table 8. The physicochemical properties of ibuprofen suspensions after 35 days of experimental studies at room temperature and humidity.
SDV: Sedimentation volume; c-MC: crosslinked methylcellulose; c-AG: crosslinked acacia gum; MC: methylcellulose; AG: acacia gum; NF (Through syringe) Not Flowable.

Suspending agent		SDV	Sedimentation Rate (cm3 day-1)	Viscosity (mPas) n=3	Degree of flocculation (β= F/ F∞) n=3	Redispersibility (no. of shaken)	Flow rate (ml s-1) (Through a syringe)
A1	c-MC	0.62	1.10	179.3+1.2	2.6+0.2	3	NF
A2	c-MC	0.68	0.91	131.4+2.1	3.1+0.1	4	NF
A3	c-MC	0.70	0.86	155.5+2.5	3.3+0.3	6	NF
B1	MC	0.69	0.89	448.2+1.3	3.2+0.1	13	NF
B2	MC	0.80	0.57	822.8+1.4	5.0+0.0	23	NF
B3	MC	1.00	0.00	1066.3+2.5	100+0.0	∞	NF
C1	c-AG	0.66	0.97	65.3+0.3	2.9+0.3	3	NF
C2	c-AG	0.68	0.91	104.4+0.6	3.1+0.1	4	NF
C3	c-AG	0.70	0.86	174.1+0.5	3.3+0.1	4	NF
D1	AG	0.50	1.43	81.1+0.5	2.0+0.0	7	NF
D2	AG	0.53	1.34	109.4+0.2	2.1+0.1	6	NF
D3	AG	0.60	1.14	124.8+0.2	2.5+0.2	3	NF

Drug–polymer compatibility

Figures 5 A-E showed the FT –IR Spectroscopy A, Methylcellulose(A), Crosslinked MC (B), Acacia gum (C), Crosslinked Acacia gum (D), and Pure Ibuprofen (E).

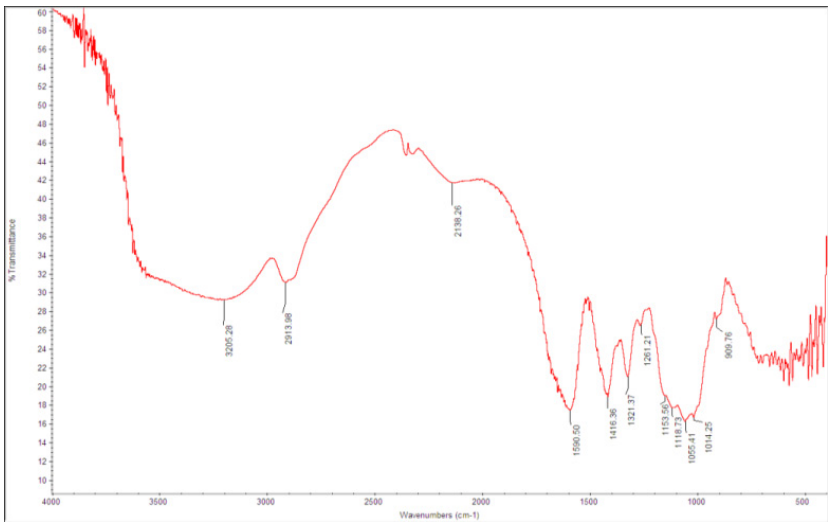

Figure 5A. FT –IR Spectroscopy: of, Methylcellulose;

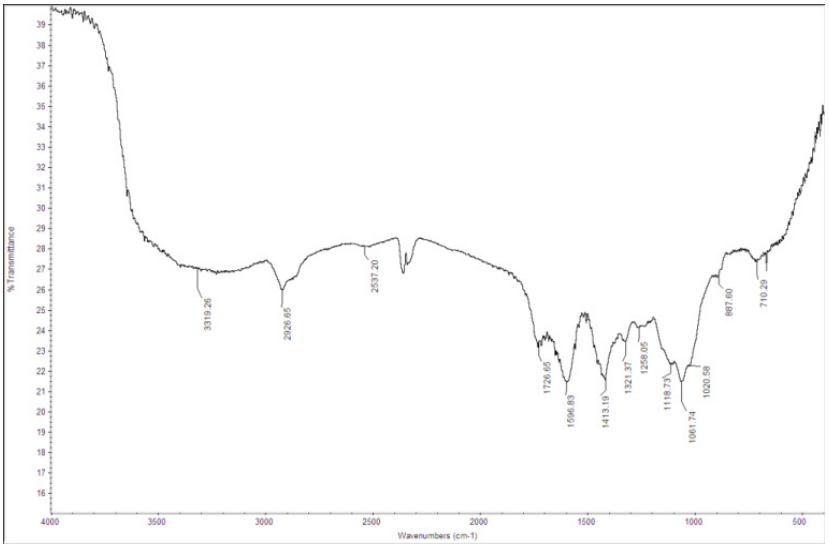

Figure 5B. FT –IR Spectroscopy; of, Crosslinked MC

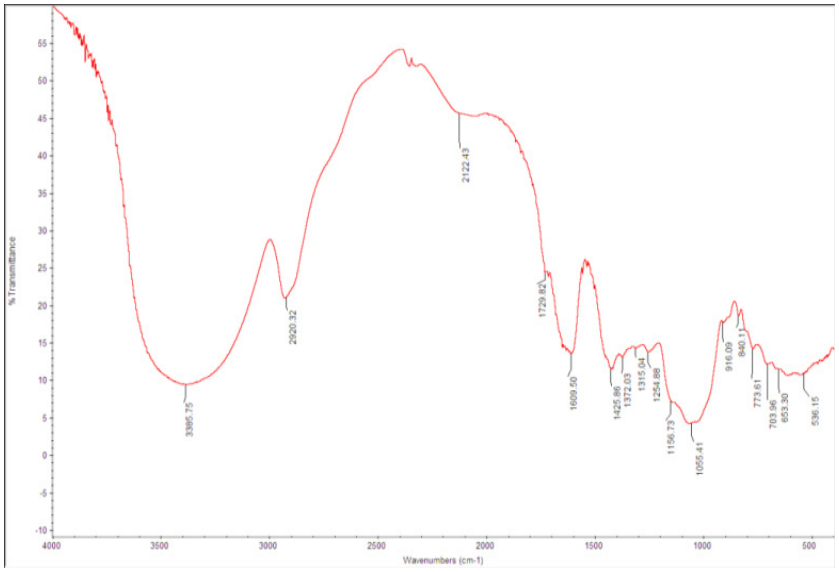

Figure 5C. FT –IR Spectroscopy of Acacia gum

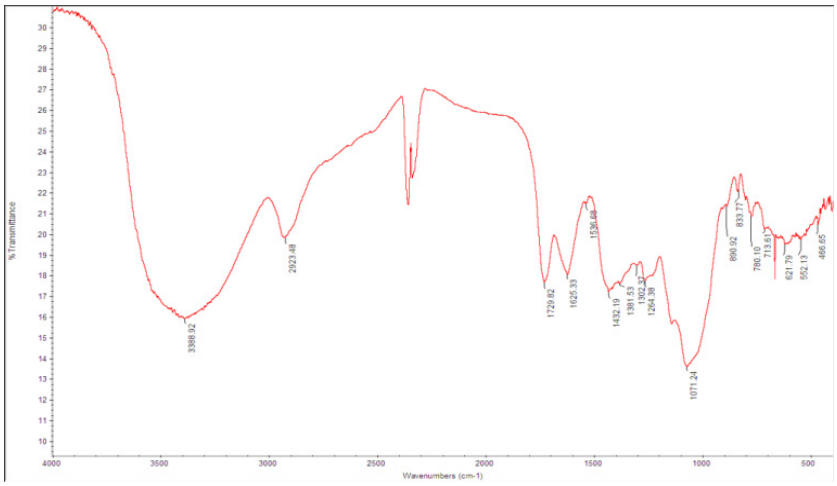

Figure 5D. FT –IR Spectroscopy of, Crosslinked Acacia gum

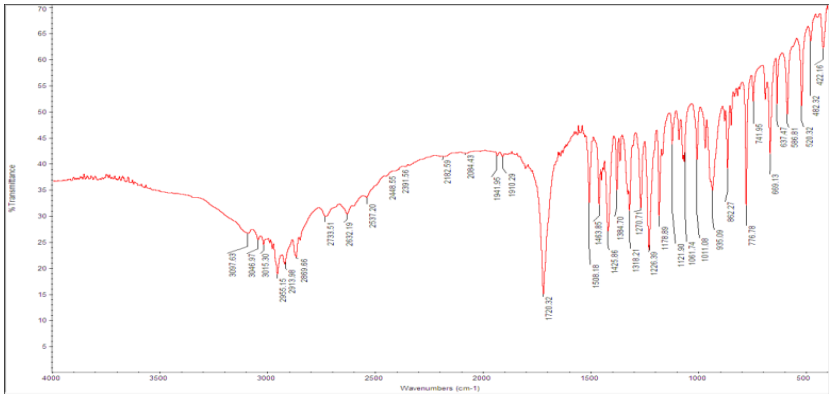

Figure 5E. FT –IR Spectroscopy of Pure Ibuprofen

FT-IR revealed major characteristic peaks of functional groups present in both MC and AG (Fig. 5A & C). The same results were observed for the crosslinked polymers c-MC and c-AG (Fig. 5B & D).

FT-IR spectrum of Methylcellulose (Fig. 5A) showed a broad peak at 3205.28 cm-1 of –OH stretching vibration and a peak at 2913.98 cm-1 of C–H stretching vibration, carbonyl C–O stretching peak was observed at 1590.50cm-1, and the peak at 1373 cm-1 corresponded to Methylcellulose C–H bending [10].

Crosslinked MC FT-IR showed O-H peaks at 3319.26 cm-1, aliphatic CH stretching vibrations at 2926.65 cm-1, and C=O carbonyl at 1726.65 cm-1. There was a shift of the carbonyl C=O bond after cross-linking. C-OH in plane bend at 1413.19 cm-1 and a ring stretching at 887.6 cm-1. It was observed that the -OH and carbonyl peaks increased.

Gum acacia exhibited characteristic bands at 3385.75 cm−1 due to -OH and 2920.32 cm−1 representing aliphatic (-CH2,-CH3) groups. The band at 1609.58 cm−1 is due to asymmetric and symmetric stretching of the COO− group. The band at 1425.86 cm−1 is due to the bending of the acid-OH group [11]. Crosslinked Acacia gum showed peaks at 3388.92 cm−1 and 2923.48 cm−1 corresponding to -OH and aliphatic C-H stretching vibration respectively. The peak at 1729.82 cm− which is due to C=O and that of 1432.19 cm−1 is due to the bending of the acid -OH group. The only observation made was the increase in C=O.

FTIR spectrum of ibuprofen showed a very strong band at 2955.15 cm−1 assigned to CH3 asymmetric stretching, free acid carbonyl peak at 1720.32 cm−1 with high intensity, a very high intensity peak at 1226.39 cm−1 due to C-C stretching, and CH2 asymmetric stretching vibration (3097.63 cm−1 and 2869.66 cm-1). C-O stretching (1178.89 cm−1), CH2 scissoring vibration (1463.85 cm-1) and CH-CO deformation (1425.86 cm−1) were present strongly in ibuprofen [12, 13].

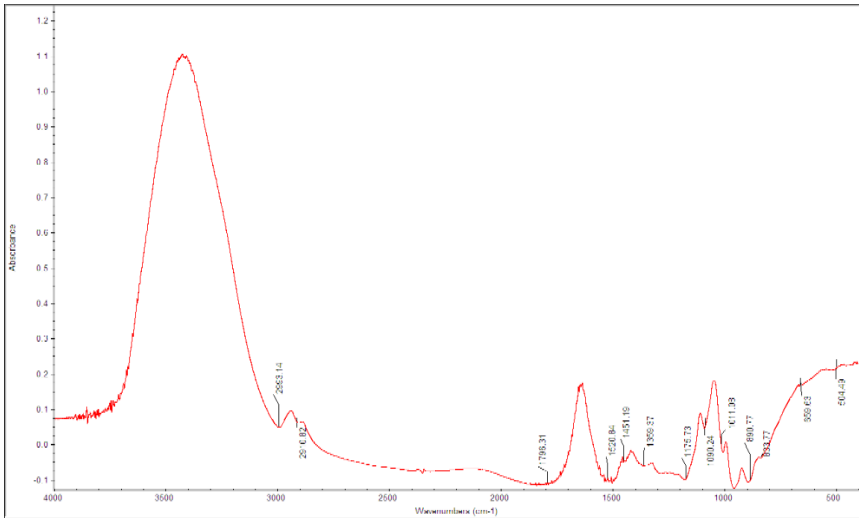

Figure 6A. FT-IR results of suspension formulated with crosslinked methylcellulose (A3)

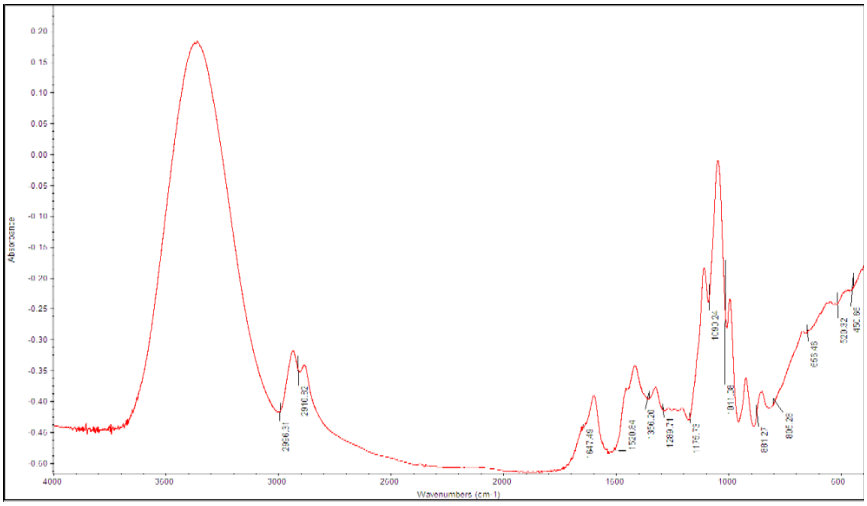

Figure 6B. FT-IR results of suspension formulated with methylcellulose (B_3)

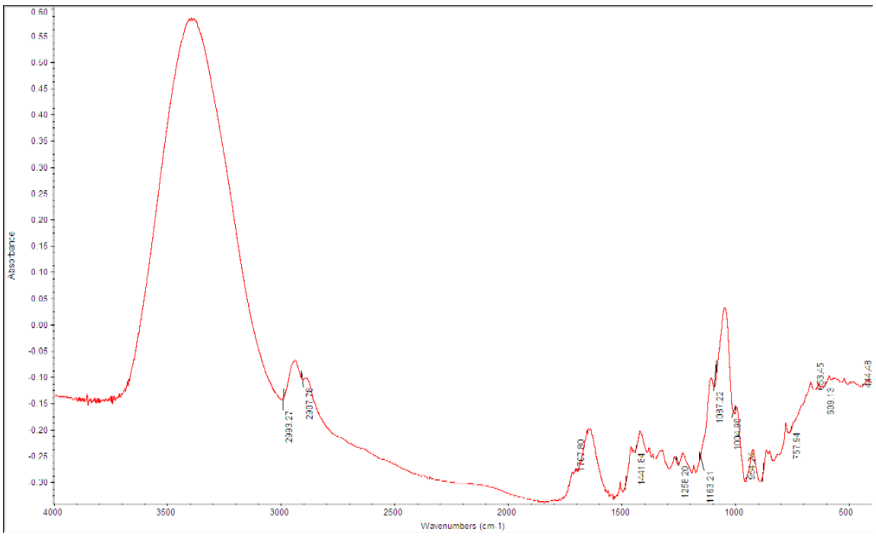

Figure 6C. FFT-IR results of suspension formulated with crosslinked acacia gum (C_3)

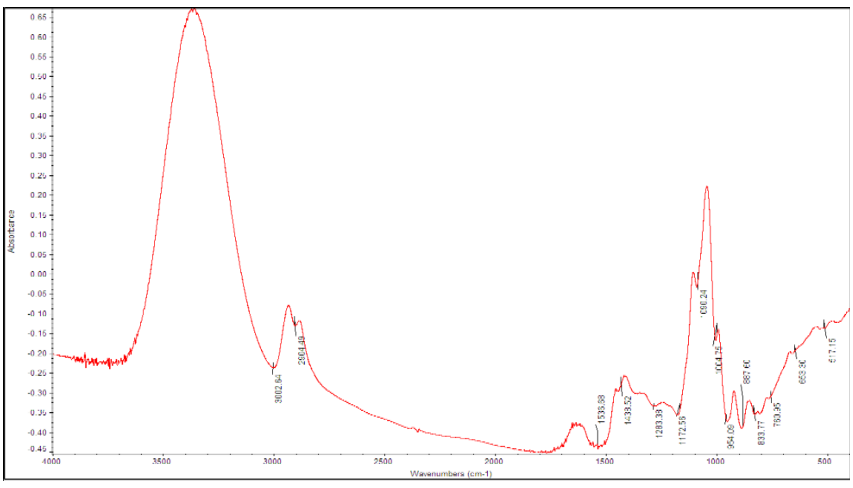

Figure 6D. FT-IR results of suspension formulated with Acacia gum (D_3)

Figures 6 A-D showed the FT-IR spectroscopy of suspension samples containing primary and crosslinked polymers as suspending agents, crosslinked methylcellulose (A3); methylcellulose (B3); crosslinked acacia gum (C3); Acacia gum (D3)

Figure 7 illustrates the calibration curve of ibuprofen in a Phosphate buffer of pH 7.2 at 265nm wavelength. The curve was found to be linear within the range of 20-140µg/mL.

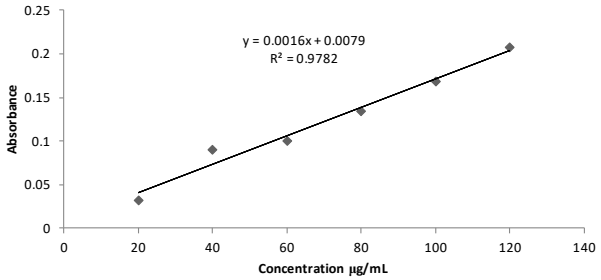

Figure 7. Calibration curve of Ibuprofen in phosphate buffer of pH 7.2 at 265nm

Figure 8 illustrates the dissolution pattern of various batches of ibuprofen suspension

The analysis yielded T90% for batches A1 –A3 and C1-C3 in the following order: 25, 30, 35 and 15, 19, 25 min. respectively. A higher dissolution time was observed for batches A1 – A3.

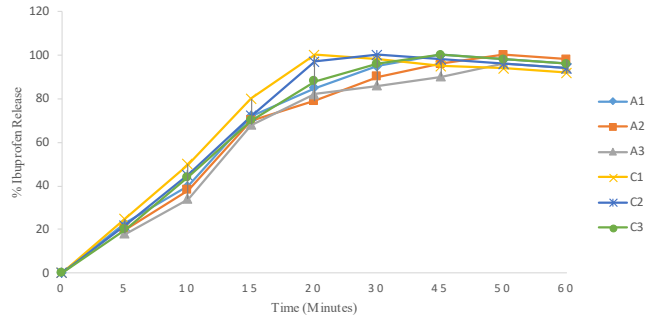

Figure 8. Dissolution profiles of Ibuprofen suspension in phosphate buffer (pH 7.2+ 0.5).

(A1-A3 and C1-C3 contained c-MC and c-AG as suspending agents)

Discussion

Color change

Citric acid crosslinking is reported to cause yellowing, especially when cured at high temperatures and/or for long periods. This might be due to a change in the morphology, formation of complexes addition, or removal of functional groups during the crosslinking. [14, 15].

FT-IR analysis of microstructural properties of crosslinked polymers

Functional groups are identified by their vibrating bonds which absorb energy measured as frequency. This frequency is a property of such a vibrating bond. The vibrational spectrum of a molecule is therefore a unique physical property of that molecule.

The spectra of the crosslinked polymers were analyzed after CA characteristic bands were established. The absorption band at 1724 cm-1, revealed the presence of characteristic carbonyl groups, such as carboxylic acids and esters. According to Olsson et al., [16], research work showed a similar band appearance between CA and polymer (figure 5B, D). Another comparable result is that of chitosan films crosslinked with tannic acid [17]. Several other authors reported the absorption band of citric acid crosslinked with different polymer matrices [17, 18]. The possible mechanisms involved during the crosslinking reaction of polymers with CA have been proposed. Xie and Liu [19] found that when CA is subjected to heat, dehydration takes place forming a cyclic anhydride that reacts with the polymers. Zhou et al. [20] also explained that the reaction of polyfunctional carboxylic acids involves two stages, one, is a result of the fixation of carboxylic acids with a hydroxyl group of a polymer through esterification and its subsequent reaction with another polymer hydroxyl, which produces a complex crosslinking between the polymer chains.

From Figure 5 A, the MC spectrum showed a strong broad peak at 3338cm-1 corresponding to the stretching vibration of the –OH group. The sharp peak located at 2926cm-1 belongs to the stretching vibration of the –CH group (sp3 hybridized system). In addition, the absorption band at 1425cm-1 represents the bending vibration of the –CH group. The bands at 1244cm-1 and 1149cm-1 correspond to the stretching vibration of the C-O group. The spectrum of the primary polymer (Fig. 5A) shows almost identical absorption bands to the FT-IR spectrum of the crosslinked polymers (Fig. 5B), although there is a noticeable decrease in the stretching and bending vibrations of –OH group in the case of the crosslinked sample. This confirms that the ester linkage (crosslinking) was formed between the MC and citric acid in the crosslinked sample 'c-MC' (figure 5B).

In Figure 5 C, the AG spectrum shows the strong broad peak at 3385cm-1 corresponds to the stretching vibration of the –OH group, and the sharp peak situated at 2920cm-1 represents the stretching vibration of the –CH group (sp3 hybridized system). The absorption band at 1425cm-1 is a result of the bending vibration of the –CH group. Furthermore, the stretching vibration of the C-O group is featured at 1254cm-1 and 1156cm-1. The FT-IR spectrum of the crosslinked polymers 'c-AG' (Fig. 5D) shows an identical absorption band to AG, although there is a noticeable decrease in the stretching and bending vibrations of the –OH group in the case of the crosslinked sample. This confirms that the ester linkage was formed between the gum and citric acid in the crosslinked sample.

Pure ibuprofen (Fig.5 E) showed characteristic peaks at 3109.19 cm-1 indicating C-H stretching in the aromatic ring, 2864.02 cm to -1 2958.00 cm indicating C-H stretching in alkanes, and a -1 sharp stretch at 1719.86 cm indicating C=O band in carboxylic acid (COOH) group present in ibuprofen. The carbonyl group in ibuprofen confers a degree of hydrophilicity on ibuprofen, but the non-polar alkyl and benzene groups decrease its polarity significantly.

Coma *et al.*[21] stated that the formation of a more compact structure after crosslinking prevents swelling of the polymer (21). Citric acid was found to be a cross-linking agent for AG and MC polymers when used in low concentrations (5% w / w). Crosslinking (esterification) took place between the carboxylic group of the citric acid and the hydroxyl groups of the MC.

The FT-IR spectra of the crosslinked polymers showed no

significant shift and no disappearance of characteristic peaks found in pure ibuprofen. There was no change in the chemical structure of the ibuprofen after the crosslinking reaction.

The results of the FT-IR investigation of ibuprofen stability in the formulation suspensions containing 3% polymers are featured in Figure 6. Figures 6 A & B showed all functional groups of ibuprofen as displayed in Figure 5E (Pure ibuprofen). Also, figure 6 C & D displayed all functional groups of ibuprofen as appeared in pure ibuprofen (Fig.5E). The only noticeable difference is the reduction in intensity of the ibuprofen in suspensions containing c-MC and c-AG when compared with those in MC and AG suspension. This implies that there is no interaction between the polymers and ibuprofen which may lead to degradation in the drug molecule.

The c-MC features lower bulk density and tapped density over MC. The c-MC had a lower angle of repose and a higher flow rate than the MC. The c-MC also showed better compressibility than the MC (Table 3), while c-AG showed a higher bulk and tapped density, lower flow rate, higher angle of repose, and higher compressibility than the primary powder (AG).

The SI (%) for MC dropped from 1504 % to 640 % after crosslinking with citric Acid (Table 4). This is a reflection of the reduction in viscosity following cross-linking. The result obtained after crosslinking showed that the SI (%) increased from 0 to 610 %.

Swelling Index

The swelling index for methylcellulose, crosslinked methylcellulose, and crosslinked acacia gum was found to be 1504%, 640%, and 610% respectively at the end of 1hr indicating an increase with time. This is attributable to their ability to absorb water.

Viscosity measurement

Evaluation of the viscosity of all suspension formulations revealed a declined trend with an increase in rpm as seen in Figures 1a & b. The batch containing methylcellulose was found to be more viscous; the ranking of viscosity of suspensions ranked batches B>A> C>D. The average viscosity measure increased with an increase in the concentration of polymers. MC showed an average viscosity of 700 mPas with spindle 1 at 30 rpm, while c-MC viscosity value measured at 155 mPas for the same spindle and rpm. AG showed an average viscosity of 100 mPas with spindle 1 at 30 rpm, while c-AG viscosity value measured at 120 mPas for the same spindle and rpm (Figures 1a &b). Figure 1b shows a much reduced viscosity in mPas at 60 rpm. By doubling the shear stress, it was observed that the viscosity reduced for all suspension batches indicating a shear-thinning nature of the suspensions.

Evaluation of sedimentation volume after 35 days

The viscosity of the continuous phase for each batch made with primary polymers and crosslinked polymers, the MC, AG, and c-MC, c-AG respectively played a vital role in determining the rate of sedimentation and eventual sedimentation volume daily. The MC suspension with the highest value of viscosity showed zero sedimentation, as such, sedimentation volume remained at 1 (Fig. 2). B3 remained flat throughout the observation. AG, c-MC, and c-AG demonstrated varied degrees of sedimentation according to their viscosity (Fig. 2). The B3 batch sedimentation volume of 100% and was not pourable from a measuring cylinder this was due to immobilization of ibuprofen particles as a result of extreme concentration and viscosity of the suspension. The sedimentation volume is inversely proportional to the concentration of the suspending agent (Fig.2). All batches except B3 were pourable from a cylinder and had various sedimentation volumes below 100 %.

Characteristics of various formulated suspension

The rheological properties of suspensions will depend strongly on the degree of flocculation of the dispersed particles. The batch B3 had extreme viscosity leading to the immobilization of suspended ibuprofen particles. All batches except batch B3 were easily redispersed. The crosslinked batches A and C series were easily dispersible with a maximum of 4 shakings after (35 days). Redispersibility was found to be inversely proportional to the amount of suspending agent present in the formulation, as viscosity is directly proportional to the concentration of the polymer used. The high viscous nature of methylcellulose caused it to be difficult to disperse when shaken and also reduced its pourability as the concentration of methylcellulose increased.

It was observed that B1-B3 featured the lowest sedimentation rate (0.84 0.00 cm3/day) due to the higher viscosity of the suspension batches measured as 384.9, 404.1, and 508.8 mPaS respectively. In another development, A1-A3 and C1-C3 had similar sedimentation rates as follows: 1.10, 0.91, and 0.86 cm3/day and 0.97, 0.91, and 0.86 cm3/day respectively, while D1-D3 exhibited the highest rate of sedimentation in the following order: 1.43, 1.34 and 1.14 cm3/day respectively.

C1-C3 formulated suspension (c-AG as suspending agent) was observed to have improved viscosity over D1-D3 (AG formulated suspension) which translates to stability and more accurate dosing due to a slower sedimentation rate. Moreover, A1-A3 formulated suspension with c-MC yielded an improved sedimentation rate, easily redispersible than B1-B3 containing suspension. As the concentration of the MC increases, the sedimentation rate tends to zero for B3.

A1-A3 were redispersed with 3-6 shaken respectively. C1-C3 were redispersed with 3-4 shakes respectively. A2 and C2 had a sedimentation rate of 0.91 cm3/day, while A3 and C3 had a sedimentation rate of 0.86 cm3/day. As the polymer concentration increases, the ease of redispersibility becomes more difficult. A1-A3 and C1-C3 with c-MC and c-AG polymers as thickening agents featured similar ease of redispersibility. The degree of flocculation was found to increase with the polymer concentration as well as the viscosity.

Stability of suspension

A higher degree of flocculation means a better suspending ability of the polymer. The degree of flocculation increases with an increase in the concentration of the suspending agent [7].

The most important factors affecting the stability of the entire suspensions are the nanoparticle's concentration, dispersant, viscosity of the base liquid, and pH value [7].

Conclusion

In this experimental work, citric acid was found to crosslink AG successfully in one development and MC in another. Crosslinking (esterification) took place between the carbonyl group of the CA and the hydroxyl groups of AG in one reaction, and MC in another. A compact structure was obtained which prevents swelling of the polymers. The effect of crosslinking therefore decreased water permeability and swelling properties. More structured ibuprofen dispersions were obtained. Among the formulated suspension batches A3 and C3 containing 3 % c-MC and c-AG respectively showed better sedimentation rate, redipersibility, degree of flocculation, as well as better physical stability (pH) and in vitro drug release profiles compared to other formulated suspensions (MC and AG). Both A3 and C3 formulations meet the characteristics of an ideal pharmaceutical suspension. Summarily, c-MC and c-AG containing 3 % crosslinked polymers can be employed to formulate a stable, more accurate dosing, easily dispersed, and acceptable medicated oral suspension.

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The Extent, Quality and Features of HIV Cost Evaluation Publications in Nigeria: A Systematic Review

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Abstract

Introduction: Pharmaco-economics identifies, measures, and compares the costs/consequences of pharmaceutical products and services thus affecting treatment outcomes. This is crucial in the case of chronic conditions such as HIV/AIDS which can be a burden to the affected people.

Objective: This study aimed to determine the extent, features, and quality of cost-evaluation studies, regarding HIV/AIDS in Nigeria.

Methodology: This study was a systematic review and meta-analysis of HIV cost evaluation publications in Nigeria. A search on scientific databases was conducted using relevant search strategies. Eleven HIV cost-evaluation studies published in 9 journals outside Nigeria were identified.

Results: Based on a 14-point score, the mean score of the studies was found to be 10.56. Five studies were fair and six rated as good. The quality of the study was not significantly related to the country, type of publication, and funding source ($p>0.05$). There was no significant correlation between the quality of studies and the number of authors, year of publication, cost estimates, and sample size of studies ($p>0.05$).

Conclusions: HIV Cost-evaluation studies were found to be limited in number though of good quality. The economic assessment of pharmaceuticals in Nigeria should be encouraged.

Keywords: *Assessment, Cost- evaluation, HIV/AIDS, Nigeria.*

Introduction

Pharmaco-economics has been defined as the description and analysis of costs of drug therapy to health care systems and society. It identifies, measures, and compares the costs and consequences of pharmaceutical products and services [1]. Pharmaco-economics can be used to compare the total cost and outcomes of treatment options [1]. Figure 1 shows a pharmaco-economic equation in which the left side of the equation represents inputs or costs used to obtain a pharmaceutical product or service. The right side of the equation represents outcomes associated with this option. The centre of the equation is the drug product or service being assessed, symbolized by RX. If only the left-hand side of the equation is measured without regard for outcomes, it is a cost analysis/evaluation (or a Partial Pharmaco–economics analysis). However, if only the right-hand side of the equation is measured without regard to costs, it is a clinical or outcome study (not an economic analysis) [1]. In general terms, cost-evaluation is the process of determining how resources are used [1]. Cost-evaluations provide important insight into the economic burden of disease and can be useful for understanding the resources incurred by health systems, other payers, and patients. Such understanding will aid in the planning of quality care and provide insight into system performance [2]. All these indicate that data obtained from Cost-evaluation studies are important for decision-making.

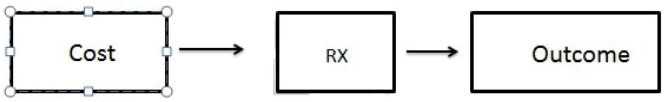

Figure 1. Pharmaco-economic Equation [1]

HIV/AIDS is not only the most serious epidemic in modern times but also the greatest public health challenge in history. The concerted effort of scientists was rewarded with success as they were able to turn the epidemic from a fatal to a chronically manageable one. As a result, the life expectancy of patients improved except for patients who started therapy with low CD4 cell counts [3].

High financial commitment in industrialized countries together with rapid uptake and retention of patients in therapy has led to the so-called "Lazarus syndrome" [4]. The syndrome is characterized by the restoration of the health of many terminally ill people in these countries. The challenge here is that the majority of people living with HIV/AIDS (PLWHIV) reside in developing countries/ resource-limited settings where the huge expenditure required for the

management of the disease is not affordable [4]. This problem of affordability is further aggravated by an increase in the life expectancy of these patients which increases the cost of management of the disease as these patients are more affected by comorbid conditions associated with old age [5].

Africa is experiencing a triple burden of disease [33]. This is defined by the growing prevalence of chronic non-communicable diseases (NCDs) and the fight against infectious diseases [6]. Nigeria has been faced with many problems in recent years. Apart from the rise in the burden of HIV/AIDS, malaria, and tuberculosis, healthcare costs have soared and medical treatment is costly and unaffordable for most people [1, 7]. Universal health coverage is very low. Funding for HIV/AIDS is largely borne by international donors in Nigeria [8]. The donor community is increasingly looking for ways of moving responsibility for support to developing countries, Nigeria inclusive [8]. Since the commencement of antiretroviral therapy use, there has been a large gap between available funding and the funding needed to meet global HIV/AIDS targets [8]. This is why sustained and coordinated efforts across international and domestic development partners are needed to end AIDS by 2030 [9]. Evidence of increasing funding requirements is shown in the fact that total HIV / AIDS spending in Lower Middle Income Countries (LMICs) increased from $4.0 billion to $19 billion between 2000 and 2016. Most of these potential resources are concentrated in 10 middle-income countries, including Nigeria. Increased funding in future years is anticipated as a result of changes in antiretroviral therapy initiation strategies [10].

Having emphasized the importance of Cost - evaluation studies to decision making, it will be significant to evaluate the extent, features, quality, and of Cost -evaluation studies in the field of HIV and ascertain if these studies are of good quality as good quality data would serve as a reliable guide to effective and efficient use of healthcare resources by decision-makers. This was the objective of this systematic review conducted for Nigeria. However, it has been reported that the conduct of health economic (including pharmaco-economic) research in Nigeria was limited and about two-thirds of published articles were of sub-optimal quality [7]. Another study reported that the use of health economic (including pharmaco-economic) evaluation research in Zimbabwe was low and 31% of the studies were of poor quality [11]. China-based pharmaco-economic studies written in English were found to be limited in number, but on average, were of good quality [12].

Objective

This study aimed to determine the extent of features and quality of Cost-evaluation (Partial Pharmaco- economic) studies, regarding HIV/AIDS in Nigeria.

Methodology

The preferred reporting items for systematic reviews and Meta-Analysis (PRISMA) statement was used to conduct this systematic review similarly to other studies [13].

Search Strategy

The PUBMED, Econlit, Embase, and Health Technology Assessment (HTA) databases were searched for all relevant published articles. The duration of 10 years before now was considered. The subject headings (MESH) and text words were used to identify related articles. This strategy is stated thus: (cost*) or economic*) or valu*) or pharmac*) or impact) or burden) or drug expenditure*) or willingness) or employment) or resource*) or use*) or utilization) and HIV*) or AIDS*) or anti-retroviral therapy) and Nigeria and "last 10 years"[PDATat] and humans [mesh]. The literature searches were imported into EndNote (version X8) to integrate collected references from different databases, eliminate duplication, and promote the review process.

Inclusion criteria

This work was structured to identify and include all original articles published in Nigeria over the past 10 years (for recent data) that included Cost - evaluations of HIV/AIDS. The original articles of interest were those that sourced information from databases and patient questionnaires. All included studies were Partial Pharmaco-economic evaluations such as cost of illness analysis, willingness to pay, catastrophic expenditure, and cost effect of decentralization.

Exclusion Criteria

The review excluded studies that were not cost-evaluation studies, not conducted in humans, not including HIV/AIDS treatments, not for Nigeria, and not performed within the last 10 years.

Data extraction

All retrieved articles in the initial search were read independently by two reviewers (HB and AZ). First, titles and abstracts were screened, based on the eligibility criteria. Then full-text screening was subsequently carried out, which was also based on eligibility criteria. Any disagreements were discussed and resolved by consensus or by a third independent reviewer (MD) if necessary. The results were then recorded on tables summarizing selected articles and their journal of publication, features of the studies (distinctive attributes), and cost estimates (product of cost estimation process) across the studies. The mean cost from each study was adjusted using the Medical Consumer Price Index (MCPI) inflation rates found on the Bureau of Labour Statistics website and converted to the 2019 value [14]. The Medical Consumer Price Index (MCPI) inflation rate for this study was 5% with a factor of $(1+MCPI)^t$. The small letter (t) indicated the number of years into the future.

Quality assessment

A Data collection form was designed from the Drummond checklist for economic evaluations, which was adapted for the assessment of the quality of the included studies [14]. The Drummond checklist is an existing critical appraisal tool for economic evaluations. The checklist has a total number

of 10 questions for consideration when carrying out full pharmaco-economic evaluation studies.

The adaptation that was done involved the removal of 3 questions that were irrelevant to the cost-evaluation study, leaving only 7 relevant questions. This checklist has been known for its reliability and validity[14]. Between 2010-2018, the Drummond checklist has been reported as the most commonly used for the assessment of health economic evaluations [7, 11, 15, 16]. All adapted questions were considered to have equal weights. The assessment was executed independently by two reviewers (HB and AZ), and discrepancies were resolved by a third-party MD. The grading was done using a maximum grade of two points for each question, as this makes the award of points easier. Thus, the full mark for each study was 14. Studies with scores below 7 were considered poor, those with a 7- 10 score were considered fair, while those with between a score of 10–14 were considered very good.

Another data collection form included general information like the country in which the journal is based, the type of journal: medical journal or non-medical journal, funding source, and country coverage. There was also cost-evaluation information such as type of cost estimate, value of cost estimate, and sample size for each study. The subjective scores were also included in this form.

Data analysis

Each of the reviewers was labelled as either reviewer 1 or 2 and the total score for each study was then assessed for correlation using Cohen's Kappa test. The average of these two scores was then found and used as the quality score wherever the quality score was required.

To determine the difference between the mean of categorical groups such as the country of origin of the journal, independent t-tests or ANOVA were used, while Pearson's correlation coefficients were used to determine the relationship between the mean scores and the number of authors, year of publication, and sample size. Data analysis was done using the Statistical Package for the Social Sciences, version 14.0 (SPSS Inc., Chicago, IL, USA). An alpha level of 5% was used for statistical significance (p 0.05)

Results

The results consisted of 3 major sections; first the results of the search, two, the quantity and features of the studies, and lastly the technical quality of the studies.

Search results

The initial search identified 1461 citations through PUBMED, Econlit, Embase, and Health technology assessment (HTA) databases; of these 161 of which were duplicates. Following the removal of duplicates, there were a total of 1300 references, which went through title and abstract screening of which 1100 were removed leaving a total of 200 studies. After full-text screening 11 potentially eligible studies were retrieved. The flow chart of the literature search is shown in Figure 2.

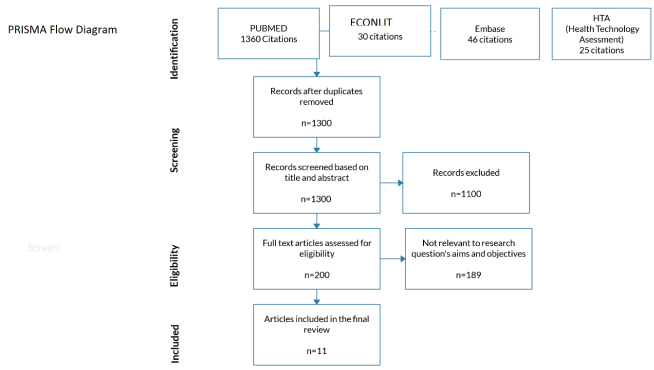

Figure 2. Prisma-Flow-Diagram300 [1]

Quantity and features of the study

All selected studies (eleven in number) were published between 2011 and 2018 and outside Nigeria in four different countries. There was no published study in 2014; but 2016 recorded the highest number of published studies, a total of three studies, and then a decline of the number of published studies in 2018 with only two published studies. Three (27%) of the studies were published in the United States-based journals, six (54 %) in the United Kingdom-based journals, and one in Switzerland and Ireland-based journals each (Table 1). Seven (63%) of the articles were published in medical journals and four (37%) in non-medical-based journals. The policy-related (non-medical) journals involved included Health Expectations, Health Policy, and Health Policy and Planning journals. A public health journal was also involved which was the Global Public Health Journal. Regarding the authors, 53% were residents in Nigeria while the remaining 46% resided outside Nigeria, with 82% of them having medical affiliations.

Table 1. A summary of the included journal articles and their countries of publication.

Author	Journal	Country of Publication
[8]	J Acquired Immune Defic Syndr	United States
[17]	PLoS One	United States
[18]	Aids	United Kingdom
[19]	PLoS One	United Kingdom
[20]	PLoS One	United States
[21]	J Int AIDS Soc	Switzerland
[22	Health Expect	United Kingdom
[23]	Health Policy	Ireland
[24]	Health Policy Plan	United Kingdom
[25]	Glob Public Health	United Kingdom
[26]	AIDS Care	United Kingdom

The funding sources of the journals ranged from Non-Governmental Organizations (NGOs) such as GHAIN NIGERIA, PEPFAR, and USAID, for 9 articles (81%): the rest of the authors, 2 articles (19%), did not state their funding sources. Five (45%) of the studies covered more than one country with Nigeria inclusive while six (55%) covered only Nigeria as summarized in Table 2. Six (55%) of the studies had the perspective of the national health payers while five (45%) had the perspective of the patients. Ten of the studies utilized primary data with only one using secondary data.

Table 2. Summarized features of the studies

		Number of studies	Percentage%
Country In Which the Journal is Based	United States United Kingdom Other Counties	3 6 2	27 54 19
Totall		11	100
Type Of journal	Medical Journal Non-Medical Journal	7 4	63 37
Total		11	100
Type Of Cost Estimate	Annual Average Cost Per Patient Other Costs	4 7	37 63
Total		11	100
Funding Source	Non –Profit Organizations Not Stated	9 2	81 19
Total		11	100
Country Coverage	National Multinational	6 5	55 45
Total		11	100
The perspective of study	Health payers Patients	6 5	55 45
Total		11	100

Of all the eleven published articles, 4 of them, [8,17-19] estimated the average annual cost per patient of anti-retroviral therapy (ART), catastrophic expenditures were investigated by 2 studies, [20,21] willingness to pay for antiretroviral by 2 studies, [22,23], cost-effect of decentralization by 1 study [24], effects of criminalization on the cost of management of ART in countries that criminalize same-sex sexual practices compared to those that do not criminalize same-sex sexual practices (SSSP) by 1 study[25] and the last study [26] investigated funding and expenditure of community-based organization as summarized in table 3. The developmental stage of the disease (viral load, CD4 counts, and clinical staging) was not indicated by all the studies.

Table 3. Focus areas of the selected studies

Author	Outcome measure	Computation of cost	Data source
[8]	Average annual cost per patient of ART*	Top to bottom	Databases
[17]	Average annual cost per patient of ART*	Bottom to top	Case notes, patient interviews
[18]	Average annual cost per patient of ART*	Bottom to top	Retrospective record review, including accounting records, prescribing logs, equipment inventories, and routine reports. Key informant interviews
[19]	Average annual cost per patient of ART*	Bottom to top	Accounting records, prescribing logs, equipment inventories, and routine reports, structured interviews with site personnel
[20]	Catastrophic	Bottom to top	Patient interviews
[21]	Catastrophic	Bottom to top	A pre-tested interviewer-administered questionnaire
[22]	Willingness to pay	Bottom to top	Pre-tested questionnaire
[24]	Cost effects of service decentralization	Bottom to top	Facilities and patient records
[25]	Other related cost studies	Bottom to top	All publicly available documents
[26]	Other related cost studies	Bottom to top	Facilities and patient records

ART* - anti-retroviral therapy

The average annual cost per patient of ART was $ 241 or $294 for facilities located in Nigeria. The main cost drivers were ART, human resources and test kits, and willingness to pay for anti-retrovirals. Unsubsidized cost was catastrophic to households (10-40% higher than household cost) and was $6.355 or $7.06 for outpatients. Decentralization of facilities either increases or decreases costs in some settings. (Table 4).

Table 4. Cost estimates across studies

Author	Sample size	Type of outcome measure	Mean cost USD($)	Present value 2019 $ using a 5% inflation rate
[8]	9 Facilities	Average annual cost per patient of ART*	HTC* 7.4 ART*209	HTC * 10.46 ART*294
[17]	c80 facilities	Average annual cost per patient of ART*	National- 157 Facility-level 231	National 164.9 Facility-level 241
[18]	Botswana, Nigeria, Ethiopia, Uganda, Vietnam 43 PEPFAR-supported outpatient clinics	Average annual cost per patient of ART*	Pre ART 202 (2009 USD) Without ART* 880 With ART*298.	Pre ART 329.03 Without ART*1433.42 With ART* 485
[19]	54 clinical sites	Average annual cost per patient of ART*	Pre-ART treatment 177 < 6 months 353 (255-468) >6months 222 (161-296)	Pre-ART treatment 249 <6months 496 >6months 312
[20]	3 states	Catastrophic	Outpatient direct medical 5.49 Inpatient direct medical 122.10	Outpatient direct medical 6.355 In-patient direct medical $ 141.34
[21]	1200	Catastrophic	Outpatient visits (OPV) 6.1	OPV 7.06
[22]		Willingness to pay	Willingness to pay WTP* 15.32	WTP 16.08
[23]c	tertiary institutions in Enugu, Nigeria	Willingness to pay	WTP* 3.2	4.96
[24]	3 states	cost effects of service decentral-ization	Cross river increased cost by 40%; Kaduna reduced by 29%	Cross river increased cost by 40%; Kaduna reduced by 29%
[25]	8 countries	Other related cost studies	Countries that criminalize SSSP spend less money	Countries that criminalize SSSP spend less money

[26]	3 countries	Other related cost studies	An average CBO* received 29,800 annually or about 2480 per month	An average CBO* received 39,934 annually or about 3323 per month

OPV* Outpatient visits, SSSP* Same Sex Sexual Practices, CBO* Community based organizations, HTC* HIV Testing and counselling, WTP* Willingness to Pay, ART* Anti-retroviral therapy *

Quality of studies

The scores apportioned by the two reviewers were found to have a moderate Cohen's Kappa correlation of 0.610 ($p<0.05$). The mean score of the studies was found to be 10.56 (SD 1.29, range 3.95). Five studies had fair scores (7-10), while the remaining six fell into the category of good scores (10 -14). The quality of the study was found not to be significantly related to the country of publication ($p>0.05$) (Table 5). There was also no significant correlation between the quality of studies and the number of authors, year of publication, cost estimates achieved, and sample size ($p>0.05$) (Table 6).

Table 5. Relationship between Categorical groups and mean scores

	Categorical data	Mean of quality* score	Standard Deviation
Country In Which The Journal Is Based P>0.05	United States (3) United Kingdom (6) Other Counties (2)	10.70 10.60 9.93	1.48 1.46 0.81
Type Of Publication. P.>0.05	Medical Journal(7) Non-Medical Journal (4)	10.76 10.21	1.37 1.23
Type Of Cost Estimate P>0.05	Annual Average Cost Per Patient{4} Other Costs (7)	11.64 9.95	0.94 1.17
Funding Source P >0.05	Non –Profit Organizations(9) Not Stated(2)	10.54 10.68	1.43 0.25
Country Coverage p >0.05	National (6) Multinational (5)	10.47 10.68	1.06 1.65
The perspective of study p>0.05	Health payers(6) Patients(5)	11.00 10.03	1.58 0.68

*Scale 1=lowest quality; 14=highest quality

Table 6. Relationship between mean quality scores and numerical variable

	Number of Authors	Year of Publication	Sample size	Cost estimates
Pearson Correlation coefficients	- 0.456	0.418	-0.789	0.580
p-value	0.159	0.200	0.21	0.606
n	11	11	4	3

Discussion

Within 10 years there were only 11 studies on the cost-evaluation of HIV/AIDS in Nigeria. The research area of HIV/AIDS is not expected to have a low turnover of studies since it is one of the chronic diseases with the highest burden in Africa and also in Nigeria. This low turnover is in accordance with the work of other studies [27][28] which shows that there is a low turnout of cost-evaluation studies in resource-limited settings. It also agrees with another study done [7] which showed that there are few health economic evaluations for Nigeria. This work also shows similarity to another other author's work [5], who evaluated the economic impact of HIV/AIDS for 5 European countries and had only 26 studies included for 10 years. The challenge of obtaining high-quality data in the Nigerian environment is a factor contributing to the dearth of pharmaco-economic studies [7]. This modest number of Health Economic Evaluations (HEE) shows that more studies need to be carried out in this area.

This challenge of low turnover of studies can be approached by attempting to improve the number and quality of health economics experts, and this can be done with the government providing scholarships, grants, and incentives for the study of health economics and pharmaco-economics at the master and Ph.D. levels. This specialty could also be made a compulsory part of the curriculum in medical-related programs, and resource persons to run these programs could be sourced at local and international levels. All these will create an upsurge in research, more so in high-quality research in this area. Enhancing the linkage between these institutions and policymakers will increase the value of HEE to them. Policymakers could also facilitate the procurement of research grants. According to other authors [11], the establishment of priority settings, research facilities, and procedures for synthesizing and decentralizing results is also important in improving the quality and quantity of health economic evaluations. They also emphasized that the improvement of the peer review process and adoption of health economic guidelines will serve to increase quality, reduce bias, and increase comparability of the studies.

Furthermore, the problem of affordability in countries classified as LMIC such as Nigeria with low health spending per capita ($247- $303) has increased the need for more health economic evaluations to guide decision-making [6]. The estimated funding of $814.7 ($742.8 to $923.8) on HIV/AIDS per prevalent case for LMIC exceeds the value ($241 or $294) obtained in this study for Nigeria [27]. This is evidence that the national and international health goals for the disease have not been achieved in Nigeria since the achievement of these goals was found to correlate with appropriate funding of the health system [27].

In the current study, HIV/AIDS funding of ($241 or $294) apart from indirect and intangible costs not considered by authors of included articles represents 97% - 97.6% of health expenditure per capita for Nigeria ($247- $303) [32]. Spending 97% of health expenditure per capita on HIV/AIDS alone is a great burden because Nigeria's Health System is already overwhelmed with other communicable and non-communicable diseases [6]. All this goes a long way to demonstrate that improved funding for the Nigerian health system is essential to make healthcare targets achievable. The low willingness to pay underscores the need for public

sensitization to enhance willingness to pay and advocacy to the Government and Donors for sustainable funding.

The fact that more than half of the authors were residents of Nigeria implies more local involvement in these high-quality studies. These resourceful individuals could serve as a pool of potential reviewers, lecturers in medical-affiliated institutions, and links between schools and policymakers.

One of the reasons that could explain the high-quality studies is that most of the authors have medical affiliations and hence more experience in the medical field. The high quality of all included studies in the current research is a positive development. However, previous workers have found some low-quality studies in their inclusions [7, 12].

Conclusion

Eleven (11) Cost - Evaluation studies, regarding HIV/AIDS were carried out for Nigeria within the past ten years. These studies had high quality and the majority of the authors were residents in Nigeria and with medical affiliations. There is a need for funding for more pharmaco-economics research studies to allow for more cost-evaluations for high-burden diseases so that appropriate policies may be passed.

Limitations

The quality scores were subjective and could be scored differently by other assessors. The sample size of 11 studies included in this review did not allow for regression analysis, which is one of the limitations of this study based on available secondary data, in which case sample size cannot be influenced beyond availability. Indirect Medical Costs were not obtained in the results of this study as this category of cost was not presented in the various included studies.

Acknowledgment

Appreciation goes to the Tehran University of Medical Sciences for funding this work.

Conflict of Interest Disclosures

The authors reported no conflicts of interest.

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Pre-exposure prophylaxis (PREP) use in HIV vulnerable individuals: A systemic benefit-risk assessment using the MCDA framework

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Abstract

Introduction: Antiretroviral therapy medications provide an innovative strategy for preventing Human Immuno-deficiency Virus (HIV) type-1 transmission. Multi-criteria decision analysis (MCDA) simple scoring is an evidence-based health technology evaluation approach for appraising health products and technologies (HPTs). The options appraised included; the pre-exposure prophylaxis (PrEP) arm outcome or use of tenofovir/ emtricitabine (TDF/FTC) centred on benefits and risks versus the Placebo or no PrEP arm.

Objective: To assess the MCDA framework as an ideal tool for evaluating medicines and therapeutics in a hospital's M&TC setting using PrEP for HIV-1 deterrence as an example.

Methodology: The benefits and the risks of PrEP were assessed and compared alongside the Placebo using data from the randomized clinical trials (RCTs) and systematic review-meta-analysis of RCTs. To evaluate the PrEP benefits versus its risks, the MCDA framework was used. Publication websites were searched for literature reporting clinical outcomes of taking PrEP to prevent HIV infection. A value tree was built with key benefits and risks, and these were scored, weighed, and analysed using the Hiview3 analytical tool (catalyse. U.K.).

Results: The utilization of PrEP in averting HIV in the population presents benefits (51% efficacy) compared to the Placebo/No-PrEP arm (23.99%). PrEP presents potential risks to the PrEP users, e.g., declining kidney function at 3.2% vs. 1.7% and osteoporotic fracture at 12% vs. 3.3%. The PrEP is better at preventing HIV-1 in at-risk individuals (weight score 22.9) and reducing cholesterol levels (5.4). The placebo/No-PREP arm shows a better reduction of hepatitis C virus (10.8) infection but fewer benefits of prevention of HIV-1 (0), more risk of declining kidney function (5.4), and reduced bone mass density (11.6) than the PrEP arm.

Conclusion: From the model, PrEP benefits in preventing HIV-1 outweigh its potential risks to the users. MCDA framework is ideal for evaluating medicines and therapeutics in a hospital's medicine and therapeutics committee (MTC) setting, as it integrates quantitative and qualitative criteria relevant to an MTC setting.

Key words: *Anti-retrovirals, MCDA, MTC, PrEP, HPTs.*

Introduction

Background and decision context

Antiretroviral (ARV) medications provide a promising and innovative strategy for preventing HIV type-1 transmission and mitigating the spread of HIV-1 [1,2]. The use of antiretroviral therapy (ART) medicines in people infected by HIV-1 offers critical medical benefits and lessens that individual's infectiousness thus reducing their capability to transmit the virus to their spouses [3]. However, it has been noted that additional prevention strategies are needed since the number of new HIV cases continues to increase in key vulnerable populations. Antiretroviral prophylaxis is a prospective HIV-1 deterrence approach for those HIV-1 infection-free; it is administered either as post exposure prophylaxis (PEP) after high-risk occupational or non-occupational HIV-1 contact or as pre-exposure prophylaxis (PrEP) in those with continuous HIV-1 contact. In clinical studies of PrEP, evidence has shown 44% to 75% efficacy in an overall HIV-1 prevention package [4,5].

Studies have evaluated the efficiency of tenofovir disoproxil fumarate (TDF) in protection against HIV-1 infection in humans in varying formulations like vaginal gel/cream or an oral TDF or oral TDF and emtricitabine (FTC) fixed-dose combination. Animal studies have shown that TDF-FTC offers superior defence against HIV-1 than TDF alone [6].

The co-formulation of TDF/FTC obtained approval by various competent regulatory authorities for use as PrEP after several placebo-randomised controlled trials demonstrated that once-daily TDF/FTC lowers HIV infection risk in gay and bisexual men and heterosexual women and men. [1]. Some randomised clinical trials (partners PrEP, iPrEX, TDF2, and Bangkok TDF study) proved the efficacy of oral PrEP among HIV serodiscordant couples, MSMs, PWIDs, and heterosexual individuals [1]. Demonstration projects (PROUD, IPERGAY, Partners PrEP Demonstration Project) also provided evidence of the acceptability/willingness of users to take PrEP. [7-9]. High adherence with confirmation that HIV PrEP is effective is reflected in 86-96% effectiveness rates across demonstration projects in MSM and HIV discordant couples' studies [10,11]. Poor adherence to PrEP has been identified as the main factor associated with low PrEP efficacy [11]. Adherence to PrEP is vital to achieving HIV prevention. In an initiative RCT involving MSM, the relative reduction in the

risk of HIV-1 infection provided by PrEP (TDF-FTC) was 44% in general, and it was 73% among individuals with adherence of 90% and above and 92% in individuals with detectable TDF levels in their blood [12].

These ARV-based HIV-1 prevention strategies, like PrEP, are essential for individuals in a discordant partnership who want to have a child. In addition, PrEP gives an HIV-1 prevention strategy for uninfected persons with partners who do not know their HIV-1 status or are infected with HIV-1 but have not initiated ARV treatment or have used ARV medications for less than six months [12].

Several barriers exist to the global delivery of PrEP to all suitable, high-risk individuals in a population [13]. One barrier to general use is the cost, however, there is proof that PrEP can be economical in specific populations [3, 14] depending on HIV prevalence [3,15]. The other hurdle is PrEP uptake and adherence [15], which is worsened by patient anxieties about adverse events and costs [3]. In addition, stigma toward marginalized, vulnerable groups of people affects the political inclination to offer PrEP to these groups of people [15]. However, studies have shown proof of demand for PrEP in vulnerable populations worldwide [3]. Thirdly, a barrier to promoting PrEP utilization programs globally is apprehensions over the drug's safety profile. Safety fears affect providers', patients', and policymakers' attitudes toward PrEP. The important apprehensions are about renal and bone toxicity; there have been mentions of sub-clinical declines in kidney function and bone mineral density [15].

The prospective benefits of PrEP differ significantly amongst populaces, dependent on risks, which depend on the incidences of HIV in that society. For illustration, in a populace with an HIV incidence of 5%, the number of individuals needed to treat to benefit (NNTB) with PrEP to avoid a single infection is 23, supposing that PrEP contains 86% of new HIV infections, as observed in the PROUD research [5]. On the contrary, if the risk were only 1%, the NNTB would become 115. The risk differs significantly across regions and countries and between at-risk groups. The HIV risks are highest in identified vulnerable groups like MSM, showing a 3.3% collective incidence globally according to the current research [3]. In higher-risk populaces, PrEP has been demonstrated to be largely favourable. However, some risk cut-off arises beneath which it is not helpful to use PrEP [15].

Considering large-scale prevention would involve putting a significant number of healthy people on medication. Hence, any potential safety worries pose a significant hurdle. The greater the concern over the Safety of PrEP, the more conventionally one should give it; hence, the greater the hazard threshold should be fixed.

Additional investigation and quantitative measurement of the possible risks of PrEP against the background of the prospective benefits are required to apprise endorsements for widespread PrEP use. This report targets to evaluate PrEP safety and inform policy and medical decision-making processes on PrEP use. The PrEP risks determined are the severe adverse effects (grade 3 and above) described in PrEP RCTs. These severe risks are more similar to the danger of HIV than mild or moderate adverse effects. The dissimilarity in risks of adverse effects between PrEP and control/placebo in the RCTs is used to evaluate the potential for harm from PrEP. These risks of adverse effects (A.E.s) can then be compared with the benefits of PrEP in reducing the threat of HIV infection [15].

Multi-criteria decision analysis (MCDA) using a simple weight scoring method is an evidence-based health technology assessment (HTA) practice for appraising health products and technologies (HPTs), particularly in low and middle income countries (LMICs) with limited resources. During HTA, policymakers must balance drug cost with drug safety, level of interchangeability, active component quality, and delivery track record among others. MCDA's simple weight-scoring framework can be used during pharmaceutical pricing, drug formulary listing, and medicine procurement [16].

In this report, the benefits and risks of PrEP (TDF/FTC were assessed and compared alongside the Placebo using data from the RCTs and meta-analysis and systematic reviews of RCTs. The report after that makes recommendations on PrEP and whether we should adjust the current guidelines on the use of PrEP.

The options appraised and report objective.

The options appraised include the following;

1. The report appraises the PrEP Prophylactic outcome options (TDF/FTC) centred on the accrued benefits and the risks obtained from the research publications reviewed. The PrEP prophylaxis includes the TDF only, TDF/3TC or TDF/FTC tablet fixed drug combination, or the intra-vaginal gel/cream and ring impregnated with TDF only.
2. Placebo: Since the Placebo is the primary control used in the numerous studies, it was used as a control in this benefit and risk assessment.

Report objective

This study aims to assess the Multi-Criteria Decision Analysis (MCDA) framework, which is an ideal instrument for evaluating medicines and therapeutics in a hospital's medicines and therapeutics committee (M&TC) setting using PrEP as an example, and conduct a benefit-risk assessment of PREP use in the HIV at-risk individuals applying the MCDA model and make recommendations on the current guideline on the PREP

Methodology

Study design

The benefits and risks of PREP (TDF/FTC) were assessed and compared alongside the Placebo using data from the randomized controlled trials (RCTs), meta-analysis, and systematic review of RCTs. To evaluate the PrEP benefits versus its risks and suitability for use in a clinical setting, we

used the multi-criteria Decision Analysis (MCDA) framework.

PubMed, Google Scholar, and the iCITE websites were searched to identify literature reporting clinical use and outcomes in patients taking PREP to prevent HIV infection. The data from these papers were selected and sorted, scoring was given to each benefit and risk identified, and weighing the benefits and risks was carried out. A value tree was built, and clinicians ranked vital benefits and risks in order of considered importance. The benefits and risks of the appraised options were analysed using the Hiview3 analytical tool (by catalyse ltd. U.K.). The PrEP candidates in the studies included in this review were individuals with continuous risk of procuring HIV, diagnosed as HIV negative, and over age 18 years.

In this report, the benefits and risks associated with using PrEP were evaluated compared to Placebo in HIV-1 negative persons classified as being at continuous risk of acquiring HIV, using the methodology of Multi-criteria Decision Analysis (MCDA.)

Taking into consideration the literature reviewed, the benefits and the risks evaluated include the following:

Benefits

- Protection against HIV infection in at-risk individuals (HIV serodiscordant couples, MSMs, casual sex workers (CSWs), people who inject drugs (PWIDs), and heterosexual individuals]
- Protective effect against hepatitis C virus (HCV) acquisition
- lowered cholesterol

Risks

- Increased risk of declining kidney function
- Declining bone mineral density
- Increased incidences of Osteoporotic fracture (12 %)
- Increased incidence of Gastrointestinal disturbances, including nausea and vomiting
- Increased incidences of Atopic dermatitis
- Increased incidences of Metabolic defects, including uncontrolled blood sugars and weight gain
- Increased incidences of Emergent drug resistance associated with TDF/FTC
- Increased risk compensation behaviour and hence increased other sexually transmitted infection (STI) rates

Data Selection

Studies with literature relevant to this study were identified and selected, that is, studies reporting clinical use and outcomes in patients taking PREP to prevent HIV infection. The data from these papers were extracted and summarized in a table (Appendix, A). The table describes the data obtained from selected studies and identifies them as important for this evaluation. It includes data from studies that describe the different benefits and risks of PrEP. Important information includes the total sum of participants involved in the research, participants with the outcome of importance, and the percentage of participants with the main outcome.

Scoring

The scores were defined on a 0 to 100% scale for every benefit and risk. Regarding the benefits, the maximum level (100%) was indicated as the maximum benefit derived from the PrEP or Control, and the minimum level (0%) was indicated as the minimum benefit offered by the PrEP or Control. The scores awarded to the benefits and risks are indicated in the table in Appendix B.

In this analysis, the PrEP is greater than the Control except in the inhibition of HCV, hence nearly all the maximum levels (100%) are delivered as a consequence of the PrEP. In the case of the risks, the scale is inverse since the desire is that the maximum or favoured preferences will be fewer adverse drug events. So the maximum level is near 0% or close to the bottom risk of the specific disease (Risk of declining bone mineral density (BMD) and declining renal function), and the minimum, or fewer favoured preference, will be the adverse event.

Weighing

The important argument to consider before the discussion of weighing is that, since HIV infection does lead to AIDs, which significantly interferes with an individual's quality of life and diminishes their longevity, the benefits of PrEP mean a lot and a significant amount of risks posed by PrEP may be acceptable by the PrEP candidates due to the benefits accrued. The identified benefits and risks of PrEP were weighed and the corresponding weight was given to each based on its significance to the benefit/risk balance of PrEP. This weighing and the reasoning for the awarded weight are summarized in Table 1.

Table 1. Weighing of the Benefits and Risk

BENEFITS	WEIGHT	REASON
HIV infection prevention in at-risk persons (HIV serodiscordant couples, MSMs, CSWs, PWIDs, and heterosexual individuals]	85	Deterrence of HIV infection in at-risk individuals is of primary importance
Protective effect against HSV-2 acquisition	40	vHCV is an STI that is not highly prevalent but is of significant importance to this group
Incidences of lowered blood cholesterol	20	This is unimportant to this group, but Low cholesterol is medically significant
RISK		
Impaired Kidney function	50	It is an important adverse effect but is not very common and is reversible
Declining bone mineral density	40	The prevalence is generally low but elevated in the treatment group than in the Placebo
Osteoporotic fracture (12 %)	30	It is significantly important but less common than declining BMD
GI disturbances	5	Very common but poses no serious threat to the user, short duration, and is self-limiting

Atopic dermatitis	15	Significant A.E. is common but poses no serious threat to the user
Metabolic defects, including uncontrolled blood sugars and weight gain	20	Significant A.E. but not common
The emergence of drug resistance associated with TDF/FTC (RR 3.34, 95 % C.I. 1.11-10.06, P=0.03)	30	Very significant but not very common
Risk-compensation behaviour and therefore increase in other STDs rates (rectal chlamydia/ syphilis) HR 1.35 95 CI 0.83-2.19	10	Important A.E.s but uncommon
Unwanted pregnancy fem-PREP/ Partners PREP RR	10	Important A.E.s but uncommon

Results

Weighted scores and overall weighted scores

Based on the weighted scores, the control/placebo/NO PrEP option is favoured over the PrEP because it has a score of 71, while the PrEP has a score of 42. In the figure 1 below, in the PrEP arm, the score for benefits contributes the greatest to the sum score, whereas in the control/placebo/no PrEP arm, the risk score contributes the greatest to the total score.

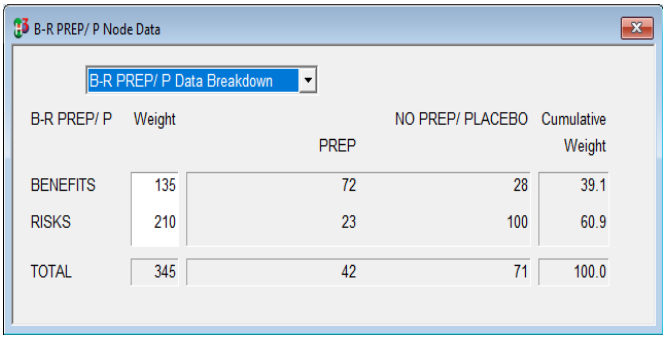

Figure 1. Benefits and Risks scores

In the Figure 2 below, it shows how specific benefits and risks contribute to the sum scores. In the PREP option, deterrence of HIV and declining kidney function add the greatest score to the total score. In the control/placebo/no PrEP arm, declining kidney function, declining BMD, and reduced HCV infection contribute the most to the total score.

Figure 2. Individual benefits and risks contribution to the total scores

The PrEP seems superior at preventing HIV in at-risk individuals (weight 22.9) and reducing cholesterol levels (weight 5.4). The placebo/no PrEP shows a better reduction of HCV (10.8) infection but fewer benefits of prevention of HIV (0) and more risk of declining kidney function (weight 5.4) and BMD (weight 11.6) than PrEP.

The Map

Figure 3 represents a map graph for benefits and risks comparison. The x-axis shows preferences for benefits, with higher benefits to the right. An ideal option on the graph would lie at (100,100), so options in the top right-hand corner are preferred. The edge of the shaded area represents the efficient frontier, where the maximum benefit is achieved for a particular risk. The PrEP option has higher benefits and, at the same time, higher risks. The no-PrEP option has low benefits and fewer risks to the users.

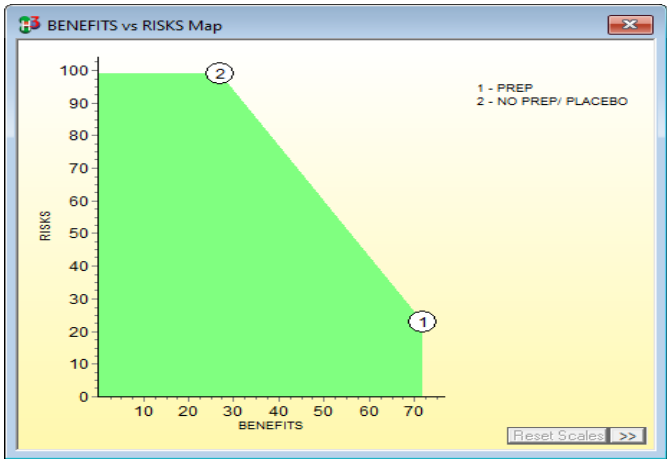

Figure 3. Map Graph for benefits and risks comparison

The sorts

The sort analysis (APPENDIX C) compares head-to-head PrEP and Placebo. In this analysis, PrEP performs much better than Placebo in preventing HIV and Lowering blood cholesterol. No-PrEP/Placebo performs better in declining BMD and reducing HCV infection.

Sensitivity analysis

Sensitivity-down

Based on the sensitivity-down evaluation (Appendix D fig 1), in these circumstances, in the prevention of HIV infection and the prevention of HCV infection, the preferred option is PrEP, and the cumulative weight would need to adjust by more than 15 points to alter the best-desired choice.

These events; lowered cholesterol, Increased risk of declining kidney function, declining bone mineral density, Increased incidences of Osteoporotic fracture, Increased incidence of Gastrointestinal disturbances including nausea and vomiting, Increased incidences of Atopic dermatitis, Increased incidences of Metabolic defects including uncontrolled blood sugars and weight gain, Increased incidences of Emergent drug resistance associated with TDF/FTC, and increased risk compensation behaviour and

therefore increased incidences of other STI rates, the preferred options is no PrEP or Placebo (appendix d fig. 2). In this case, no amount of weight score change will alter the desired choice.

Sensitivity-up

Based on the sensitivity-up analysis (Appendix D fig 3), the desired option is control/placebo/No-PrEP in the benefits node. Increased cumulative weight beyond 63 alters the desired preference from control/placebo/No-PrEP to PrEP; this is an extreme change; and hence the data, in this situation, is considered robust.

A scrutiny of the position of the risk node reveals the desired choice is placebo/control/no PrEP (Appendix D Fig 4), and a variation in the cumulative weight of more than 37 would change the favourite from placebo/control/no PrEP to PrEP; this is a substantial change, and consequently, a slight variation in weight will not alter the desired choice.

Discussion

According to the decision-making model applied in this report, multi-criteria decision analysis (MCDA), the usage of PrEP (TDF/3TC) in the deterrence of HIV among the at-risk individuals in the population presents benefits above that realized by the Placebo or no PrEP. However, PrEP presents potential risks to the users, such as declining kidney function, declining BMD, and osteoporotic fractures. Notably, these risks are present across both the PrEP users and the non-users, although they are more prevalent in the PrEP users.

This model has demonstrated the benefits of PrEP in the HIV at-risk persons in the population. The results from published clinical trials corroborate these observations from this model and are well documented in various literature. Clinical trials and meta-analyses of safety data arising from RCT have established no major dissimilarity in the risk of several severe adverse effects kinds between TDF/FTC or TDF and control/Placebo [7]. It is important to note that high-power trials described a statistically significantly bigger hazard of serious adverse events on Control/Placebo than the intervention [7]. The encouraging safety profile of TDF/FTC supports the extensive application of PrEP in groups or people with lesser danger of HIV infection.

Evidence from studies and clinical use shows PrEP can cause other harms; the use in PrEP of two drugs with the same nucleus(t)ide analogues used to manage HIV may result in the development of drug resistance [17]; it is possible, especially where adherence is low. The other potential risk is that eliminating the harm of HIV may inspire risk-compensation practices and escalate other sexually transmitted disease (STD) rates [3]. These are conflicting facts since some observational studies have confirmed this theory while other observational and clinical trials have refuted this theory [3].

This model has demonstrated that PrEP (TDF/FTC) benefits in the prevention of HIV outweigh its potential risks in the users, even in a population where the risks of HIV are low or are less prevalent. In contrast, if PrEP is not used, it may lead to the acquisition of HIV infections, necessitating lifetime treatment with ARVs, which are linked with higher risks of adverse effects [18], and HIV directly harms the liver and bone [7]. Therefore, some risks of PrEP harm are bearable compared to HIV infection. Studies have shown evidence of additional benefits of PrEP, including a protective effect against HSV-2 infection and that PrEP users may benefit from lowered cholesterol [3, 19, 20].

The data used to create this model was sourced from clinical trials whose duration of study may not have been adequate to completely evaluate the effects of prolonged use, so additional investigation on PrEP safety in long-term use is recommended. Nevertheless, there is an absence of adequate evidence of clinically significant problems, so more scrutiny through baseline hazard analysis and continuous clinical monitoring to evaluate long-term effects is essential [18].

It has been demonstrated in this MCDA model on PrEP that the Multi-Criteria Decision Analysis (MCDA) framework presents an ideal tool for evaluating medicines and therapeutics in a hospital medicine and therapeutics committee (M&TC) setting as demonstrated in the above assessment, since it integrates quantitative and qualitative criteria relevant to an MTC setting, allowing deliberate and unambiguous discussions centered on the criteria weighting score. Therefore, this tool can be used alone or with other methods to evaluate medicines in a healthcare system.

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Disclaimer

The ideas presented in the above report are personal opinions shared for knowledge purposes. They do not attempt to replace the guidelines provided by the health authority on applying PREP by clinicians, other health care providers, or an individual at risk of contracting HIV.

APPENDICES

Appendix A

Table. Summary of Results from the literature review

ASO			
	Criteria	**PrEP**	**Comparator (Control/ Placebo)**
Benefits	Prevention of HIV infection in at-risk individuals (HIV serodiscordant couples, MSMs, CSWs, PWIDs, and heterosexual individuals]	51% reduction in risk of HIV infection comparing PrEP with Placebo [risk ratio=0.49, 95% (CI): 0.33–0.73, P=0.001].	24.99%
	Protective effect against HSV-2 acquisition	2.9% p=0.02	5.9%
	Incidences of lowered blood cholesterol	Not included	Not included
Risks	Increased risk of declining kidney function	3.2 (CI per 1000, 19)	1.7 (CI per 1000, 0
	Declining bone mineral density	1.53	1.00
	Increased incidences of Osteoporotic fracture (12 %)	12	3.3
	Increased incidence of Gastrointestinal disturbances, including nausea and vomiting	17.4 (P=0.95, 95% CI)	16.8
	Increased incidences of Atopic dermatitis	9.4 (P=0.04, 95% CI)	10.1
	Increased incidences of Metabolic defects, including uncontrolled blood sugars and weight gain	5 (P=0.04, CI 95%)	3
	Increased incidences of Emergent drug resistance associated with TDF/FTC	17% (risk Ratio=3.34, 95% CI: 1.11–10.06, P=0.03,	5.1%

	Increased risk compensation behavior and therefore increased other STI rates	29%/7.2% Median number of sexual companions in the past month increased from 3 [IQR 2–4] at baseline to 4 [IQR 2–8] at month four during the trial, primarily due to an increase of 3 [IQR 1.5–4] to 5 [IQR 2–12]	27% /5.4%
	Increased incidences of unwanted pregnancies	1.48 95% CI (1.02-2.14)	1.32 95% CI (0.85-2.05)

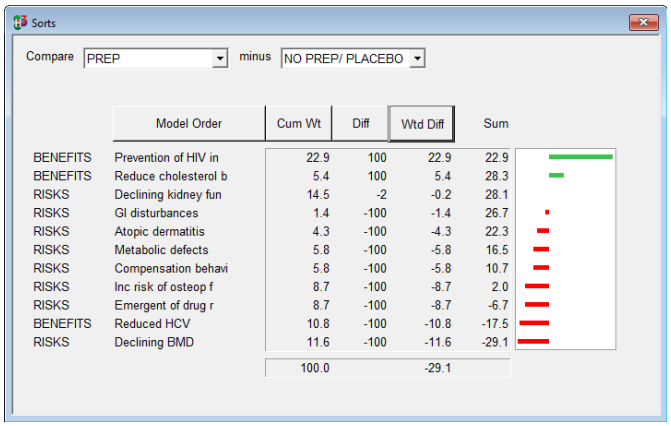
APPENDIX B

Table. Scoring of the Benefits and Risks of PrEP

Scoring			
	Criteria	**Maximum**	**Minimum**
Benefits	Prevention of HIV infection in at-risk individuals (serodiscordant couples, MSMs, CSWs, & PWIDs)	51%	24.99%
	Protective effect against HCV acquisition	2.9%	5.9%
	Incidences of lowered blood cholesterol	29	1
Risks	Increased risk of declining kidney function	3.2	1.7
	Declining bone mineral density	1.5	1
	Increased incidences of Osteoporotic fracture (12 %)	12	3.3
	Increased incidence of Gastrointestinal disturbances, including nausea and vomiting	17.4	16.8
	Increased incidences of Atopic dermatitis	10.1	9.4
	Increased incidences of Metabolic defects, including uncontrolled blood sugars and weight gain	5	3
	Increased incidences of Emergent drug resistance associated with TDF/FT	17	5.1
	Increased risk-compensation behaviour and therefore increased other STDs rates	29	27
	Increased incidences of unwanted pregnancies	1.48	1.32

Appendix C

Table. The sort analysis



Appendix D

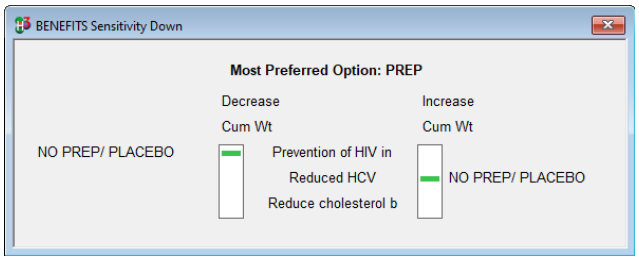


Figure 1. Benefit node sensitivity evaluation down

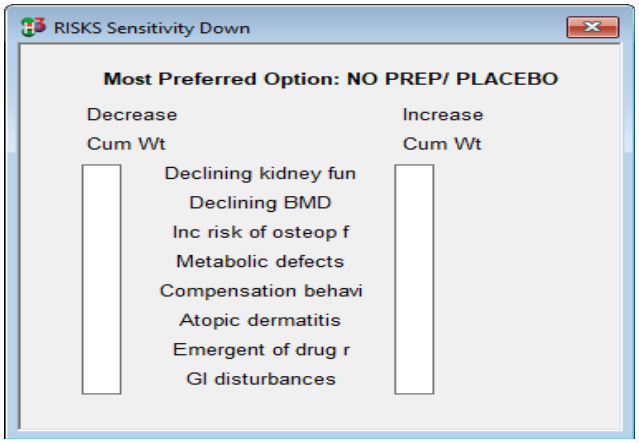


Figure 2. Risk node sensitivity evaluation down

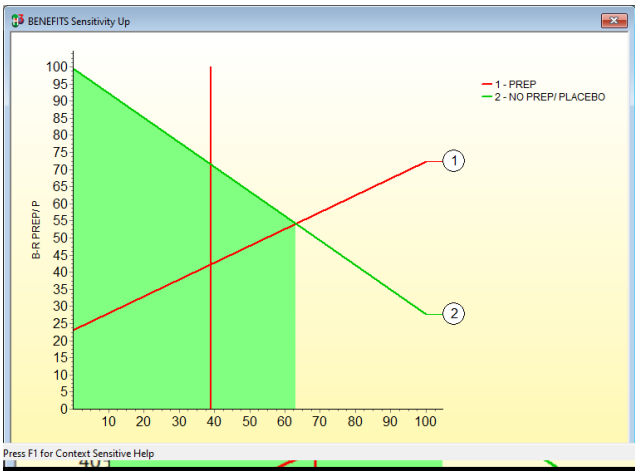


Figure 3. Benefit node sensitivity up analysis

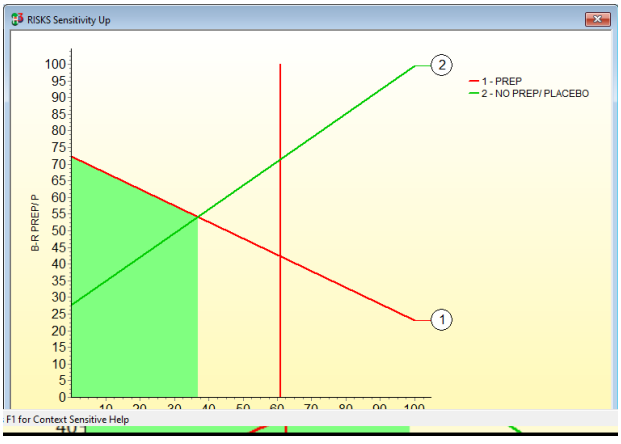


Figure 4. Risk node sensitivity up analysis

Knowledge and attitudes towards eucalyptus oil by healthcare workers at the Accident and Emergency Unit in Kenyatta National Hospital

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Abstract

Background: Eucalyptus oil is widely used for various medicinal purposes. However, like other essential oils, there are potential adverse effects associated with the use of eucalyptus oil, some of which may be very severe. It is therefore important for healthcare workers to be knowledgeable about the uses and adverse effects that may be caused by this essential oil and how to manage these adverse effects.

Objective: The primary objective of this research was to evaluate the level of understanding among healthcare professionals regarding the advantages of eucalyptus oil and the potential hazards related to its usage. Additionally, it aimed to gauge the perspective of healthcare workers concerning the management of adverse effects caused by the oil.

Methods: The research conducted was a quantitative study using a cross-sectional approach within the Accident and Emergency Unit of Kenyatta National Hospital. The participants of the study were healthcare workers who were given questionnaires to fill out on their own.

Results: The results from this study showed that the knowledge of healthcare workers on the therapeutic uses of eucalyptus oil was varied with 79.6% knowing its use in the management of coughs and congestion and only 19.4% being aware that eucalyptus oil can be used to treat topical bacterial infections. The knowledge of the respondents on the adverse effects of the oil was generally poor with only 24.5% of them aware of its risk to cause seizures. The respondents also had very little knowledge of how to manage cases of eucalyptus oil poisoning.

Conclusion: The knowledge of healthcare workers on the benefits of eucalyptus oil was fairly high. However, their knowledge of its risks and how to manage cases of eucalyptus oil poisoning was found to be very low. Measures to raise awareness of the same should be taken to ensure good therapeutic practices involving the use of this essential oil. This is also important to ensure correct and timely diagnosis and management in case of any adverse effects due to the oil.

Key words: *Eucalyptus oil, aromatherapy, seizures, adverse effects, diagnosis, toxicity management.*

Introduction

Eucalyptus oil is extracted from the leaves of the eucalyptus tree. It is cheap and readily available and can be found in many households [1]. Eucalyptus oil and its main component 1, 8-cineole (also known as eucalyptol) are utilized in many pharmaceutical products that are used to treat a wide range of ailments such as coughs, colds, congestion, muscle and joint pain, and sports injuries. Additionally, this oil can be found in other pharmaceutical products that are used to alleviate insect bites and skin disorders. It is also a common ingredient in personal care products such as shampoos, soaps, bath foams, and body lotions. Eucalyptus oil may be used as is or mixed with other ingredients in products such as eucalyptus-flavoured throat lozenges or chest rubs. Aromatherapy, a practice that is gaining popularity, also makes use of eucalyptus oil. [2]. Aromatherapy is a practice where essential oils are used as the main therapeutic agent. [3]. A study on the use of eucalyptus oil as a food preservative revealed that eucalyptus oil had in vivo and in vitro anti-yeast potential. The minimum inhibitory concentration (MIC) values for effective inhibition varied from 0.56mg/mL to 4.5mg/ml. The use of eucalyptus oil and thermal treatment successfully inhibited the growth of yeast in fresh fruit juices. These results showed the potential of eucalyptus oil in the preservation of beverages [4].

The use of eucalyptus oil medication should be limited to patients who are 12 years or older if it is being taken orally. However, patients who are 4 years or older can use eucalyptus oil medication when it is inhaled, applied topically, or added to a bath. It is recommended to follow these guidelines to ensure the safe use of eucalyptus oil medication [5]. Children with a history of seizures must not be given eucalyptus oil medicines. Such medicines must also not be administered to children under 30 months of age since they are in danger of experiencing spasms of the larynx. Patients with large skin injuries and open wounds, acute skin disease, high fever, severe infections, severe problems with blood circulation, and heart failure must not take hot baths with eucalyptus oil [6]. For a long time, the oil has been utilized as a remedy for colds, influenza, sinusitis, and other respiratory ailments due to its ability to combat bacteria, fungi, and viruses [7]. Research done by a university in Algeria proved that high concentrations of Eucalyptus oil

from *E. camaldulensis* and *E. globulus* species of eucalyptus produced distinct zones of inhibition in cultures containing *Staphylococcus aureus* and *Escherichia coli* [8]. This is the basis for the use of the oil in dentistry as the essential oil-based mouthwash, Salviathymol N, has been shown to have activity against oral plaque-forming microorganisms [9].

The common side effects of eucalyptus oil poisoning in children include vomiting, ataxia, depression in the level of consciousness, and seizures. The main organs affected are the gastrointestinal system, the central nervous system, and the respiratory system. Mild toxicity will manifest as vertigo and ataxia [1]. It is uncommon for adults to experience seizures from eucalyptus oil poisoning because they are less likely to consume the oil orally compared to children. The patient may vomit while drowsy and aspirate. Aspiration may lead to bronchospasm, pulmonary oedema, or pneumonitis. Respiratory depression may also occur. Severe toxicity may also lead to tachycardia, hypertension, or cardiovascular collapse. Toxicity with a dose higher than 30ml has been shown to cause nephritis. In the case of a patient suffering from adverse effects of eucalyptus oil, prompt medical attention in the intensive care unit, proper management of hemodynamic conditions, and swift correction of metabolic acidosis can result in their speedy recuperation [10].

At the Parathima Institute of Medical Sciences in India, three paediatric patients were successfully treated for seizures caused by eucalyptus oil. Two of the children received anticonvulsant treatment for a period of two weeks. All three children recovered within just two days and did not experience any further seizures [4]. Another case of a 4-year-old has been reported where she experienced a self-limiting tonic-clonic seizure after dermal application of eucalyptus oil as prescribed for treatment of head lice [11]. This shows that not only is there a risk when using orally or when inhaled but also on topical use of the oil. Another instance has been recorded where a 3-year-old boy presented with status epilepticus 10min after ingesting 5ml of eucalyptus oil. He was successfully treated with phenytoin given intravenously [12]. Extreme toxicity following oral ingestion of the oil has been well-documented but public awareness is lacking. It can be concluded that healthcare providers who have knowledge or awareness of EOIS may be able to reduce unnecessary diagnostic procedures and long-term anticonvulsant treatment. As a result, clinicians are advised to inquire about eucalyptus oil exposure in patients experiencing seizures, particularly those who are having seizures for the first time or those who have not had a seizure for a long time.

Eucalyptus oil poisoning management should be mainly supportive because there is no known antidote. One should not attempt to induce emesis because there is a risk of aspiration. If there is a risk of vomiting or aspiration of oil, gastric lavage should be taken into account. In cases of severe poisoning, peritoneal dialysis or haemodialysis may be necessary [13]. Eucalyptus oil is lipid-soluble and therefore its absorption is enhanced in the presence of milk [1].

A research study where healthcare workers were taken through a continuing education module that provided them with current information on essential oils demonstrated that the healthcare workers had benefited from the module. Most of the participants said that they were more comfortable discussing essential oils with their patients after learning more about them. They also said that they intended to ask their patients about their use of alternative therapy after going through that module [14]. This shows that healthcare workers would benefit greatly from learning more about eucalyptus oil and that it would be also great for the practice of medicine as it would probably lead to better patient care. It is therefore important for healthcare workers to be well informed about eucalyptus oil and essential oils in general for them to remain up to date.

Objectives

The study aimed to assess the understanding of healthcare workers regarding the advantages and disadvantages of eucalyptus oil, as well as their knowledge of how to manage any toxic effects related to its usage.

Methodology

Study design

This study conducted at the Accident and Emergency Unit in Kenyatta National Hospital (KNH) was a hospital-based, cross-sectional research that collected data from healthcare workers. Structured questionnaires were used to obtain the information, and this approach was favoured because it enabled the investigation of various population groups simultaneously.

Study population

The focus group for this study consisted of healthcare professionals working in the Accident and Emergency Unit at KNH. This unit was selected because it is potentially the main entry point for patients who may come to the hospital with eucalyptus oil-related adverse effects or toxicity. The exclusion criterion was the unwillingness to participate in the study. Trainee healthcare workers in their undergraduate years were also not included in the study.

Sampling and sample size determination

To select participants for the study, stratified random sampling techniques were used to specifically target healthcare workers at the Accident and Emergency unit located in KNH. The unit has a total of 150 healthcare staff members including 24 medical officers, 15 pharmacists, and 91 nurses who are employed either on a permanent or contractual basis. Additionally, 10 medical officers and 10 nurses work on a locum basis at the department. A total of 109 participants were selected.

Participant recruitment and consenting process

The researcher ensured that the individuals chosen for the study were willing to take part. Adequate time was given to the participants to comprehend the study's objectives and purpose, enabling them to make informed decisions. Those who agreed to participate were requested to sign a consent form.

Research instruments and Data collection

A structured questionnaire comprising of both open-ended and closed-ended questions was used to collect data. The questions were specific enough to meet the objectives of the study. The study was first explained to the healthcare workers in a deliberate effort to make them understand the benefit of the study. Their confidentiality and right to withdraw from the study were ensured. After that, willing participants were asked to sign a consent form before being issued the self-administered questionnaire which they were asked to fill out.

Quality Assurance, Reliability, and Validity of the collected data

In order to guarantee the dependability of the research, the questionnaires were made consistent through standardization. The accuracy of the questionnaires and data collection forms was preserved by using appropriate

language, sentence construction, and pertinent inquiries. While the questionnaires were self-administered, participants were informed of the study's goals and advantages before being asked to complete them.

Data analysis

Data were collected using questionnaires and stored in a locked cabinet during the data collection period. Only the researcher had access to them. Both sections of the questionnaire were essential in gathering information from the participants. The first section gathered social-demographic information, while the second section contained inquiries that allowed for an evaluation of the participants' understanding and perspectives regarding the advantages, drawbacks, and potential hazards of eucalyptus oil. The data obtained from questionnaires were summarized, coded, tabulated, checked for omissions then analysed using Excel 2016. The study variables were presented using frequency and percentages for categorical variables. Cross tabulations and charts were used to present the data.

Ethical considerations

Ethical approval was granted by the Kenyatta National Hospital-University of Nairobi Ethics and Research Committee (ERC) (UP77/02/2022). The study was also registered by the KNH Medical Research Department.

Results

Response rate

The sample size for this study was 109 healthcare workers at the Accident and Emergency unit in KNH with only 98 of them providing feedback on the questionnaires giving a good response rate of 90%.

Social-demographic characteristics

Majority of the respondents 53.1% were female while 46.9% were male as summarized in Table 1. In terms of the number of healthcare professions serving at the Accidents and Emergency unit of KNH, nurses formed a majority (46.9%). In terms of age, 55.1% of the respondents were between 21-30 years and only 20.5% had post graduate degrees.

Table 1. A summary of the socio-demographic characteristics of the respondents.

VARIABLES	FREQUENCY (n)	PERCENTAGE (%)
SEX		
Male female	46 52	l46.9 53.1
AGE		
Below 20 21-30 31-40 41-50 Above 50	- 54 38 6 -	- 55.1 38.7 6.1 -
HIGHEST EDUCATION LEVEL		
Undergraduate Postgraduate Doctoral	78 20 -	79.5 20.5 -
PROFESSION		
Medical doctors Pharmacists Nurses Students	12 10 46 30	12.2 10.2 46.9 30.6

Benefits, Risks, and Toxicity of Eucalyptus oil

Knowledge of the benefits and risks of eucalyptus oil

Most of the healthcare workers who participated in the study (81.6%) knew medicines that contain eucalyptus oil. About 89.8% were also knowledgeable about the practice of aromatherapy. However, many of them did not know of any situations where eucalyptus oil is contraindicated with only 28.6% claiming to be aware as summarized in Table 2. Those that did mainly sighted hypersensitivity and allergic reactions as the situation where eucalyptus oil is contraindicated. Most of the respondents (91.8%) showed an interest in learning more about eucalyptus oil.

Table 2. Knowledge of respondents on the benefits, risks, and toxicity of eucalyptus oil

Description of knowledge and attitudes	Yes no. (%)	No no. (%)
Knowledge of medicines containing eucalyptus oil	80(81.6%)	18(18.3%)
Knowledge of the practice of aromatherapy	88(89.8%)	10(10.2%)
Knowledge of any situation where eucalyptus oil is contraindicated	28(28.6%)	71(71.4%)
Interest in learning more about eucalyptus oil	90(91.8%)	8(8.2%)

Most respondents, 61.2%, cited both topical and inhalation routes as the methods of administration through which medicines containing eucalyptus oil are administered as

shown in Figure 1 while 49.0%, chose the oral route with only 2% and 8.16% choosing the rectal and parenteral routes respectively.

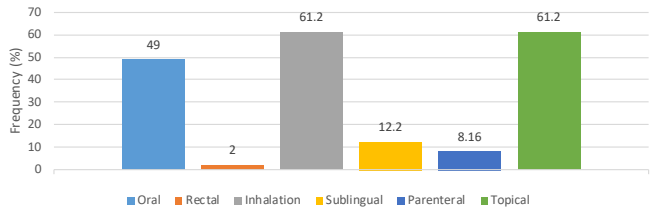

Figure 1. Knowledge of respondents on the modes of administration

The knowledge of the respondents on the uses of eucalyptus oil was fairly high with 79.6%, 75.5%, and 73.5% respondents citing coughs, sore throat, and congestion as conditions that can be managed by eucalyptus oil, respectively. Management of joint pain and topical bacterial infections were the lesser known uses with 46.9% and 19.4% of them citing these uses respectively as shown in Figure 2.

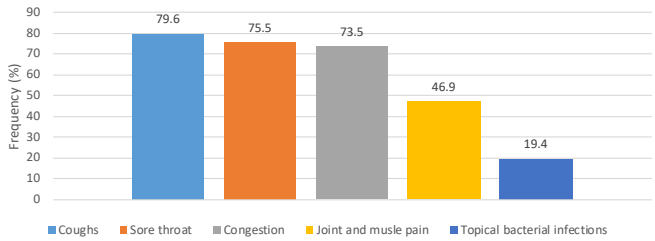

Figure 2. Knowledge of respondents on the uses of Eucalyptus oil

Knowledge and attitudes towards the management of eucalyptus oil-related adverse effects and toxicity

The knowledge of the healthcare workers on the potential adverse effects of eucalyptus oil was found to be fairly low. Only 44.9% of the respondents cited vomiting as a potential adverse effect, 24.5% were able to sight seizures and lowering of the level of consciousness, and only 16.3% cited ataxia as shown in Figure 3.

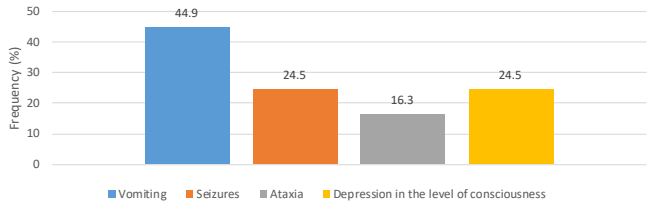

Figure 3. Knowledge of healthcare workers on the potential adverse effects of eucalyptus oil

The study found that a small percentage (6.1%) of healthcare workers had come across patients suffering from eucalyptus oil poisoning. The majority of them were unaware of the appropriate course of action to take in such cases. From this study, 21% of the respondents said they would use an antidote while 12% of them would induce emesis to manage eucalyptus oil poisoning. Only 14% and 12% of them said they would use gastric lavage and cathartics respectively as shown in Figure 4.

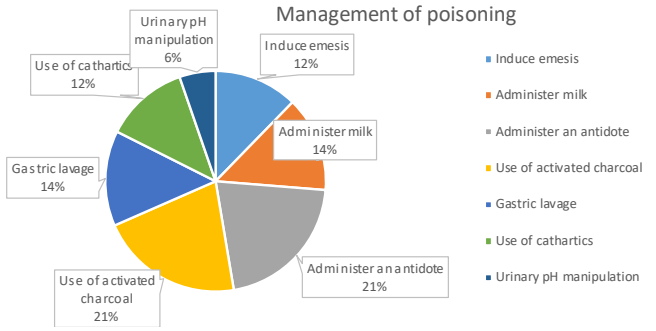

Figure 4. Measures healthcare workers would take to manage eucalyptus oil poisoning

In terms of the attitude of the healthcare workers towards the use of eucalyptus oil, about 87.8% of the healthcare workers who participated in the study said that they use or were willing to use eucalyptus oil for personal use. Most of them, 89.8%, were also willing to recommend the use of eucalyptus oil to their patients.

Discussion

Knowledge of healthcare workers on the benefits of eucalyptus oil

With alternative and complementary medicine becoming more and more popular, the use of eucalyptus oil in treatment has been on the rise. Studies show that concomitant therapy with eucalyptus oil prevents the worsening of chronic obstructive pulmonary disease [15]. Eucalyptus oil has also been used to manage other respiratory problems such as bronchitis and asthma [16]. It can also be used for the topical treatment of fungal and bacterial infections as it has been shown to have activities against both [7].

The respondent's knowledge of the uses of eucalyptus oil and the practice of aromatherapy goes to show that there is not much of a knowledge gap on the benefits and uses of eucalyptus oil, some uses being more popular than others. The knowledge of the healthcare workers also indicates that there is a high probability of them recommending the use of eucalyptus oil to their patients or even prescribing it and even use it personally suggesting a positive attitude towards the uses of eucalyptus oil.

The route of administration of eucalyptus oil or eucalyptus oil-containing medicines depends on its indication. For the management of muscle and joint pain, skin disorders, and topical bacterial infection, a topical route of administration would be used. For coughs, congestion, and respiratory problems like bronchitis and asthma, vapor inhalation and oral routes may be used. Historically vapor inhalation was done mainly by putting a few drops of eucalyptus oil in a bowl of hot water and breathing in the vapor over the bowl with a towel tent over one's head. Now there are devices in pharmacies to allow one to inhale the vapor [16]. Topical and

inhalation methods were both selected by 61.2% of the respondents while only 49.0% of them selected the oral route of administration. This also shows that there is not a knowledge gap in the route of administration used to deliver eucalyptus oil.

Knowledge of healthcare workers on potential risks associated with eucalyptus oil

Systemic toxicity can arise on ingestion of higher than recommended doses of eucalyptus oil. The possible lethal dose of eucalyptus oil for an adult lies between 0.05ml to 0.5ml [17]. Children are more vulnerable to poisoning through dermal absorption. Severe toxicity in children may predispose them to the development of status epilepticus [18].

The knowledge of the healthcare workers on the potential adverse effects of eucalyptus oil was found to be fairly low. Only 44.9% of the respondents sighted vomiting as a potential adverse effect, 24.5% were able to cite seizures and depression in the level of consciousness, and a mere 16.3% cited ataxia. This shows that there is a knowledge gap in the healthcare system concerning the adverse effects of eucalyptus oil. Some adverse effects like seizures are very severe and may lead to loss of life or unnecessary investigations and long-term antiepileptic drug therapy [19]. Knowledge of these side effects is therefore very crucial as it would allow healthcare workers to make that link between eucalyptus oil and the side effects it causes and this would help in the diagnosis and management of the same. Most of the respondents, 71.4%, said that they did not know of any situations where the use of eucalyptus oil is contraindicated. Those who did thought that eucalyptus oil was contraindicated in infants, in case of allergic reactions, and hypersensitivity to the same. This piece of information is very important as there has been a clear correlation between the age of the patient with poisoning with eucalyptus oil. The oil is safe for adult use within the recommended doses but it is contraindicated in infants and very young children [17]. This is also a knowledge gap that needs to be filled as soon as possible as adverse effects and toxicity can be prevented before they happen by correct use and prescription of the oil. This should also be treated with urgency as adverse effects like seizures may be lethal, especially for young children. A study on the education of healthcare workers on essential oils showed that healthcare workers were more comfortable discussing the use of essential oils with their patients after learning more about their indications, safety, and contraindications [14].

Management of eucalyptus oil-related adverse effects and toxicity

The management of eucalyptus oil poisoning is mainly supportive or symptomatic. At the moment there is no known specific antidote for eucalyptus oil poisoning. In the management of poisoning, emesis is contraindicated as it may cause aspiration. In severe intoxication, peritoneal dialysis and haemodialysis are useful. Gastric lavage and activated charcoal can also be used once the airways have been secured under general anesthesia. Eucalyptus oil is lipid-soluble and therefore its absorption is enhanced in the presence of milk. Milk should therefore never be used in the management of poisoning as it may increase the systemic concentration of the oil hence worsening the toxicity [1]. Studies have shown that eucalyptus oil-induced seizures can be treated with standard antiepileptic drugs. Therapy with these drugs can be stopped after 2 or 3 weeks without recurrence of the seizures [10]. The knowledge of the management of eucalyptus oil poisoning was found to be very poor with some respondents choosing not to fill this part of the questionnaire. For those that did, the highest percentage chose the use of activated charcoal while some chose induction of emesis, a measure that is contraindicated. Based on this study, there is need for healthcare workers to be educated more on the management measures of eucalyptus oil poisoning for better management of patients. There is a clear lack of knowledge and if the situation is left as it is, many patients will not only be poorly managed but efforts by healthcare workers to treat them may be deleterious to the patients. Only 6.1% of the respondents said that they had encountered a patient with eucalyptus oil poisoning. The lack of documentation of eucalyptus oil's adverse effects and poisoning despite the popularity of the oil can also be attributed to the lack of awareness of these adverse effects therefore a failure of healthcare workers to link the two. This would therefore affect the diagnosis as well as the management of eucalyptus oil-induced adverse effects.

Conclusion and Recommendations

This research study established that the knowledge of healthcare workers on the adverse effects of eucalyptus oil is poor. Their knowledge of the management of these adverse effects and poisoning was found to be even lower with only few being aware of the recommended management. There is therefore a need to raise the awareness of healthcare workers on the risks of eucalyptus oil and their knowledge of managing toxicity due to the oil. This is crucial to ensure timely diagnosis and management of any adverse effects and toxicity that may occur due to the use of the now very popular essential oil. It is also important for healthcare workers to offer professional advice to the public on the recommended practices involving the use of eucalyptus oil. As much as the oil has many therapeutic uses, it can be drawn from literature and reports that the oil also bears great risks, and it is therefore important for healthcare to get educated on how to best use it therapeutically.

Conflict of interest

The author declares that they have no conflicting interest.

Funding

Not applicable.

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