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FEATURE ARTICLE:

Is tablet splitting a potential pitfall in drug therapy? A case study of Amlodipine Tablets

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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

ADVANCED PHARMACY PRACTICE AND TECHNOLOGY ARE THE FUTURE OF PHARMACY

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Pharmacists are healthcare providers, a status that needs to be entrenched in legislation enabling patients and other health care workers to get the full benefit of this cadre. Many developing countries still embrace a transactional approach to pharmacy services where money is exchanged for medicines. The pharmacist remains a trusted, critical, and usually underutilized resource that is closest to communities.

However, with rapid changes in the world and lessons learnt from the covid-19 pandemic, the role of the pharmacy and the pharmacist has evolved into one that requires revision of existing practice frameworks to reflect the future of this profession. There is need for Pharmacy Care Centers operated by specialist Pharmacists who get to know their clients and understand their health and wellness goals. The specialists should collaborate with patients and their physicians to optimize medication therapy, reduce out of pocket costs, and recommend beneficial clinical services, such as immunizations, packaging, supplements, family planning services that will enhance treatment and client outcomes.

Technology will be the mainstay of Pharmacy Practice in future. There will be an expanded role of telehealth and virtual health care for Pharmacists with increased access to medicines online. The traditional retail pharmacy experience will need to evolve to involve the growing population that has access to smart phones and prefer the easiest and fastest ways to addressing their medical needs and enquiries. However, the majority of the population may not fully appreciate digital health technologies and need in-person pharmaceutical care.

Disease state education, medication therapy management, quality Family Planning services, vaccinations, providing chronic care management alongside physicians, and other cognitive services are areas that are unexplored by many graduates. Seeking mentorship becomes a personal responsibility for growth. People are living longer and Pharmacy Care Centers should be comprehensively prepared to attend to patients with chronic conditions like diabetes, hypertension, and asthma. These three focus areas have been identified that will require continuous professional development of the Pharmacist to remain relevant. Technology advances are needed to manage digital therapeutics, medical knowledge to manage complex diseases and poly-chronic patients and importantly awareness of mental health issues to integrate social determinants of health (SDH) in Pharmacy Practice.

According to Timothy Aungst, Associate Professor of Pharmacy Practice at the Massachusetts College of Pharmacy and Health Sciences, "*we need to move away from product-based model to services empowered by digital technology, meeting patients where they are, and adopting a consumer-first mentality. This is how we will deliver care for patients in future.*"

Pharmacists have occupied bigger roles in the recent past including managing teaching and referral hospitals, heading government departments, preparing critical injectable medicines, providing injectable contraceptives and ensuring continuity of care in the community for patients with chronic diseases. It is the duty of all Pharmacists to be armed with current information. Recognition of specialist Pharmacists in Kenya should be fast tracked to allow access of patients to proper medication management and to support independent prescribing. International Pharmaceutical Federation (FIP) acknowledges the core competencies of community pharmacists globally and recognizes four unique skills that they should possess including: prescribing, dispensing, administering and reviewing. This is a call for collective participation to facilitate positive change in the profession.

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Prescribing Pattern of Antipsychotic Medicines Among Physicians in Federal Medical Centre, Lokoja, North Central Nigeria

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Abstract

Background: Psychosis is a symptom of several mental disorders characterized by an impaired relationship with reality which has been found to be on the increase in prevalence across the globe in recent times.

Objective: The objective of this study was to assess the prescribing pattern of antipsychotics by physicians in the Federal Medical Centre, Lokoja, Kogi State and describe the rational prescribing of antipsychotics among the physicians.

Methodology: The research design was a descriptive retrospective study assessing the pattern of antipsychotics prescribed by physicians in the Federal Medical Centre, Lokoja. Data were collected from copies of prescription sheets containing antipsychotics from 1st January, 2016 to 31st December, 2016. The data were analyzed using SPSS version 20. Chi square test was used to determine relationships between categorical variables and p-value < 0.05 was considered significant.

Results: A total of 1101 prescription sheets containing 1401 prescribed antipsychotics were obtained and analyzed. The most frequently prescribed antipsychotic was olanzapine (23.6%) closely followed by risperidone (20.7%) while aripiprazole was the least frequently prescribed (0.3%). About ninety-one percent (91.2%) of the medicines were prescribed in their generic form and 50.4% of the prescriptions were in line with treatment guidelines in selection and combination. The average number of drugs per prescription was 2.17 while average number of antipsychotics contained per prescription was 1.3. About half (52.5%) of antipsychotics were available at the pharmacy while 47.5% were out of stock.

Conclusion: Olanzapine was the most prescribed antipsychotic in the facility. Prescriptions with inappropriate doses and use of injectable drugs were not majorly observed in the study.

Keywords: *Antipsychotics, prescribing patterns.*

Introduction

Schizophrenia or psychosis is defined as a chronic disabling mental illness with far-reaching consequences on social, interpersonal and occupational functioning in affected individuals [1]. It significantly contributes to the global burden of disease. Antipsychotic medications, which are the mainstay of treatment, yield modest outcomes as they improve positive symptoms but are less effective on negative and cognitive symptoms [1]. The hallmark of psychiatric disorders is characterized by hallucinations which is a state of hearing, seeing or feeling things that are not there; and delusions which is a state of fixed false beliefs or suspicions that are firmly held even when there is evidence to the contrary. The disorder can make it difficult for the affected people to work or study normally [2]. The World Health Organization (WHO) estimated the prevalence of schizophrenia/psychotic disorders to be about 20 million worldwide [3]. Across Africa, a lifetime prevalence of 0.1 % to 1.83% has been estimated [4]. In Nigeria, strategic framework aiming at addressing mental health problems is not adequate in providing effective prevention and control of such illness with improved access to mental health care [5]. Clinical profile and socioeconomic status have been seen to determine the choice of antipsychotic drugs prescribed by physicians [6].

Major challenges in the treatment of mental disorders include poor facilities, lack of infrastructure, obsolete mental health laws, dearth of manpower and, most importantly, high cost of treatment. The burden of treatment is on the increase for a population of about 170 million people [7]. It is speculated that 64 million Nigerians suffer from one form of mental illness or the other [8]. The use of antipsychotics is on the increase and their prescriptions by psychiatrists and other physicians should be in accordance with the recommended guidelines to achieve optimal benefits to the patient with minimal side effects at lowest possible costs to the patient and the community. The cost of treatment of mental disorders is a major factor in determining therapeutic outcomes as the prevalence of mental illness in Nigeria is linked to socio-economic factors [9].

Objective

The objective of this study was to assess the prescribing pattern of antipsychotic medicines among physicians in Federal Medical Centre, Lokoja, through the review of prescriptions and assessment of rational prescribing of the drugs.

Methodology

This study was conducted at Federal Medical Centre, Lokoja, Nigeria. This was a descriptive retrospective study of the pattern of antipsychotics prescribing at the facility between the months of January through December, 2016. The sample size was determined using WHO guideline for prescribing indicators in drug utilization studies [10], with calculation done using the formulae:

$$n = \frac{1.96^2\,\sigma}{W^2}$$

where n = number of patients required, σ = standard deviation and W= level of precision. σ=13.5 , W^2 =0.05.

The value of n obtained was 1101 with 5% attrition rate inclusive. A systematic random sampling of the prescriptions was done by selecting one in every three prescriptions until a total of 1101 prescriptions from patients' case notes was obtained. Data were collected using a structured observational check list for prescribing indicators through the use of a data collection sheet that was developed to extract information on patient demographics, types of drug, dosage and frequency of administration and drug classes.

All prescription sheets containing antipsychotic drugs were collected from the Pharmacy department. Five research assistants were recruited and trained on data collection modalities. Data were extracted from the data collection sheet using Excel spread sheet and then filtered for analysis. Information collected included drug prescribed in generic or trade name, dosage of drug, availability of the drugs at the time the prescription sheet was presented to the pharmacy and categories of patients receiving the drugs.

Ethical Consideration

Permission to carry out the study was obtained from the hospital pharmacy department and confidentiality of the patients was maintained. Patient's identifiers like name and hospital number were not included in the information extracted from the drug order forms/ prescription sheets.

Statistical Analysis

The standard World Health Organization/International Network for Rational Use of Drugs prescribing indicators were used to determine the prescribing practices of physicians. The data obtained were analyzed using Statistical Product and Service Solutions (SPSS) version 20. Numerical and continuous variables were analyzed and presented as frequency tables and percentages. Chi square was used to determine association between categorical variables. P-value < 0.05 was considered to be statistically significant.

Results

Types of antipsychotics prescribed in a total of 1,101 prescription sheets containing 1,401 antipsychotics were obtained. From this, 776 (55.3%) were typical antipsychotics while the remaining 625 (44.7%) were atypical antipsychotics. A total of 1,140 (81.4%) of the antipsychotics prescribed were oral tablets while 261 (18.6%) were injectables. The most frequently prescribed antipsychotic drug was Olanzapine (331; 23.6%) followed closely by Risperidone (290; 20.7%) as shown in Table 1. Aripiprazole was the least frequently prescribed antipsychotic drug (4; 0.3%). Close to half of the antipsychotics were prescribed between September and December (612; 43.7%).

Table 1. Details of Antipsychotics prescribed at Inpatient and Outpatients departments of Federal Medical Centre (2016).

Class	Medication	Inpatient			Outpatient			Total (%)
		Jan-Apr	May-Aug	Sept-Dec	Jan-Apr	May-Aug	Sept-Dec	
Atypical Oral	Aripiprazole	0	0	0	0	0	4	4 (0.3)
	Olanzapine	44	53	79	40	9	106	331 (23.6)
	Risperidone	35	40	22	44	57	93	290 (20.7)
Typical Oral	Chlorpromazine	31	9	26	13	26	53	158 (11.3)
	Trifluoroperazine	48	13	31	18	53	57	220 (15.7)
	Haloperidol	44	9	13	26	18	26	137 (9.8)
Injectables	Fluphenazine	4	18	13	22	4	53	115 (8.2)
	Flupenthixol	13	9	4	35	22	13	98 (7.0)
	Chlorprozine	0	4	9	0	13	4	31 (2.2)
	Haloperidol	9	4	4	0	0	0	17 (1.2)

Prevalence of generic prescription among the physicians

The frequency of prescribing in branded or generic antipsychotic medicines within the period of study showed that the majority of the antipsychotics (1278; 91.2%) were prescribed using their generic names. The brand names of antipsychotics prescribed were largactil® (chlorpromazine), stellazine® (trifluoperazine), Haldol® (haloperidol), Rexolan® (olanzapine), modecate® (fluphenazine) and fluanxol® (flupenthixol) (See Table 2).

Table 2. Level of generic prescribing of antipsychotics (n = 1401)

Antipsychotics	Branded (%)	Generic (%)
Chlorpromazine	8(4.2)	181(95.8)
Trifluoperazine	35(15.9)	185(84.1)
Haloperidol	4(2.6)	150(97.4)
Aripiprazole	0(0.0)	4(100)
Olanzapine	27(8.2)	304(91.8)
Risperidone	0(0.0)	290(100)
Fluphenazine	49(42.6)	66(57.4)
Flupenthixol	0(0.0)	98(100)
Total	**123(8.8)**	**1278 (91.2)**

Adherence to Guidelines for Prescribing of Antipsychotic

Out of 1,101 prescription sheets obtained containing antipsychotics, 555(50.4%) of the prescriptions were strictly

in line with treatment guidelines [10] in the selection and combination of the antipsychotics for the patients while the remaining (546; 49.6%) were not. The prescription doses were within permissible range according to official reference books [7], without any cases of under-doses or over-doses. The proportion of prescriptions containing antipsychotic combinations were 282 (25.6%) while single drug prescriptions were 819 (74.4%). The average number of antipsychotics per prescription was 1.3.

Figure 1 indicates the number of drugs per prescription. The highest number of drugs per prescription was found to be eight (8) with this translating to 0.4% of the total number of prescriptions reviewed in the study. A large percentage of the prescriptions had 2 drugs only (Figure 1).

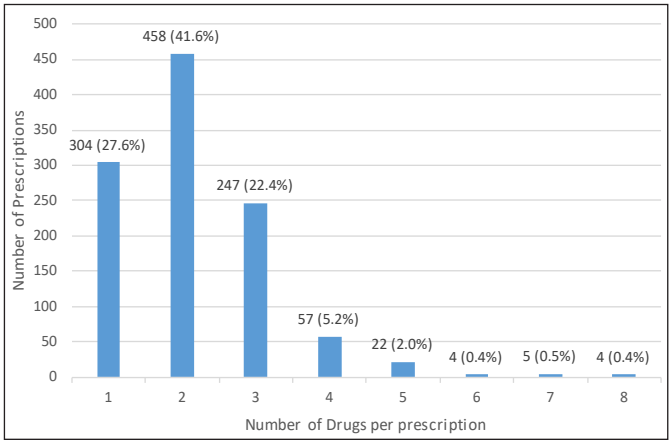

Figure 1. The number of drugs per prescription with antipsychotics (n= 1,101)

Combinations of Antipsychotics Prescription Pattern

Different combinations of antipsychotics based on different chemical classes and dosage forms are presented in Table 3. There were 15 different types of combinations observed. The co-prescription of chlorpromazine and trifluoperazine had the highest frequency of 67(23.6%) while combination of olanzapine and injectable fluphenazine had the least frequency of 3 (1.1%).

Table 3. Combinations of antipsychotics in prescriptions with more than one antipsychotic drug (n=282)

Combination type	Frequency (%)
Olanzapine + Chlorpromazine	17 (6.2)
Olanzapine + Haloperidol	5 (1.7)
Olanzapine + IM Flupenthixol	13 (4.5)
Olanzapine + IM Fluphenazine	3 (1.1)
Olanzapine + Chlorpromazine + IM Fluphenazine	5 (1.7)
Risperidone + Chlorpromazine	11 (3.9)
Risperidone + IM Flupenthixol	11 (3.9)
Risperidone + IM Fluphenazine	39 (14.0)
Aripiprazole + Chlorpromazine	5 (1.7)
Chlorpromazine + Trifluoperazine	67 (23.6)
Chlorpromazine + IM Fluphenazine	13 (4.5)
Chlorpromazine + IM Fluphenazine + Trifluoroperazine	11 (3.9)
Trifluoroperazine + IM Fluphenazine	30 (10.7)
Trifluoroperazine + IM Flupenthixol	30 (10.7)
Haloperidol + IM Fluphenazine	22 (7.9)
Total	**282 (100)**

When association between types of antipsychotics and level of generic prescribing was assessed using chi square test, there was no relationship obtained from the categorical variables (X^2 = 0.003, p-value=0.6963).

Antipsychotic Availability in the Hospital Pharmacy

The proportion of antipsychotics available in the pharmacy department was 52.5% while 47.5% of antipsychotics were out of stock. There were more out of stock between January and April than other periods. When association between types of antipsychotics and the formulation type prescribed was assessed, a significant relationship (X^2= 31.64, p < 0.001) was obtained with a noticeable higher combination of typical and atypical (69%)) among patients taking oral with injection antipsychotics compared with less (37%) number of patients taking only typical antipsychotics. More of the typical antipsychotic only combinations were also oral plus injectable (107; 62.6%).

Discussion

On the class of antipsychotics prescribed, the percentage of typical antipsychotic drugs was 55.3% while that of atypical antipsychotic drugs was 44.7%. The reference value by the WHO for drug prescribed from the essential drug list was 100%. It was observed that the newer antipsychotics (atypical) were not in the current essential drugs list (the 5th revision of the national EDL). This could have contributed to this lower value of 44.7% of prescription encountered in the institution.

The treatment of diseases by the use of essential drugs prescribed by their generic names has been emphasized by the World Health Organization. Generic prescribing was found to be highly prevalent in this study (91.2%) which was in line with the WHO recommendation although it is worth mentioning that the facility could still be improved upon to comply with the WHO standard of 100%. Similar values for generic prescribing have also been reported in psychiatric facilities in some other studies [9]. The WHO essential drugs program recommends the use of generic prescribing to save cost and enhance access to essential medicines [11]. Though prescribers may use brand names, they accept generic substitution when a different brand was dispensed. It has become conventional that prescribers were used to old popular brand names of some of these medications, for example Stellazine® in the case of Trifluoperazine [12].

The association between the types of antipsychotic combinations by class and combinations by dosage form was found to be statistically significant. Combinations of parenteral and oral dosage forms were more common in the institution than combinations of two or more oral dosage forms of the antipsychotic drugs in order to reduce or prevent non-adherence or relapse cases. Justifiable reasons for prescriptions with antipsychotic combinations as recorded in this study (75.6%) included utilization of a different route of administration which exploits different pharmacodynamics or pharmacokinetic drug-drug interactions hoping to augment the efficacy of the

antipsychotics, especially after insufficient response [13]. However, concerns may include increased acute or long term side effects, anticipated (or uncomplicated) drug-drug interactions, increased non-compliance caused by increased complexity of drug regimen, difficulty in determining causes and effects of multiple treatments and substantially higher costs [14].

The assessment of a mental health system by the WHO-Assessment Instrument for Mental Health Systems (WHO-AIMS) tool in Nigeria reported that though a list of essential medicines existed, it was not always available at the health centers [15]. The typical antipsychotic drugs (55.3%) were more frequently prescribed compared to the atypical antipsychotic drugs (44.7%). This is contrary to results obtained from Federal Neuropsychiatric Hospital in Aro, South Western Nigeria where 55% of prescribed antipsychotic medications were mostly atypical antipsychotics [16] as against the typical in this study.

The frequent use of the atypical antipsychotics was very encouraging with risperidone (20.7%) and olanzapine (23.6%) being more prescribed than any other antipsychotic medications. Atypical antipsychotics have been recommended as first choice in the treatment of schizophrenia and some other psychiatric disorders because of their better efficacy against refractory cases and fewer adverse effects [17]. The atypical antipsychotic drugs are more expensive but their use is correlated with enhanced concordance and lower hospitalization rates [18]. Extrapyramidal side effects (EPS) are more common with the typical antipsychotics which were more frequently prescribed in this study (55.3%). Anticholinergic drugs such as benzhexol are recommended to overcome the extrapyramidal side effects (EPS).

There was a slightly higher percentage of encounters with injections prescribed (18.6%) compared to the WHO standard of 10.1-17.0% [19]. Use of both depot and non-depot injections were encountered in this study. The depot injections were mostly used in patients with adherence problems. The non-depot injections were prescribed to achieve rapid effects in new or relapse patients although there has been advocacy for depot injection to enhance adherence and better prevention of relapse [20]. However, all antipsychotic drugs in this study were given in recommended doses. Drugs prescribed were below the maximum recommended dose specified in the official guidelines. This gives an impression that all medical doctors prescribing the antipsychotics were in tune with the dosage regimen of the drug and this is a very good trend. The use of high dose antipsychotics should be an exceptional clinical practice and only employed when standard treatments including clozapine have failed. Most prescriptions had a single antipsychotic drug as compared to combination antipsychotics. The use of antipsychotic co-treatment is generally discouraged by treatment algorithms and is allowed only as a last resort strategy after clozapine (the standard of care for treatment-refractory psychotic illness) has failed [21].

The average number of drugs per prescription, including non-antipsychotic drugs, obtained from this study, 2.17, was found to be slightly lower than the one obtained in a study carried out in Benin City, Nigeria (2.35) [12] but higher than WHO guideline (1.6-1.8) per prescription per encounter [22].

Polypharmacy in psychiatry is commonly referred to as the concurrent use of two or more psychiatric drugs in the same patient [9]. Polypharmacy increases the risk of morbidity and mortality in patients and also the cost of patients' treatment [23]. Psychotropic polypharmacy has also been said to put patients at risk of drug interactions with uncertain gains for quality of care and clinical outcomes [24]. Higher number of patients had only two drugs per prescription. This implies a lower incidence in drug interaction and cases of polypharmacy in the prescribed medicines.

There was high levels of stock-out records of antipsychotics in the hospital pharmacy (665, 47.5%). Much lower results were obtained in Federal Neuropsychiatric Hospital (FNPH) and University of Benin Teaching Hospital (UBTH), both in Benin-City, at 8.46% and 12.53% respectively [25]. The lower rates observed could have resulted from specialist nature of FNPH in the environment which could also impact on the sister tertiary health facility (UBTH) having a lower rate. This indicated that the availability was just slightly above average which is inimical to effective patient management where patients would not be able to receive their medication as at when due.

Conclusion

There was high levels of compliance with standard treatment guidelines by the prescribers. More medicines were prescribed using generic than brand names but the newer/ atypical antipsychotics were significantly more prescribed by brand names. Products availability at hospital facility was found to be fairly appropriate.

Limitation of the study

The study was carried out using only one heath facility therefore the results obtained was limited in application to the study area. Also, prescribers' identifiers were not studied therefore there could be variation in the standards of rational prescribing among the prescribers.

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Conflict of Interests

The authors declare no conflict of interest in carrying out the research.

Authors' contribution

All the authors contributed significantly in the success of

the research from theoretical framework, research proposal, data collection and analysis, and manuscript development.

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Formulation of methyldopa 250 mg tablets by direct compression using a Quality by Design approach

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Abstract

Background: Despite being in use for over 50 years, the physicochemical challenges posed by methyldopa remain ever present. Methyldopa is not only significantly hygroscopic, but also prone to oxidative and hydrolytic degradation that can be accelerated by moisture. Poor compression behaviour, another limitation of methyldopa, leaves the formulation scientist with a constellation of formulation hurdles that must be faced, understood, and overcome. This is a task that can be tackled using elements of the Quality by Design approach.

Objective: The study aimed at developing an optimal formulation of methyldopa into 250 mg immediate release tablets by direct compression using elements of Quality by Design.

Methodology: Excipients were selected for the candidate formulation, preliminary concentrations established for each and settings for mixing and compression variables also established. The risk posed by all these factors was evaluated using Failure Modes and Effects Analysis (FMEA). The preliminary experiment was executed using a 12 run Plackett Burman design. A 16 run Box-Behnken experimental design successfully aided in the identification of excipient concentrations and manufacturing conditions that yield methyldopa tablets of optimal quality.

Results: FMEA revealed that magnesium stearate, colloidal silica, sodium starch glycolate, citric acid monohydrate, mixing speed, duration of pre-lubrication mixing, duration of lubrication and compression speed were critical risk factors. The optimal formulation was achieved at the following settings: 50 % m/m methyldopa, 42.4 % m/m microcrystalline cellulose, 1.0 % m/m magnesium stearate, 1.0 % m/m colloidal silica, 3.9 % m/m sodium starch glycolate, 1.7 % m/m citric acid monohydrate, mixing speed of 101 rpm, 6 minutes of pre-lubrication mixing, 2 minutes of lubrication and compression speed of 20 rpm.

Conclusion: The Quality by Design tools used in this study enabled, not only achievement of optimal quality, but also a better understanding of the impact of critical formulation variables on tablet quality. Challenges to pharmaceutical development can be effectively overcome using the Quality by Design approach.

Key Words: *hygroscopy, methyldopa, direct compression, Quality by Design.*

Introduction

Methyldopa is a centrally acting antihypertensive agent approved for the treatment of essential hypertension and preeclampsia in South Africa [1]. Methyldopa is also known for being a hygroscopic material [2] that is cohesive and poorly compactable [3]. The drug is also prone to oxidative and hydrolytic degradation, exhibiting a grayish black discolouration as a result [2,4]. These properties make it important for a systematic proactive approach to be taken in the development of a methyldopa formulation. In 2006, the International Conference on Harmonisation (ICH) guidelines officially recommended Quality by Design (QbD) as a cornerstone for pharmaceutical development [5]. A sequential plan must be developed to employ such an approach using elements of the framework [5]. Such a plan would culminate in the definition of excipient and process settings that yield optimal tablet quality [6].

The manufacture of immediate release tablets is generally performed via the use of wet granulation, dry granulation or direct compression (DC) processes [7]. Both wet and dry granulation processes involve multiple steps and often more than one piece of equipment is utilized, making the manufacturing process costly and long [8]. Production time, production cost and tablet variation can be minimized by reducing the number of operations performed before tablet compression [8]. Direct compression is a cheaper but feasible method where the powder mix is uniformly fed into a die cavity in its primary state and compressed into individual tablets [9]. The quality of a pharmaceutical product is an important factor to be considered during the product development process [5]. Aspects relating to quality must, therefore, be considered at every step of the process and quality attributes evaluated after the development work [5].

The aim of this study was to develop a formulation of methyldopa into 250 mg immediate release tablets by direct compression using elements of the QbD approach, such as risk assessment and Design of Experiments (DoE).

Methodology

The excipients that were selected for use in the tablet formulation are listed in Table 1.

Table 1. Excipients used in the study

Excipient	Role in formulation
Microcrystalline cellulose	Filler-binder
Sodium starch glycolate	Superdisintegrant
Magnesium stearate	Lubricant
Colloidal silica	Glidant
Citric acid monohydrate	Antioxidant

All materials, including methyldopa sesquihydrate, were kindly donated by Aspen Pharmacare (Gqeberha, South Africa). Factors including performance [10], compactability [11], compatibility [12], hygroscopicity [5] and rheology [13] were used as criteria during the excipient selection process.

Application of Quality by Design

A risk evaluation [14] was performed on the physicochemical properties of methyldopa sesquihydrate, the excipients to be used, their ratios and the variables of the DC process to determine their individual impact on the critical quality attributes (cQAs) of methyldopa tablets.

Based on the QbD framework for risk management, Failure Mode and Effects Analysis (FMEA) was used to perform the evaluation exercise [15]. Factors with Priority Numbers (RPNs) ≥ 50 were considered as high risk. These factors were eligible for investigation in subsequent experiments.

A 12-batch Plackett-Burman design was used to perform the screening experiment [16]. The Box-Behnken design [17] for optimization of the formulation followed a 16-batch model, including 4 centerpoint batches (D3, D4, D6 and D7). Knowledge from both experiments provided the basis for an understanding of the risk posed to the DC process and tablet quality. Material and process variables studied in the experiments included but were not limited to excipient concentrations and mixing times. The influence of these variables on tablet quality was quantitatively evaluated [16]. JMP 15® (SAS Institute, USA) software was used to create the experimental plans and analyze the data.

Powder handling and compression

For each experimental batch, a Mettler Toledo® XPE205 analytical balance (Mettler Instruments, United Kingdom) was used to weigh raw materials below 200 g and an Astro® ASC 2001 compact scale (Adam Equipment, South Africa) used for heavier raw materials. The weighed materials were then assembled for mixing and transferred to a Erweka® KB15 cube mixer (Erweka GmbH, Germany). Methyldopa was used at a 50% m/m loading for all the batches. Each batch was mixed at the predefined speeds and durations. The bulk and tapped densities of 100g samples of each batch were determined, and respective Hausner ratio values determined. This parameter provided an indication of powder rheology [18].

The powder blends were transferred to the feeder hopper of an Erweka® EP1 single punch tablet press (Erweka GmbH, Germany). Convex unscored tablets of approximately 5 mm thickness and 12 mm diameter were produced at the respective compression speeds. In their respective batches, all manufactured tablets were placed in closed glass containers and stored in a storage area at 25°C kept within 30-50 % relative humidity. Tablet testing was performed after a duration of 28 days had elapsed.

Tablet testing

Uniformity of weight tests were performed by randomly sampling tablets from each batch, weighing each individual tablet, and calculating the average weights per batch [19]. Weight measurements were performed using a Model XP205 Mettler Toledo® analytical balance (Mettler Instruments, Zurich, Switzerland). The standard deviations (SD) among the average weights were calculated. The optimal weight for tablets prepared in this study was 500 mg.

The hardness tests were performed using an Erweka® TBH 325 hardness tester (Erweka® GmbH, Germany), which provided a breaking force in Newtons (N). Randomly selected tablets from each batch were tested and average hardness values calculated. Friability was measured by rotational agitation of pre-weighed tablets in a Model TA3R friabilator (Erweka® GmbH, Germany), after which the tablets are weighed again and losses in individual tablet weights calculated. These values were used to calculate average percentage loss per sample, indicating the degree of tablet friability. The friability and hardness values were used as measures of mechanical strength [8].

Loss on drying (LOD) tests [20] were carried out on a sample of 8 randomly selected methyldopa tablets per batch. The tablets were crushed into a powder and each sample weighed using a Model XP205 Mettler Toledo® analytical balance (Mettler Instruments, Zurich, Switzerland), the mass (g) recorded, and the sample dried in a drying chamber at 100 to 105°C for 2 hours. The samples were then cooled for 50 minutes, individually re-weighed and percentage losses in weight calculated to indicate the respective amounts of moisture gained.

Disintegration tests were performed in ZT 320 Series disintegration chambers (Erweka® GmbH, Germany) whose tubes oscillate vertically at a regular frequency. The glass chamber was filled with a medium of distilled water at 37 ± 0.5°C, within which 12 randomly selected tablets were agitated. The times taken for each tablet to completely disintegrate were recorded and averages for each batch calculated [8].

As described in the USP monograph for methyldopa tablets, sample solutions containing powdered tablets were assayed using ultraviolet–visible spectrophotometry to determine potency [19]. The dissolution test listed in the monograph [19] was used in the study. A Biobase® USP BK-RC8 paddle dissolution tester (Biobase, China) was selected for use. This apparatus has compartments that use a rotating paddle to agitate the tablets in a dissolution medium. Tablets were

randomly selected from each batch and placed in a medium of 0.1M hydrochloric acid (900 ml) at 37 ± 0.5°C. For each test session, the apparatus paddles were rotated at 50 rotations per minute, for 20 minutes [19]. Samples were withdrawn from the medium at regular intervals and each filtered sample analysed to calculate the quantity of drug contained. These assays were done using a Boeco® S-220 UV-VIS spectrophotometer (Boeco, Germany).

In an effort to control moisture gained by the tablets, the humidity in the storage chamber was controlled at all times [2]. The tablets were observed over 28 days, the number of discoloured tablets within each batch counted and expressed as a percentage of the batch size. The specifications of the different tests conducted on the tablets are summarized in Table 2.

Table 2. A summary of the tests performed on the methyldopa tablets prepared [19].

Test	Specification
Weight variation (mg)	475 – 525
Hardness (N)	N/A
Friability (% m/m)	< 1.0
Moisture content (% m/m)	N/A
Disintegration time (seconds)	< 900
Potency (%)	90.0 – 110.0
Dissolution after 20 min (%)	> 80
Degradation (%)	0

Results

Risk evaluation

FMEA revealed that, among others, the following factors posed considerable risk to methyldopa tablet quality: magnesium stearate concentration (X1), colloidal silica concentration (X2), SSG concentration (X3), citric acid monohydrate concentration (X4), mixing speed (X5), duration of mixing before adding magnesium stearate (X6), duration of lubrication (X7) and compression speed (X8). These factors were investigated in the experimental work.

Preliminary experiment

The preliminary experimental data is displayed in Table 3. Batch B2 showed excellent flow (Hausner ratio ≤ 1.11), while the other batches showed good flow (Hausner ratio of 1.12 – 1.18). The mean tablet weights for all the batches were within the ± 5 % limit (475 – 525 mg). However, some batches such as batches B3 and B4 were within close range of the lower and upper weight limits. Batches B2 and B12 had the greatest number of discoloured tablets, while batches B5 and B8 showed negligible levels of tablet discolouration. Discoloured tablets accounted for over 1 % batch size in seven batches. Moisture content values above 6 % m/m were observed for each of these seven batches, increasing numbers of discoloured tablets being seen with higher moisture content. ANOVA results demonstrated the significant impact of citric acid monohydrate concentration on tablet stability (p = 0.0026, f-ratio = 24.6076).

The striking impact of powder mixing speed (X5) was also

Table 3: The 12-run preliminary Plackett Burman design and results of powder and tablet testing for each batch prepared

Batch code	X1	X2	X3	X4	X5	X6	X7	X8	Hausner ratio	Potency (% ± SD)	Degradation (%)	Hardness (N)	Friability (% m/m)	Weight (*mg* ± SD)	Dissolution at 20 min (%)	Disintegration time (seconds)	Moisture content (% m/m)
B1	2	1	2	0.3	80	6	2	20	1.15	94.1 ± 0.97	0.5	85 ± 0.29	0.56	502 ± 1.90	103	241	6.2
B2	2	0.5	2	0.3	200	3	2	80	1.09	101.3 ± 0.68	2.4	107 ± 1.40	0.18	500 ± 2.60	85	380	6.3
B3	1	0.5	8	0.3	80	6	2	80	1.16	97.3 ± 0.32	2.0	55 ± 4.43	0.81	482 ± 2.78	101	51	7.2
B4	2	0.5	8	2	200	3	2	20	1.18	99.1 ± 1.00	0.2	84 ± 2.10	0.41	517 ± 3.94	99	260	5.4
B5	1	1	2	2	200	6	2	20	1.16	99.7 ± 1.24	0.1	91 ± 3.17	0.42	488 ± 0.97	108	339	5.8
B6	1	1	8	2	80	3	2	80	1.13	107.8 ± 0.07	0.2	49 ± 0.11	0.88	499 ± 1.93	101	79	5.6
B7	2	0.5	2	2	80	6	4	80	1.17	102.3 ± 1.80	1.5	71 ± 0.26	0.89	510 ± 2.10	87	125	6.2
B8	2	1	8	2	200	6	4	80	1.14	100.4 ± 0.04	0.1	94 ± 2.48	0.11	501 ± 0.96	82	371	6.0
B9	1	1	2	0.3	200	3	4	80	1.18	95.8 ± 2.26	1.6	105 ± 1.12	0.20	480 ± 3.81	65	410	6.1
B10	2	1	8	0.3	80	3	4	20	1.14	97.9 ± 0.75	2.0	68 ± 1.26	0.91	498 ± 3.82	105	104	5.7
B11	1	0.5	2	2	80	3	4	20	1.17	103.6 ± 1.95	1.4	90 ± 1.65	0.19	509 ± 1.17	108	311	6.4
B12	1	0.5	8	0.3	200	6	4	20	1.16	100.9 ± 0.89	2.2	94 ± 1.00	0.38	503 ± 1.13	77	349	6.5

X1 = magnesium stearate concentration (% m/m), X2 = colloidal silica concentration (% m/m), X3 = SSG concentration (% m/m), X4 = citric acid monohydrate concentration (% m/m), X5 = powder mixing speed (rpm), X6 = duration of powder mixing before adding magnesium stearate (min), X7 = duration of powder lubrication (min), X8 = compression speed (rpm)

revealed during data analysis, as the factor had noteworthy influence on tablet hardness (p = 0.0021), friability (p = 0.0095), disintegration (p = 0.0006) and dissolution rate (p_{10} = 0.0037). Using all the response values, MANOVA was performed in JMP 15® and the resulting p values interpreted [21]. The p-values for the investigated factors are displayed in Table 4.

Table 4. Levels of significance for each factor in the multivariate model of the preliminary experiment.

Factor	p-value
X1	0.1099
X2	0.0679
X3	0.0414
X4	0.0304
X5	0.0186
X6	0.5060
X7	0.1015
X8	0.0992

SSG concentration (X3), citric acid monohydrate concentration (X4) and mixing speed (X5) were identified as the statistically significant factors ($p < 0.05$) and selected for investigation in the subsequent definitive experiment.

The prediction profiler in JMP 15® was used to identify the best settings for the statistically non-significant factors. These settings were held constant in the subsequent Box Behnken experiment, allowing focus to be placed on the significant excipient and process factors. These settings were identified at a maximum desirability value of 0.8310 and were as follows: 1.0 % m/m magnesium stearate, 1.0 % m/m colloidal silica, 6 minutes of pre-lubrication mixing 2 minutes of powder lubrication and a compression speed of 20 rpm.

Definitive experiment

Good to excellent rheology was achieved for all the definitive batch samples tested. In contrast to the preliminary experiment, three samples of the definitive batches showed excellent flow.

Despite the poor compressibility of the API, all the tablets manufactured were of satisfactory mechanical strength, before and throughout storage. This contrasted with the preliminary batches, where batch B3 had extensive tablet softening as a result of excess moisture. However, neither capping, lamination nor chipping occurred in both experiments. The results of tablet testing are displayed in Table 5. Tablet hardness values ranged between 68 – 87 N, and friability did not exceed 0.5% m/m. The target mean weight of 500 mg was achieved for most tablets sampled from batches D1, D13 and D15. Deviation from the desired tablet weight of 500 mg was generally negligible, evidenced by the narrow standard deviation values. In contrast to the preliminary experiment, distinctly lower levels of degradation and reduced batch-to-batch variation was observed. The highest numbers of discoloured tablets were observed in batches D2 and D11, discoloured tablets accounting for over 1% of the respective batches. On the other hand, percentage discolouration as low as 0.1 % was seen with batches D3, D7 and D14. Likewise, discoloured tablets constituted only 0.05% of batch D9. Using regression analysis, it was learned that the rate of tablet discolouration decreases significantly with increasing concentrations of citric acid monohydrate.

The data from the definitive experiment was subjected to polynomial regression in JMP 15®. Using the prediction profiler tool in the software, the factor settings that yield the optimal methyldopa DC formulation were identified. An image of the profile predicted is displayed as Figure 1. The settings determined were as follows: 50% m/m methyldopa, 42.4% m/m microcrystalline cellulose, 1.0% m/m magnesium stearate, 1.0% m/m colloidal silica, 3.9% m/m SSG, 1.7% m/m citric acid monohydrate, powder mixing at 101 rpm, 6 minutes of pre-lubrication mixing, 2 minutes of lubrication and tablet compression at 20 rpm. A confirmatory batch of methyldopa tablets was prepared at these settings and tested. The batch met all test specifications, achieving hardness values of 76 - 77 N and adsorbing only 5.05% m/m moisture. Optimal tablet weight, potency and dissolution were also attained.

Discusion

It was learned from both experiments that an SSG

Table 5. The 16-run Box Behnken design for the definitive experiment and results of powder and tablet testing for each batch prepared.

Batch code	X3	X4	X5	Hausner ratio	Potency (% ± SD)	Degra-dation (%)	Hard-ness (N)	Friability (%m/m)	Weight (mg ± SD)	Dissolution at 20 min (%)	Disinte-gration time (sec)	Moisture content (%m/m)
D1	6	1.5	120	1.10	100.2 ± 0.45	0.6	77 ± 1.00	0.1	500 ± 0.05	100	61	4.9
D2	6	1.5	80	1.12	100.9 ± 1.88	1.3	68 ± 0.03	0.33	499 ± 3.03	100	63	5.6
D3	4	1.5	100	1.16	101.2 ± 0.02	0.1	76 ± 1.12	0.18	501 ± 2.05	100	128	5.2
D4	4	1.5	100	1.14	101.8 ± 1.50	0.15	78 ± 0.97	0.18	498 ± 2.60	100	134	5.3
D5	4	2	80	1.16	102.7 ± 2.01	0.4	77 ± 0.04	0.36	491 ± 4.72	100	101	5.1
D6	4	1.5	100	1.15	99.5 ± 1.10	0.15	75 ± 2.51	0.21	497 ± 1.92	100	131	5.2
D7	4	1.5	100	1.14	99.6 ± 1.40	0.1	77 ± 1.72	0.19	501 ± 2.38	100	130	5.2
D8	2	1	100	1.16	103.4 ± 1.14	0.45	84 ± 0.80	0.07	503 ± 1.50	100	171	4.6
D9	4	2	120	1.16	99.6 ± 0.04	0.05	73 ± 0.04	0.15	502 ± 2.20	100	95	4.8
D10	4	1	80	1.12	101.0 ± 2.50	0.9	69 ± 1.76	0.4	496 ± 2.71	99	105	4.7
D11	4	1	120	1.14	99.7 ± 0.07	1.05	73 ± 1.08	0.1	502 ± 0.04	100	64	5.5
D12	2	1.5	120	1.18	98.1 ± 2.52	0.45	87 ± 2.81	0.07	494 ± 3.30	92	206	4.7
D13	6	1	100	1.11	100.5 ± 0.98	0.8	74 ± 0.01	0.12	500 ± 0.22	100	69	5.0
D14	2	2	100	1.17	97.8 ± 1.00	0.1	86 ± 3.23	0.09	505 ± 4.17	91	181	4.7
D15	6	2	100	1.11	100.4 ± 0.10	0.25	72 ± 1.26	0.47	500 ± 0.72	100	70	5.4
D16	2	1.5	80	1.17	102.9 ± 0.15	0.1	81 ± 0.60	0.26	504 ± 3.92	93	159	4.9

X3 = SSG concentration (% m/m), X4 = citric acid monohydrate concentration (% m/m), X5 = powder mixing speed (rpm)

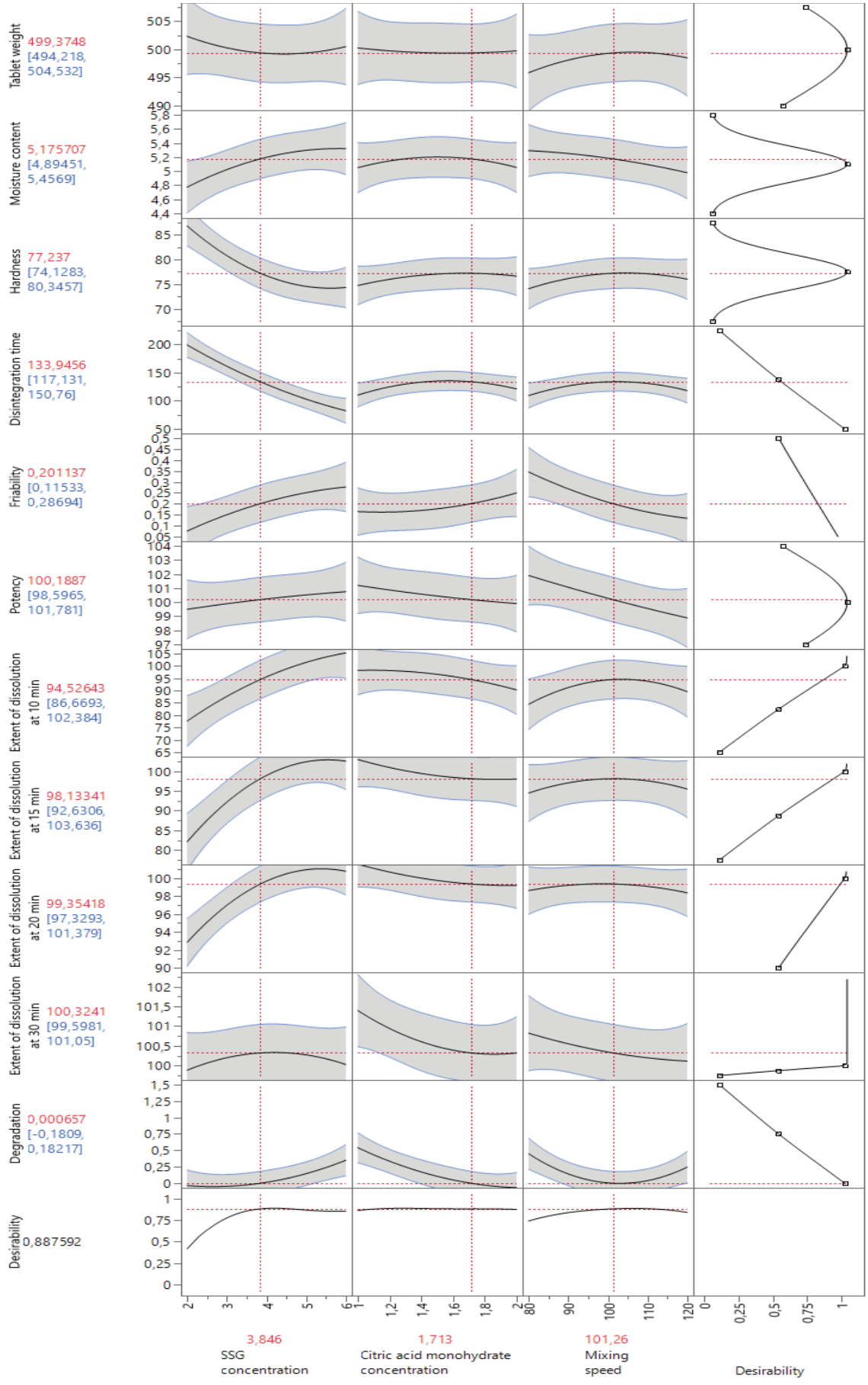

Figure 1. An image of the prediction profiler in JMP indicating selected factor settings that yield methyldopa tablets of optimal quality.

concentration of 2 % m/m is adequate for the disintegration of methyldopa tablets to occur within 900 seconds, thus meeting specifications. This was testament to the high effectiveness of superdisintegrants on the market today, including SSG.

Several batches including but not limited to B5, B8, B12, D1, D3, D9, D11 and D12 were mixed at speeds over 100 rpm ($p = 0.0186$) for over 6 minutes. As shown in the experimental data, these batches generally had potency values closest to 100% and showed relatively less variance than other batches. Cohesive forces exist between particles of pharmaceutical powders, arising from various surface phenomena [22]. Surface liquid films, for example, can exert tensional forces between particles of a hygroscopic powder, giving rise to increased cohesion [23]. Cohesive forces hinder powder flow, creating the need for prolonged mixing at high velocities [22]. It can thus be noted that the higher mixing speeds employed during the manufacture of these batches may have contributed to decreasing the cohesive forces between particles which subsequently improved powder rheology. This stabilised die fill rate and resultant tablet potency, as substantiated by the low standard deviation values recorded for these batches during uniformity of weight testing.

In the preliminary experiment, some batches were prepared using colloidal silica at a concentration of 0.5 % m/m. Several of these batches, including B3, B4, B7 and B11 showed relatively significant variation in tablet weight ($p = 0.0461$) and potency ($p = 0.0401$). These inconsistencies can be attributed to erratic flow that may have occurred as the respective powders were fed into the hopper. On the other hand, low standard deviation values were recorded for batches such as B1, B6 and B8 that were formulated using the higher 1% m/m concentration. Despite the statistical insignificance of the factor, these observations demonstrate the flow enhancing impact of colloidal silica. Colloidal silica exists as loose agglomerates which are broken down into small aggregates during powder blending. These aggregates adsorb to the surfaces of powder particles to form an interactive mix, which increases particle coarseness and overcomes the van der Waal's attraction between cohesive particles [22]. As seen with batches B6 and B10, the flow of such powder blends is improved due to reduced cohesion. The generally improved weight and potency results achieved in the definitive experiment are a testament to the excellent glidant properties of colloidal silica. Colloidal silica also has desiccant properties [8], which could be exploited when handling significantly hygroscopic materials. The moisture gained by a material such as methyldopa can be adsorbed by colloidal silica, consequently protecting it from oxidation and the associated discolouration. In this study, the glidant augmented the antioxidant capabilities of citric acid monohydrate.

Several attributes of tablet quality are dependent on the moisture content of the formulation [12]. During processing and storage, a strict range of equilibrium moisture levels must be maintained to ensure that tablet quality is not compromised. This is specifically true for a hygroscopic formulation that is being directly compressed [12]. The risk to tablet moisture content was substantially mitigated by implementing 30 - 50 % humidity control during the experimental work. As demonstrated by the definitive experimental results, humidity regulation can ensure that the moisture content of resulting tablets will remain within an acceptable range.

It is important that factors affecting the absorption and ensuing bioavailability of a BCS Class III drug such as methyldopa are contemplated before product development. Potency is one of these factors [24]. As seen in this study, oxidative and hydrolytic degradation of an API can lower the potency of the pharmaceutical product. This would manifest in reduced bioavailability, a phenomenon which is detrimental for a BCS Class III drug such as methyldopa. However, it is expected that methyldopa tablets manufactured using 1.7 % m/m citric acid monohydrate and the other optimal settings shown in Figure 1, will be free of degradative activity and thus maintain acceptable potency levels during storage.

Conclusion

Formulation development involving physicochemically challenging drugs can be a daunting task. However, this study has demonstrated the benefits of taking a proactive experimental approach to the task. The QbD paradigm has become the standard framework for pharmaceutical development globally, ensuring quality is instilled in the developed product before attempts to scale up are made.

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Ethical declarations

The authors would like to state that this research did not involve any human or animal subjects, therefore ethical clearance was not required. Furthermore, no financial or any other conflicts of interest were identified in this work.

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Sun Protective Factor and Antioxidant Activity of *Salvia rosmarinus* and *Artocarpus heterophyllus* oil-based Sunscreen

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Abstract

Skin cancer cases have been on an increase in the recent years. This is linked to the rapid climate change and global warming due to the destruction of the ozone layer. The harmful ultraviolet radiation penetrates the skin and causes mutation of skin cells, resulting in skin cancer. Several drugs and preparations have thus come up in the market for combating this phenomenon. However, a number of formulations contain chemicals that are absorbed into the skin and remain in the body for extended durations. Ingredients from these formulations like oxybenzone usually exhibit adverse effects to physiological functions of certain body tissues like breast development, infant birth weight, and sperm cell function. Additionally, when deposited in the environment they contribute to degradation of natural resources, for instance, the killing of coral reefs. This paper reports the development of herbal based sunscreen utilizing oils of *Salvia rosmarinus* (common name – rosemary) leaves and *Artocarpus heterophyllus* (common name – jackfruit) seeds that are readily available and underutilized natural products. The two plants will hereafter be referred to using their common names, rosemary and jackfruit.

Hydro-distillation and the Folch methods were employed for extraction of the oil. The oil was then assayed for the phytochemical profiles before evaluation of the antioxidant activity. Considering jackfruit oil as the active ingredient for sun protection while rosemary oil as the preservative, a sunscreen product was prepared as a semi-solid formulation. Results from the evaluation of the cream revealed that flavonoids, phenols and alkaloids were the main phytochemicals in jackfruit oil while phenols and alkaloids were abundant in rosemary oil. The prepared sunscreen cream exhibited a sun protective factor of 18.8 illustrating significant shielding of the ultraviolet rays. Ferric reducing antioxidant power (FRAP) assay confirmed significant antioxidant activity based on the reducing power high absorbances at 700nm. Jackfruit seed and rosemary leaf oils exhibited sufficient sun protective factor and antioxidant activity thus are promising as ingredients for sun-shield therapeutics.

Keywords: *Antioxidant; Cream; Jackfruit; Rosemary; Sunscreen, Oils.*

Introduction

Skin cancer, hyperpigmentation, photo-aging and erythema are some of the common skin conditions that have been associated with harmful ultraviolet (UV) radiation from the sun [1]. The rise in the number of these conditions has been associated with climate change which contributes to destruction of the ozone layer thus allowing harmful UV rays into the earth's atmosphere. These harmful rays cause damage to plants, animals and humans by causing mutational changes, which contribute to cutaneous disorders in humans [2].

There has been a recent boom in the pharmaceutical market with more dermatological products containing SPF activity being introduced into the market [3]. These formulations include sunscreens, moisturizers with SPF activity, soothing balms with SPF activity, among others. The products being introduced are key in preventing the harmful effects of the UV rays. Unfortunately, a number of these formulations contain ingredients which are harmful to the body and the environment thus somehow contradicting their purpose [4].

A sunscreen that will protect the skin from varying degrees and types of radiation as well as one that is safer compared to the chemicals that are now being used to formulate sunscreens is required. Recently, therefore, there has been an increase in the use of various plant materials to formulate new medications and topical formulations. Herbal sunscreen formulations have been reported to be safer than a chemical based sunscreen and also have fewer side effects [5]. The phytochemical constituents of various plants and herbs have potential to provide the needed protection against the UV radiation from the sun.

This study focused on the development of an herbal-based sunscreen utilizing oils of two plants, rosemary leaves and jackfruit seeds. These are readily available and underutilized natural products which have less detrimental effects on the environment, especially in terms of pollution. In addition, creams with a combination of herbal extracts have previously been shown to have enhanced activity [6]. Very little research has been carried out to assess the sun protection factor (SPF) activity of rosemary and jackfruit oils or their preservative activity on topical preparations. The rosemary polyphenols rosmarinic acid, carnosic acid and carnosol have been postulated to be effective agents for attenuating cell-damaging effects against UV radiation and also ionizing radiation [6].

Preservation of pharmaceutical products is essential. This is because the products and formulations are prone to oxidation as well as forming a suitable living ground for bacteria and fungi. When this occurs, there is loss of the desired pharmacological activity of the formulation meaning that the product can no longer be used for its intended purpose. The use of preservatives when preparing pharmaceutical products ensures a longer half-life of the product [7].

The preservatives currently in use include parabens which are harmful as they mimic hormones in the body. Key research has been carried out on whether rosemary and jackfruit oils can be used as preservatives. It has been found that the phenolic compounds found in jackfruit oil do have antioxidant, antifungal and antimicrobial activity [8]. Moreover, rosemary oil is currently being used as a preservative in foods due to rosemary oil containing phenolic compounds, which have antioxidant properties [9]. The research carried out has presented a novel way of using rosemary and jackfruit oils as preservatives and active ingredients for topical preparations. The radical scavenging components in the oils are known to contribute to the antioxidant activities and may also contribute to the sun protection capabilities.

The study involved acquiring rosemary leaves and jackfruit seeds. These components were used to obtain oils that were evaluated to determine their phytochemical properties and if any of the phytochemicals can contribute to sun protection capabilities or have any antioxidant effects. The extracted oils provided the base for the sunscreen cream formulated and thereafter, the sun protection capabilities and antioxidant activity of the cream were determined.

Methodology

Chemicals

The chemicals and reagents used in this study were sourced from Merck Millipore (Germany) and Sigma-Aldrich (Germany). They included stearic acid, lanolin, liquid paraffin, distilled water, sodium lauryl sulphate (SLS), ferric chloride, chloroform, methanol, ethanol, sodium hydroxide, picric acid, potassium ferricyanide, trichloroacetic acid and sodium phosphate buffer.

Sample collection plants identification and oil extraction

The rosemary leaves were collected from Karamaini, Thika, Kenya: 1.0500°S, 37.0006°E. The samples were collected at 8:00am when the temperature was about 18°C. The jackfruit was obtained from Kenol market, Murang'a County in Kenya: 1.3696° S, 37.2257° E. Specimens of the collected samples were identified and deposited by a botanist and taxonomist based at the USIU-Africa School of Pharmacy and Health Sciences herbarium with the accession voucher specimen numbers as THIANI.T.N/044 and THIANI.T.N/045 for *Salvia rosmarinus* and *Atorcarpus heterophyllus* respectively.

The extraction of rosemary oil from the plant samples was carried out by the method of hydro distillation using Clevenger apparatus as described by Umaru et al. protocol with minimal modifications [10]. Meanwhile, jackfruit oil was extracted by means of Folch lipid extraction process as described in the extraction process of lipids from green microalgae, with minimal modifications [11]. The oil yield was determined as follows:

$$Yield\ \%=100^{*} = \frac{Amount\ of\ oil\ extracted\ (g)}{Amount\ of\ dry\ vegetal\ matter\ (g)}$$

Phytochemical screening

The extracted oils from rosemary leaves and jackfruit seeds were used for phytochemical assessments. Hager's test was used for detections of alkaloids where by 2-3 drops of picric acid were added to 2 ml of each oil extract [12]. $FeCl_3$ test was used for phenols where 2mL of each sample oil was placed in a test tube and 3 drops of 1% $FeCl_3$ added to each sample [12]. Alkali reagent test was used for detection of flavonoids where 3 drops of an aqueous solution of NaOH was added dropwise to test tubes containing 2mL of each sample oil [13].

Design and preparation of herbal based sunscreen

The oils that were extracted were used in formulation of the sunscreen cream as described by Kaur and Saraf with modifications [13]. The simple skin cream was formulated using 10g of stearic acid, 7g of lanolin, 10g of liquid paraffin, 2mL of sodium lauryl sulphate (SLS) and 48mL of distilled water. The stearic acid, lanolin and liquid paraffin were placed in a beaker then put in a water bath of 50^0C. The SLS was dissolved in the distilled water and placed in a water bath of 80^0C. Once the oil phase ingredients had melted and formed a homogenous mixture, they were slowly added to the aqueous phase mixture of SLS and distilled water while continuously stirring. Once a smooth and uniform paste was formed, 1mL of jackfruit oil and 0.3mL of rosemary oil were added to the uniform paste and stirred in until a uniform mixture was made. The 1mL of jackfruit oil was used so as to prepare a 1% formulation of the sunscreen while 0.3mL of rosemary oil was used as previous attempts using 0.5mL and 1mL volumes proved to make the formulation's odor too strong. The prepared sunscreen was set aside to cool then stored in an airtight container and labeled [13]. The summary of the optimized sunscreen formula is presented in Table 1.

Table 1. Optimised sunscreen formula.

Ingredient	Purpose	Percentage (w/v)
Stearic acid	Emulsifier	12.45%
Lanolin	Emollient	9.94%
Liquid paraffin	Emollient and occlusive agent	12.45%
Sodium lauryl sulphate	Surface active agent	2.57%
Water	Vehicle	60.78%
Rosemary oil	Preservative	0.51%
Jackfruit oil	Active ingredient	1.30%

Characterization of the prepared herbal-based sunscreen

Sun protecting factor determination

The in vitro sun protection factor (SPF) screening method was employed as per Kaur and Sarat and Ashal et al., [14, 15].

A sample solution of jackfruit oil was prepared in 95% ethanol while a sample solution of herbal sunscreen was prepared in distilled water. The absorbance of each sample was measured using a UV spectrophotometer. The experimental UV spectra were recorded from 290 nm to 320 nm every 0.5 nm for each sample [16].

Into 100 mL volumetric flask, 1g of each sample was transferred. Each sample was then diluted a hundred-fold by using ethanol for jackfruit oil and distilled water for the herbal sunscreen. Absorbance values of each dilution were determined from 290-320nm at 5nm intervals, with ethanol being used as the blank for the jackfruit oil and distilled water as the blank for the sunscreen. The SPF was then determined using the following formula:

$$SPF\ spectrophotometric = CF * \sum_{290}^{320} EE(\lambda) * I(\lambda) * Abs(\lambda)$$

Where CF = correction factor (10), EE (λ) = erythmogenic effect of radiation with wavelength λ, I (λ) = solar intensity spectrum, Abs (λ) = spectrophotometric absorbance values at wavelength λ. The values of EE multiplied by I are constants used in calculating the SPF at wavelengths between 290-320nm [14]. These values are summarized in Table 1b.

Table 1b. Values of EE multiplied by I.

Wavelength (nm)	EE(λ) x I employed
290	0.0150
295	0.0817
300	0.2874
310	0.1864
315	0.0837
320	0.0180

The samples prepared were scanned between 290 and 320 nm, and the obtained absorbance values were multiplied with the respective EE (λ) values. Then, their summation was taken and multiplied with the correction factor of 10 [14].

Antioxidant capacity determination

The sunscreen was evaluated for antioxidant activity using the FRAP assay [17]. One percent (1%) concentrations of each extract were prepared. A quantity of 2.5mL of each prepared sample was put in a conical flask and 2.5mL of freshly prepared 200mmol/L sodium phosphate buffer (pH 6.6) was added to the samples. A volume of 2.5mL of 1% potassium ferricyanide solution was also added to each mixture in the conical flasks and the resultant mixtures were incubated at 50^0C for 20 minutes. After incubation, 2.5mL of 10% trichloroacetic acid (TCA) was added to each conical flask and centrifuged at 3000xg for 8 minutes. 2mL of the upper layer of each flask was removed and placed in another conical flask where 5mL of distilled water and 1mL of 0.1% ferric chloride were added to each flask. The absorbance of each sample was then measured at 700nm.

Data Analysis

Microsoft Excel was the statistical tool of choice for analysis of the data from the experiments. The data was collected, compiled and presented in the form of tables and charts. The various tests were carried out in triplicates thus the results obtained were as an average of the triplicates. This ensured consistency and preciseness in the results obtained.

Results

Oil extraction from Rosemary leaves and Jackfruit seeds

The weight of seeds obtained from three jackfruits was 850g and upon drying, the weight reduced to 753g. This presented 88.5% dry matter content. The dried rosemary leaves weighed 751g from a gross weight of 974g, which presented 77% dry matter content. The amount of dried plant material used for the extraction was 650.0g and 336.0g for rosemary and jackfruit respectively. The weights used were determined based on the sizes of the apparatus used for extraction. The oil yield from each of the sample is as shown in Table 2.

Table 2. Extraction yields of rosemary and jackfruit oils.

Sample	Dry weight of plant material (g)	Weight of extracted oil (g)	Oil Appearance	% yield
Rosemary Jack fruit	650.0 336.0	7.1 90.8	Light yellow Brown	1.1 27.0

Phytochemical profiles of oil extracts from rosemary leaves and jackfruit seeds

Flavonoids, phenols and alkaloids were the phytochemical groups detected in both rosemary and jackfruit oils as indicated in Table 3.

Table 3. Phytochemical screening results of the rosemary and jackfruit oils.

Sample/test name	Flavonoids	Phenols	Alkaloids
Rosemary oil Jackfruit oil	- +	+ +	+ +

+ = Present - = Absent

Formation of crystalline yellow precipitate using Hager's test indicated presence of alkaloids, the formation of a greenish-black color using $FeCl_3$ indicated the presence of phenols while the appearance of a yellow-orange color in alkaline reagent test indicated the presence of flavonoids. Flavonoids were only present in jackfruit oil since drop-wise addition of sodium hydroxide to the sample oils led to the appearance of an orange color. In the jackfruit sample in $FeCl_3$ test, there was a significant color change of the jackfruit oil from brown to a greenish black while that of rosemary was a change from a slight yellow to a darker yellow-green color indicating presence of phenols in both oils. In Hager's test, yellow crystalline precipitate was more pronounced in jackfruit oil than rosemary oil.

Physicochemical properties and SPF of the herbal – based sunscreen

The prepared sunscreen exhibited organoleptic and physical properties shown in Table 4 and Figure 1. The UV absorbances of the jackfruit oil and the formulated cream at different wave lengths are as shown in Figure 2. The absorbances

were used to determine the spectrophotometric SPF. The normalized EE values for the seven wavelengths used were 0.018, 0.0837, 0.1864, 0.3278, 0.2874, 0.0817 and 0.015 from 290-320 nm.

Table 4. Formulated sunscreen characteristics.

Parameters	Observations
Color	Cream/off white
Odour	Strong and pleasant odour
Spreadability	Good and uniform
pH	6.6
Viscosity	150.32 cps
Homogeneity	Uniform and homogenous
Texture	Smooth
Appearance	Cream like

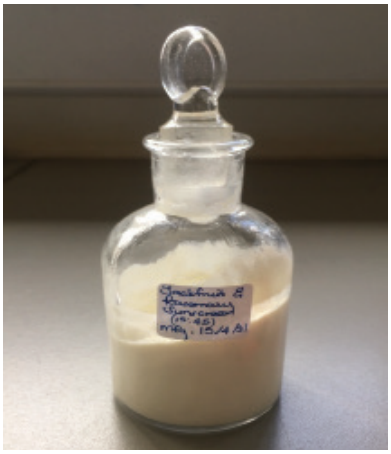

Figure 1. Formulated jackfruit and rosemary sunscreen.

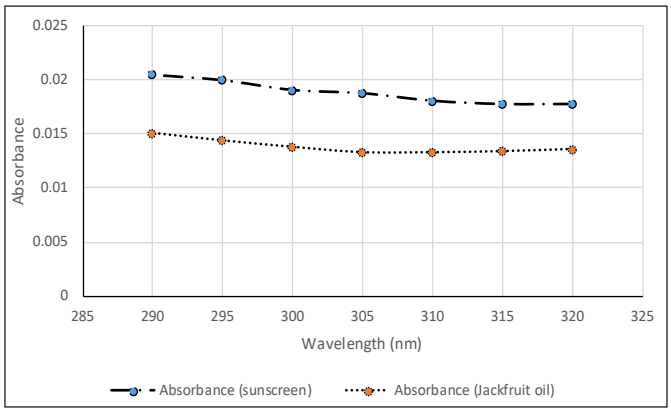

Figure 2. Absorbance of jackfruit oil and formulated sunscreen at wavelength range of 290-320.

The samples that were prepared were scanned between 290 and 320 nm, and the resultant absorbance values recorded. The recorded values were then multiplied with their respective EE (λ) values. Their sum was then taken and multiplied with the correction factor of 10 [14]. The SPF of jackfruit oil was determined to be 13.57 while that of the formulated sunscreen as 18.78.

Antioxidant capacity of the herbal – based sunscreen

The antioxidant activity of the rosemary oil, jackfruit oil and formulated sunscreen was evaluated using the ferric reducing antioxidant power assay. From the results, it was noted that the reducing power was directly proportional to the concentration of the sample with samples at 10000 ug/ml having a higher absorbance as shown in Figure 3. The formulated sunscreen showed better reducing power than individual oils from rosemary leaves and jack fruit seeds as shown in Figure 3 by the higher absorbance exhibited by the sunscreen. The negative control used in the FRAP assay was the extraction solvent which was also used as the spectrophotometer blank, while the positive control used was ascorbic acid which is a powerful antioxidant hence its use in this experiment. The experiment was done in triplicates with the standard deviation showcased in the form of error bars in Figure 3.

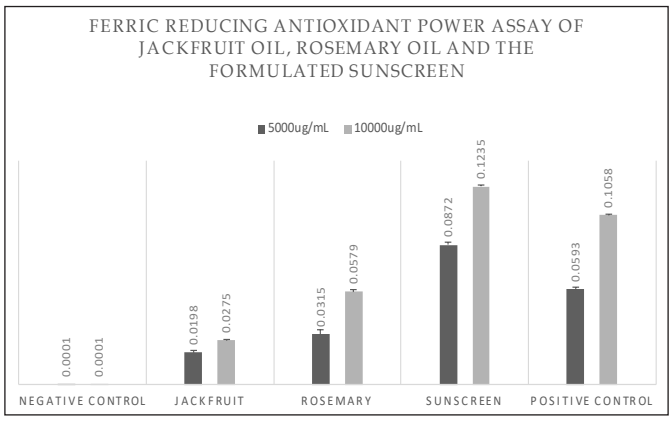

Figure 3. Absorbance of jackfruit oil, rosemary oil, formulated sunscreen, negative and positive controls at different concentrations for the FRAP assay.

Discussion

Different techniques were used to extract oil from dried rosemary leaves and jackfruit seeds, with jack fruit that used solvent extraction attaining a better oil yield. Clevenger technique was used for extraction of oil from rosemary leaves because rosemary oil is a volatile oil which can be extracted solely through hydro-distillation. Essential oil from rosemary aerial parts has been reported to comprise of oil containing a complex mixture of 95.10% of monoterpenes and 4.77% of sesquiterpenes with major compounds identified as 1,8-cineole, camphor, α-pinene, β-pinene, camphene and β-caryophyllene [18]. Clevenger technique was not effective for jackfruit seeds as they do not contain volatile oils but instead contain lipids rich in omega-6 and omega-6 fatty acids which are insoluble in water [19].

Hager's test demonstrated presence of alkaloids in both oils with a yellow crystalline precipitate being more pronounced in jackfruit oil than in rosemary oil. Ferric chloride test indicated higher phenol content in jackfruit oil than rosemary oil while no flavonoids were detected in rosemary leaf oil. The yield of oils as well as their composition may be affected by the method and solvents of choice for the extraction [20]. The use of different solvents results in differences in the type and yield of phytochemicals extracted as the phytochemicals have different polarities that affects their solubility in different solvents. Absence of flavonoids in rosemary oil as well as low content of phenols could be attributed to their higher solubility in ethanol and methanol

and low solubility in water [21]. The jackfruit seed oil on the other hand was extracted using a mixture of methanol and chloroform hence the more intense color changes and positive results [22].

The results indicate that jackfruit seed oil has SPF activity and can be used to formulate a sunscreen with a higher SPF activity, most probably due to the presence of other ingredients such as the rosemary oil which contains phenols. From literature, it is said that phenols play a role in SPF activity. According to Ebrahimzadeh et al. [21], they may be involved in redox-sensitive signaling cascades which help inhibit DNA damage. They may also prevent UV induced oxygen free radical generation and lipid peroxidation which are key in causing photo aging and skin cancer. This indicates that antioxidant activity brought about by phenols is what imparts SPF activity shown by the jackfruit oil. SPF values of different herbal oils have been reported at a range of 1-7 (volatile oils), with rose oil having SPF of 0.24 and 2-8 for non-volatile oils [14].

Inclusion of rosemary oil in this study was for its preservative properties. Rosemary oil, used as food preservative, is known to have high antioxidant activity which contributes to this activity. According to a study carried out on the antioxidant and antimicrobial properties of rosemary [23], it reduces lipid oxidation in oils hence is able to exert its preservative effect on the sunscreen formulated using lipid-based jackfruit oil. The results indicated that indeed rosemary oil has a better antioxidant activity than jackfruit oil despite results showing low content of alkaloids, phenols and no flavonoids.

Reducing power assay methods indicated jackfruit oil, rosemary oil and the prepared cream had antioxidant activity. The assay is based on the reducing power of the compound or sample being tested. A potential antioxidant reduces the ferric ion (Fe^{3+}) to the ferrous ion (Fe^{2+}), which is an important mechanism of phenolic antioxidant action [24]. The sunscreen showed greater reducing power hence antioxidant power than individual oils, this could be as a result of the combination of both rosemary and jackfruit oils which contains large amounts of phenols which contribute to the antioxidant activity. The reducing capacity of a compound may serve as a significant indicator of its potential antioxidant activity [25]. From the results, the sunscreen also shows a higher degree of absorbance as compared to the positive control which was used as seen in Figure 3. This again could be due to the combination of the jackfruit and rosemary oils which in turns suggest a synergistic activity between the two resulting to a more powerful antioxidant as opposed to the activity of the individual oils. The sunscreen formulation also showed better antioxidant power than ascorbic acid as seen in Figure 3 where ascorbic acid was used as the positive control.

Conclusion

A sunscreen cream can be prepared from the oils extracted from jackfruit seeds and rosemary leaves. Jackfruit seed oil has the necessary SPF to act as a suitable active ingredient in sunscreen formulations while rosemary oil is also a suitable preservative in formulations due to it antioxidant activity. The activities of herbal extracts are enhanced when the herbal extracts are combined as in the case of the combined jackfruit and rosemary oils formulated sunscreen having a greater antioxidant activity than that of the individual oils as shown by the higher absorbance of the sunscreen in relation to the absorbances of the individual oils in Figure 3.

There are a few notable limitations in the research:

- Lack of previous research studies on the topic, in particular, on jackfruit oil proved challenging as there was no literature to compare to or use as reference.
- The study proved time consuming in the process of formulating a cream and generating quantities which would yield a good consistency of the cream.
- The methods of extraction used in the study were time consuming and the lipid extraction method requires the use of non-environmentally friendly chemicals like chloroform.

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Conflict of Interest

The authors declare no conflict of interest.

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Cost-effectiveness of alternative strategies to start antiretroviral therapy in Nigeria: A model-based analysis

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Abstract

The aim of this paper was to study the cost and health outcomes measured by Disability-Adjusted Life Years (DALYs) and cost-effectiveness of old and new methods with regard to the initiation of antiretroviral therapy in HIV/AIDS patients in Nigeria.

Decision-analytic tree and Markov model were used to evaluate the clinical and economic consequences of the new WHO recommendations. Two arms of initiation evaluated were the deferred therapy arm (CD4<350clls/ml) and the immediate therapy arm (CD4 > 500cells/ml). Major outcome measures were DALYs averted, percentage DALY averted, costs from health payer's perspective, Incremental cost and Incremental Cost-Effectiveness Ratio (ICER). The main input parameters were hazard rates from the Strategic Timing of Antiretroviral Treatment (START) trial and risk of sexual transmission of HIV, disability weights, adjustment rates, discount rates, life expectancy, and the annual cost of treatment, cost of clinical events, death and transmission. Deterministic and probabilistic sensitivity analyses (Monte Carlo simulations) were then executed. The immediate ART arm caused 0.595 DALY aversion compared with the delayed arm. This is equivalent to a 94% DALY aversion. It also caused a reduced financial burden of -$345.93. The incremental cost-effectiveness ratio was -$581.00 (dominant). This ICER was robust to both probabilistic and deterministic sensitivity analyses.

For the Nigerian healthcare system, starting antiretroviral therapy in HIV/AIDs patients with CD4 count > 500cells/ml was found to be less costly and more effective than the old initiation strategies. The decision to adopt the new strategy by the Nigerian health policy makers is highly justified.

Keywords: *Cost-effectiveness analysis, antiretroviral therapy, HIV/AIDS, Nigeria.*

Introduction

The HIV/AIDS pandemic has significantly influenced the economy, the workforce, individual employees and their families; healthcare costs, labor costs, savings and investments. In developing countries, AIDS is the second leading cause of death among adults [1]. By 2020, HIV is expected to be responsible for approximately 40% of all infectious illness deaths [1]. AIDS, in particular, has a high expensive consequence, especially for the poor. Because AIDS strikes people at their most productive years, it has a negative impact on worker productivity, family income, and national income. The gap between available funding and care demands is widening as the pandemic progresses. The entire cost of care in developed countries has steadily increased owing to an increase in the number of AIDS cases, longer survival times, and increased use of costly therapies [1]. Total HIV/AIDS spending in lower middle-income countries (LMICs) increased from $4.0 billion in 2000 to $19.0 billion in 2016. Most of these potential resources are concentrated in 10 middle-income countries, including Nigeria [2].

Antiretroviral therapy (ART) is the main therapy for the management of HIV, although different methods have been involved in its initiation. Initially, the World Health Organization (WHO) recommended the initiation of therapy just for patients at a highest risk of morbidity and mortality, of which most patients in this category had low CD4 cell levels [3]. In recent years, three major randomized controlled trials: START, TEMPRANO and HIV Prevention Trials Network (HPTN 052), demonstrated the clinical benefit of early initiation of antiretroviral therapy [4]. The outcome of these clinical trials led to the WHO's gradual increase in the initiation thresholds. As of 2015, recommendations were made for therapy to be administered instantly to all patients irrespective of CD4 levels [4]. This includes patients with CD4

cell count >500cells/ml.

Nigeria has the second largest HIV epidemic in the world [5], although its prevalence among adults (1.4 %) [5] is much less than in other sub-Saharan African countries such as South Africa (18.9%) and Zambia (12.4%) [6]. Her estimated population as of 2019 was 200 million [7]. This means that considering the prevalence of 1.4%, 2.8 million people were living with HIV in 2019. Unprotected heterosexual sex accounts for 80% of new HIV infections in Nigeria, with the majority of remaining HIV infections occurring in key affected populations such as sex workers [8].

The WHO guideline of 2015 has been adopted for Nigeria as shown by the Nigeria National Strategic plan and implementation, which has commenced at the facility level [9]. This gives a pointer to the increased resources (human, financial, institutional, material) and policy requirements [9]. More so, when the relatively high prevalence of this disease has to be considered, there is great cause for concern as annual per capita health-care expenditures for Nigeria are not as high as those applicable to high-income and upper-middle-income countries. Besides, there has been the problem of donor stagnation since 2015 with the high-income countries decreasing their foreign aid. Domestic funding for the HIV response now exceeds funds provided by international donors, accounting for 57% of the global total funding in 2015. In the face of donor stagnation, there is increasing emphasis on countries most affected by HIV to finance their responses and find more efficient and cost-effective ways to do so [8]. Given the above facts, it will be relevant to ascertain the affordability of the 2015 ART initiation strategy to the National health systems of Nigeria.

This was achieved using the generic DALY framework [10] provided by the global disease burden report. Previous studies reported that the clinical and economic value of the 2015 guideline was on the basis that ART prevents transmission rather than treating infection [4]. As a result of this, the findings from a recent systematic review/ meta-analysis assessing the risk of sexual transmission of HIV/AIDS with and without ART treatment was included as part of the input parameters.

Objectives

The aim of this paper was to study the cost, health outcomes measured by DALYs and cost-effectiveness of old and new methods with regard to initiation of antiretroviral therapy in HIV/AIDS patients in Nigeria.

Methodology

The Decision Analytic Model and Markov Model [4] were used to evaluate the clinical, economic consequences and cost-effectiveness of initiation of antiretroviral therapy in a model population of HIV/AIDS Nigerian patients (Figure 1). The Markov model was based on a 5-year Markov state-transition cohort with annual cycle lengths and half-cycle corrections. The economic consequences were from the perspective of the national healthcare payers of Nigeria. The simulated populations were HIV positive individuals with CD4 cell counts >500cells/ml, which population was categorized into two groups:

a. Immediate arm: defined by immediate initiation in to ART (Pathway A Figure1). This arm of initiation was made to simulate the 2015 WHO recommendations because none of the previous recommendations included administration to patients with >500cells/ml.

b. Deferred therapy arm: Defined by administration of ART only when the CD4 count falls below 350 cells/ml or the patient develops AIDS symptoms. (Pathway B in Figure 1, B1 Received Therapy, B2 No therapy). This arm represents the old criteria for initiation which entails only those with a CD4 cell count of below 350 cells/ml to be initiated in to therapy.

Initiation to therapy is expected to occur at a rate of 14% per year and reach 70% by the fifth year. [14]

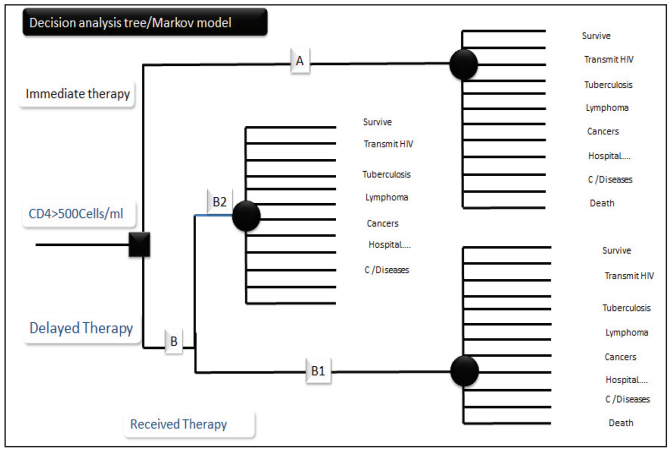

Figure 1. Decision Analytic Tree and Markov model

Outcome measures

The major outcome measures were DALY averted, percentage DALY averted, costs from health payer's perspective, Incremental cost and Incremental cost-effectiveness ratio (ICER).

Disease model

Any patient who enters the model is expected to be followed for 5 years. Each arm of initiation was expected to be controlled or exhibit AIDS-related events such as tuberculosis, Kaposi's sarcoma, malignant lymphoma or NON-AIDS-related events such as cancers, cardiovascular disease or unscheduled hospitalizations. These events were chosen to reflect the occurrence of both AIDS and NON-AIDS-related events that are common to HIV patients across CD4 categories and geographical locations. They could also transmit infections or proceed to death (Figure 1). All events were assumed to be mutually exclusive. The patient in the deferred arm of initiation, in addition to all, could also get initiated to therapy if CD4 cell count reduces to <350cells/ml or they develop AIDS. Model structure and time horizon were carried out in reference to the START trial [4], the strategic timing of antiretroviral therapy (A recent randomized controlled trial with the same randomization of patients to ART therapy).

Model input data

Effectiveness measures

The input data for DALYs computations were hazard rates from the START trial [4] and from a meta-analysis on the risk of sexual transmission of HIV. The disability weights were obtained from the global burden of disease study [11] (Table 1).

Table 1. Model Parameters for Disability-Adjusted Life Years computation

Parameter		
	Hazard rates [12]	
Event	**Immediate Therapy number/ 100 person years**	**Deferred Therapy number/100 person years**
Mortality	0.17 (0.08-0.35)	0.30(0.15 -0.61)
Tuberculosis	0.09(0.03 -0.20)	0.28(0.12 -0.75)
Kaposi sarcoma	0.01(0.00 -0.11)	0.16(0.01 -1.00)
Malignant lymphoma	0.04(0.01 -0.15)	0.14 (0.00 -0.30)
Other cancers	0.13(0.06 -0.29)	0.26(0.12 -0.59)
Cardiovascular Disease	0.17(0.08 -0.36)	0.20(0.09 -0.43)
Other hospitalizations	3.94(3.33 -4.64)	4.31(3.65 -5.04)
New transmission	0`.85(0.28 -2.99)	5.6 (3.26 -9.62)
Disability weights[12]		
HIV	0.053(0.034–0.079)	Each year for lifetime
Tuberculosis	0.399(0.267–0.547)	6months
Kaposi sarcoma	0.2740.(199–0.411)	3months
Malignant lymphoma	0.274(0.199–0.411)	3months
Other cancers	0.274(0.199–0.411)	3months
Cardiovascular Disease	0.082(0.053–0.117)	2months
Other hospitalizations	0.053(0.033–0.081)	2weeks
New transmission Treated	7.2	7.2, incurred one time at time of infection
Discount rates	0.03(0.00 -0.06)	

These rates were converted to transition probabilities using the natural exponential function. These were converted to prevalence for each event in the two major arms. Prevalence were then computed to DALYs for each arm using standard methodology [11] (Figure 2). All events were assumed to be mutually exclusive. The risk of sexual transmission was obtained from a recent systematic review/meta-analysis [13].

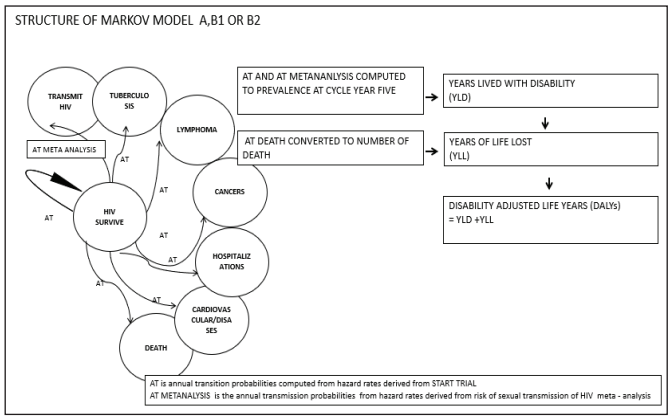

Figure 2. Markov Model and DALY computation

Cost measures

Annual costs for each event were considered. These costs, which were from the perspective of the national healthcare payers of Nigeria, were ART costs [14] which consist of a sum of the cost of ART, diagnostic tests and personnel costs and PRE-ART costs. All costs were obtained from hospital patients [15]. The cost of ART for year 5 was used to simulate the cost of patients who received ART. This was in addition to the cost of other events, while the cost of PRE-ART simulated the cost of patients who did not receive ART and also included all the event costs. The cost of death, new transmissions (discounted) and cost of each clinical event were included [4] (Table 2). Costs of hospitalization were obtained from relevant published literature adjusted to the present value of 2019 dollars. The GDP per capita was obtained from relevant published sources [16] and life expectancy was of a 25 years old HIV positive patient with CD4 greater than 200 cells/ ml for Nigeria [17]. This life expectancy was chosen to align with 25 years which was the average age for the commencement of ART among HIV patients for Nigeria. The outcome measures were then computed based on standard methodology [11].

Table 2. Model Input Parameters for cost computation

Annual cost inputs (Adjusted to 2019$)	
Parameter	**Cost**
ART	$294.00 [18]
Cost of pre-ART care	$10.46 [15]
Annual ART drug and management Cost	$304.46[15]
Cost of tuberculosis	$122.82 [19]
Cost of Kaposi's sarcoma	$ 2620.00 [19]
Cost of malignant lymphoma	$3306 [19]
Cost of other cancers	$1734 [19]
Cost of Cardiovascular Disease CVD	$953.38 [20]
Cost of other hospitalizations	$51.30 [21]
Cost of death	$63.81 [22]
Cost of new HIV infection, (discounted)	6847. 00 [3]
Average local life expectancy, years	38.20 years [23]
GDP per capita, in 2019 US$	$2222.01 [24]

Sensitivity Analysis

Deterministic one-way sensitivity analysis and Monte Carlo simulations

A deterministic one-way sensitivity analysis was carried out by 10%, 20% then 50% increase followed by a decrease in the value of the base-case incremental cost, and then DALY averted to produce a range around the base-case ICER which was reported as tables and tornado diagrams (Figure 3). Probabilistic sensitivity analysis (Monte Carlo simulation) was conducted using 1000 iterations of the base-case incremental cost and DALY averted. The probabilities of the ICERs being dominant and being cost-effective were found.

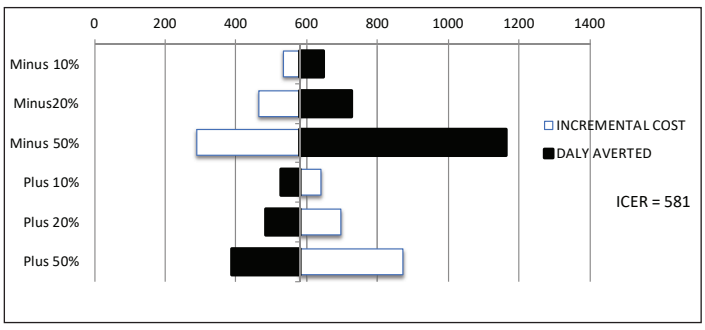

Figure 3. Tornado anlysis for Incremental Cost effectiveness ratio for Nigeria.

Statistical analysis

Statistical analysis was done using the Statistical Product and Service Solutions (SPSS) version 22, and STATA software version 12 (STATA Corp., College Station, TX). The STATA software was used in meta–analysis and production of the forest plots.

Results

As shown on Table 3, the immediate therapy arm resulted in a decline in patients cost by $ 345.93. There is also lower burden of disease in the immediate therapy arm of initiation, which resulted from lower number of clinical events. Dividing the cost by the DALY reduction gave an ICER of -$581.40 which gives an indication of the immediate therapy arm being dominant when compared to the deferred therapy arm.

Table 3. Cost effectiveness Analysis Base Case Results

Parameters	Immediate ART arm	Delayed ART arm	Base Case Results
Cost per patient($)	626.95	972.90	
Incremental cost ($)			-345.95
Effectiveness (DALYs)	0.035	0.63	
DALY averted			0.595
Percentage DALY averted			94%
Incremental cost effectiveness ratio (Cost per DALY Averted $)			-581.43
Probability of ICER dominant<0			99%
Probability of ICER<one GDP/Capita			95.6%

Implementation of immediate therapy of initiation accounted for a 94 % reduction of the burden of disease. This shows immense benefit of this recent innovation. The results of the deterministic one - way sensitivity analysis showed the major driver of ICER variation was 50% reduction in DALY averted (Table 4 and Figure 3).

Table 4. Cost effectiveness Sensitivity Analysis Results for Nigeria

Immediate versus deferred therapy	Incremental cost	DALY averted (effectiveness)	Incremental cost effectiveness (ICER) Cost per DALY saved
	-345.95	0.595	-581.43
Decrease in Incremental cost			
A[1]	-311.355	0.595	-523.29
B[2]	-276.76	0.595	-465.14
C[3]	-172.975	0.595	-290.71
Increase in Incremental cost			
A[1]	-380.53	0.595	-639.55
B[2]	-415.13	0.595	-697.70
C[3]	-518.9	0.595	-872.10
Decrease in DALY averted			
A[1]	-345.95	0.5355	-646.03
B[2]	-345.95	0.476	-726.79
C[3]	-345.95	0.298	-1162.86
Increase in DALY averted			
A[1]	-345.95	0.655	-528.57
B[2]	-345.95	0.714	-484.52
C[3]	-345.95	0.893	-387.62
A -10% B -20% C -50% Changes			

The 1000 iterations in ICER had the probability of the ICER (dominant<0) as 99% and probability of the ICER cost effective (< GDP/capita of Nigeria $2222.01) as 95.6%. The Meta-analysis for the risk of transmission showed a decrease from 5.6PY (3.26 -9.62) untreated groups to 0.85 PY (0.28 -2.99) treated groups (Figures 4 and 5).

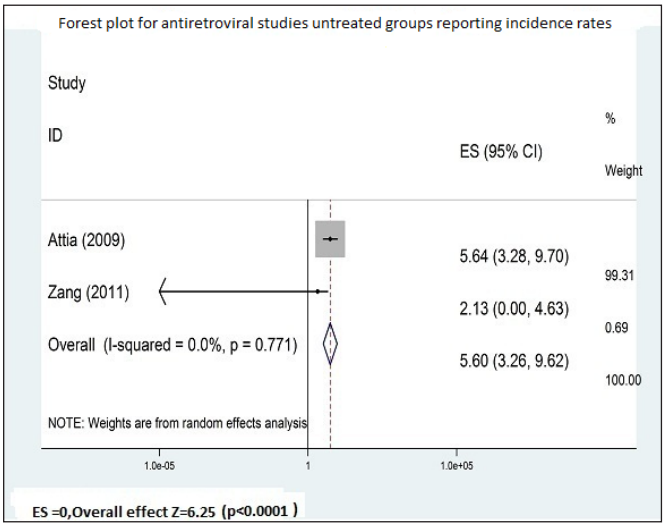

Figure 4. Forest Plot for antiretroviral therapy untreated groups reporting incidence rates.

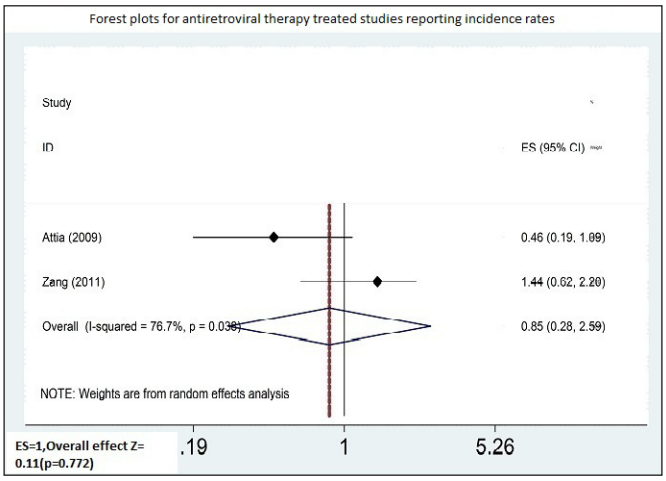

Figure 5. Forest Plot for antiretroviral therapy treated groups reporting incidence rates.

Discussion

The clinical and economic consequences of the new WHO recommendations for starting antiretroviral therapy in Nigeria over five years were evaluated and the findings were as follows: The first major finding was the Meta-analysis that showed 84% reduction in risk of sexual transmission on ART therapy which could translate to positive impact in the community levels as evidenced in a study by Tanser et al [24] although the same authors recommended cluster randomized controlled trials at the population level to verify the findings of the study.

The second major finding is that the new recommendations (methods) dominated the deferred therapy arm by being

more effective and less costly. This is found to be consistent with a recent study that stated that the new recommendations were having more clinical and financial benefits [23]. The Nigeria population of > 200 million people for 2019 [7] , the prevalence of HIV/AIDS is 1.4% [5], the highest HIV prevalence age group is 15-49 years [6] and the number of HIV/AIDS patients in this age group is 102,240,177 [6]. The results of this study (DALY averted 0.595/person) may therefore be interpreted to mean a total of 60,832,905 DALYs will be averted for this age group alone and would amount to an increase in productivity of the affected people and for the country.

The negative incremental cost for the new recommendations as implied for this study does not translate to an immediate negative budget impact for the population at the program or the national level but an increase in productivity is most probable. The ICER obtained was most robust to changes in model parameters as Monte Carlo simulations reflecting 1000 iterations of ICERs and showed very high probabilities of ICERs being dominant and being cost-effective.

All findings herein together with the most recent systematic reviews/meta-analyses of the risk of sexual transmission of HIV demonstrate that, for the Nigeria health system, the 2015 WHO recommendations for initiation of antiretroviral therapy are very cost-effective. Such early initiation of ART can enhance the achievement of the Joint United Nations Program on HIV/AIDS (UNAIDS) 90-90-90 targets for ending the HIV epidemic. However, it is noteworthy that these targets cannot be achieved by implementation of this guideline alone. At the population level, success can be more realistically achieved through widespread testing uptake, linkage with care, uptake of therapy, retention of those in therapy, adherence to medications and a favorable social context for the occurrence of all these [18]and reduction of the time between diagnosis and initiation of therapy [23].

Conclusion

For the Nigerian healthcare system, starting antiretroviral therapy in HIV/AIDs patients with CD4 count > 500cells/ml was found to be less costly and more effective than the old initiation strategies. The decision to adopt the new strategy by the Nigerian health policy makers is highly justified.

Limitations

The model used projected the costs and consequences over five years but could not project for more than 5 years. The model did not put into consideration that the annual transition probabilities and cost for events could vary over the 5 years. Furthermore, in real-world situations, the asymptomatic patients with CD4 counts more than 500cells/ml may not be motivated to give strict adherence to therapy.

Funding source

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Conflict of Interest

The authors declare no conflict of interests.

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Is tablet splitting a potential pitfall in drug therapy? A case study of Amlodipine Tablets

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Abstract

Background: Tablet splitting is a widely employed technique in primary healthcare settings. It involves subdividing tablets into lower-dose fragments for multiple reasons, including optimal dosing where commercial equivalents are unavailable, treatment compliance, and cost savings. However, the practice is beset by multiple concerns and limited data regarding its appropriateness.

Objective: This study assessed the appropriateness of the practice of tablet splitting with reference to the uniformity of weight and drug content in the split fragments of amlodipine tablets.

Methodology: Four brands of amlodipine tablets, in higher- and lower-dose strengths, were purchased from retail pharmacies in Nairobi Central Business District and identified by high-performance liquid chromatography. Higher-dose tablets were subdivided by hand and by tablet cutter. Whole tablets and their split half-tablets were subjected to the test for weight uniformity and assay for amlodipine by ultraviolet-visible light spectrophotometry and evaluated for compendial compliance with the British Pharmacopoeia (B.P.) 2020 specifications.

Results: All whole-tablet samples complied with the B.P. 2020 acceptance criteria for identity, uniformity of weight, and assay for amlodipine. Of the hand-cut half-tablets, 25% and 41.7% complied with the B.P. 2020 acceptance criteria for uniformity of weight and assay, respectively, while only 25% of the device-cut half-tablets complied in each case. Tablet weight and tensile strength influenced the accuracy of tablet splitting. Cost savings of up to 44% were realized upon splitting the higher-dose amlodipine tablets.

Conclusion: From the results obtained in this study, neither dosing accuracy nor ideal patient outcomes are assured by the splitting of amlodipine tablets. This may expose the patient to drug therapy problems such as uncontrolled hypertension from underdosing and adverse effects from overdosing. As such, splitting amlodipine tablets should be avoided as much as possible, and manufacturers are encouraged to formulate appropriate doses for patients.

Key words: *Tablet-splitting, amlodipine, weight and content uniformity, cost-saving.*

Introduction

Tablet splitting (pill splitting) is the practice of prescribing and dispensing drug dosages in half-tablets [1]. It can also be defined as the practice of subdividing higher-dose tablets into lower-dose fragments to achieve optimal dosing or in pursuit of other beneficial motives [2]. Tablet splitting could be viewed as a form of extemporaneous preparation and is also regarded as compounding [3]. It is one of the most widely employed practices in primary healthcare settings, with about 25% of all prescribed medicines in tablet dosage form being cut into two [4]. Tablets are split for multiple reasons, including medical and financial considerations [5]. In terms of both significance and frequency, the chief motivation for tablet splitting is to achieve optimal dosing [6]. About 31% of all tablets dispensed are split to achieve desired dosages hence flexibility in dosing [7]. Tablet splitting is also commonly applied in dose titration. Here, drug therapy begins with low doses and is gradually increased to optimal doses to avert possible adverse drug reactions (ADRs) associated with the abrupt introduction of xenobiotics [8]. In addition, appropriate dose tablets may be unavailable commercially in tapering off drug therapy. A research study in a chronic care facility evinced that about 68% of tablets are split because ready doses are not available commercially [8].

In the recent past, consumer prices of prescription medicines have increased by an estimated 60%, presenting significant access barriers to quality and effective medicines. Patients assisted by their physicians and other health care practitioners (HCPs) have adopted several strategies to counter the ever-increasing cost of prescription drugs. These strategies include generic prescribing, selecting more cost-effective drug regimens, and tablet splitting [9]. A research study conducted in 2014 showed that cost savings of up to 45% could be realized through pill splitting despite limitations to certain drugs [6]. This is especially the case when the cost of prescription tablets does not increase proportionately with increasing tablet strength. For instance, one study showed that prescribing lisinopril 20 mg for hypertensive patients on a 10 mg dose will realize cost savings of up to 47% by using half-tablets of lisinopril 20 mg [9]. Worth noting, the likelihood of subdividing highly-priced tablets is twice that of cheaper alternatives [5]. In terms of its economic feasibility, tablet splitting is an efficient way to reduce the cost of access to quality medicines and healthcare.

It is a simple and effective cost-saving tool that can double the number of people receiving healthcare services with the same financial resources [10].

A more practical intention of pill splitting is to assist the patients in complying with their dose regimens [6]. One study estimated that 13% of all prescribed tablets are subdivided to improve adherence to medication [7]. This is especially important in patients experiencing difficulties swallowing large tablets, such as dysphagia, pediatric and geriatric patients. Therefore, subdividing large tablets into smaller fragments is necessary to ease the administration of the medicine [4]. Nevertheless, the practice of tablet splitting is fraught with multiple concerns and challenges. The HCPs and patients alike face difficulty splitting the tablets, and the resultant dissimilar fragments may affect the patients' adherence to and confidence in their therapy [11]. Further, there are concerns regarding the chemical stability of the drug after splitting, loss of crucial pharmacokinetic properties such as controlled-release, excessive powdering leading to loss of the active pharmaceutical ingredient (API), and inaccurate dosing and unequal doses. In geriatric populations, poor eyesight and reduced cognitive abilities may compromise the reliability of tablet splitting [9].

Although tablet splitting is commonly practiced in multiple healthcare settings, it is most prevalent at the community pharmacy. Despite the challenges and concerns expressed by various critiques, there is limited data on the safety and appropriateness of the practice. Concerns such as weight and content variation, and consequently dosing accuracy, expose a gap in available information, creating the need for research in this field to generate informative data to guide the practice of tablet splitting.

Objective

This study sought to evaluate the appropriateness of splitting amlodipine tablets considering weight variation, drug content, and cost benefits.

Methodology

Study design and setting

The study was a laboratory-based quality analysis of amlodipine-containing tablets, in two strengths, currently marketed in Kenya to manage hypertension and angina pectoris. It involved the evaluation of whole amlodipine tablets and their split half-tablets for uniformity of weight, drug content, and cost savings. The study was conducted in the Drug Analysis and Research Unit (DARU) laboratory within the Department of Pharmacy, University of Nairobi.

Materials, reagents, and apparatus

Four brands of amlodipine besylate tablets, each in two strengths, were conveniently sampled from community pharmacies within Nairobi Central Business District. The tablets comprised the 5 mg and 10 mg strengths of Amlong® (Micro Labs Ltd, Mumbai, India), Amlodenk® (Denk Pharma GmbH & Co. KG, Munich, Germany) and Amlosun® (Sun Pharma Laboratories Ltd, Gujarat, India), and 5 mg and 2.5 mg strengths of Asomex® (Emcure Pharmaceuticals Ltd, Pune, India). Amlodipine besylate chemical reference substance (United States Pharmacopeial Convention, Rockville, Maryland) was a kind donation by the National Quality Control Laboratory while DARU provided HPLC-grade methanol. Using a high-performance liquid chromatograph (Shimadzu corp., Tokyo, Japan), the tablets were identified by comparing their retention times against that of the amlodipine chemical reference substance (CRS).

Tablets were split using a Safe and Sound 3-in-1 tablet cutter (Paul Murray PLC, Southampton, England), while an electronic analytical weighing balance (Sartorius Research, Göttingen, Germany) was used to measure weights. Whole amlodipine tablets and their split half-tablets were assayed for amlodipine content using a Genesys 10S ultraviolet-visible spectrophotometer (Thermo Fisher Scientific, Waltham, Massachusetts). A Schleuniger–2E/205 tablet hardness tester (Dr. K. Schleuniger & Co., Zurich, Switzerland) was used to determine the hardness of whole tablets, while the diameter and thickness of whole tablets were measured using hand-held vernier calipers.

Test for identity

A 10 mg aliquot of amlodipine CRS (potency = 0.9975) and a sample powder equivalent to 10 mg amlodipine base were weighed in volumetric flasks, dissolved in the diluent, sonicated for 10 min, made to volume, and filtered. The filtrate constituted the sample for injection (10 µL) into the HPLC machine. A Gemini® octadecyl silyl silica gel column (250 mm × 4.0 mm, 5 µm) was used. The mobile phase, which also served as the diluent, constituted of 2.3 g/L ammonium acetate (30%) and HPLC-grade methanol (70%), maintained at 30°C and delivered isocratically at a flow rate of 1 mL/min. Detection was done using a UV-Vis spectrophotometer at 237 nm. Each sample had a chromatographic run of 20 min, which was more than twice the retention time of amlodipine.

Splitting of tablets

For each brand, 20 higher-dose strength tablets were split by hand, and another 20 split using a tablet cutter. By hand, the tablets were firmly held between the thumb and index finger and split along the plane of the score-line. The tablets were carefully placed between the guides, and the cover bearing the blade was brought down fully when using the tablet cutter. The split half-tablets were collected into a suitable container, evaluated for uniformity of weight, and assayed for amlodipine content.

Uniformity of weight

For each brand, 20 tablets and 20 half-tablets were subjected to the test for uniformity of weight as per the British Pharmacopoeia (B.P.) 2020 acceptance criteria [12], as shown in Table 1. The uniformity of weight was computed using Equation 1.

Table 1. British Pharmacopoeia 2020 acceptance criteria for uniformity of weight of tablets.

Average weight of tablet	Deviation (%)	Number of tablets
Less than 80 mg	+/- 10 +/- 20	Maximum 2 None
80 mg to 250 mg	+/- 7.5 +/- 15	Maximum 2 None
More than 250 mg	+/- 5	Maximum 2

$$\pm\%\ Deviation = \frac{Tablet\ weight\text{-}Mean\ weight}{Mean\ weight} X100\% \quad \text{(Equation 1)}$$

Assay for amlodipine

Amlodipine standard solution

A 2.5 mg aliquot of amlodipine CRS was accurately weighed, transferred to a 50 mL volumetric flask, dissolved in sufficient distilled water, sonicated, and made to volume with distilled water. The resultant standard solution was scanned using the UV-Vis spectrophotometer at a dilution of 50 ppm in the 200-400 nm range. The maximum absorption wavelength (λ max) was determined as 239 nm. Seven dilutions of the standard solution were prepared in the range 10 ppm to 70 ppm of amlodipine. The absorbance of each solution was determined at 239 nm, and a calibration curve of absorbance versus concentration of amlodipine plotted.

Amlodipine test solutions

Ten tablets were weighed and ground to a fine powder using a mortar and pestle for each brand of amlodipine. A quantity of powder equivalent to 5 mg of amlodipine was weighed and transferred to a 100 mL volumetric flask, dissolved in sufficient distilled water, sonicated, made to volume, and filtered. The filtrate constituted the sample stock solution. The same procedure was followed for the split half-tablets. A dilution of 12.5 ppm was prepared for each sample stock solution, and absorbance determined at 239 nm. The corresponding concentration was extrapolated from the calibration curve. Triplicate determinations were carried out for all samples.

Tensile strength

The diameter (D) and thickness (T) of the higher-dose strength tablets for each brand were measured using vernier calipers. Ten tablets of the higher-dose strength for each brand were selected at random and placed between the jaws of the tablet hardness tester in a reproducible manner. Pressure was applied, and the force at the breakpoint was recorded. The mean force (P) expressed in Newtons (N) was calculated by averaging the ten measurements. The tensile strength was determined using Equation 2.

$$Tensile\ strength = \frac{2 \times Mean\ force\ (P)}{\pi \times Diameter \times Thickness} \quad \text{(Equation 2)}$$

Data analysis

The collected data was analyzed using Microsoft Office Excel 2016. Data points included weight deviation, deviation from the calculated label claim, the standard curve, relative standard deviation (RSD), and Pearson's coefficients.

Ethical considerations

The sampled amlodipine tablet brands were coded for confidentiality.

Results

Test for identity

The retention times of the peaks due to amlodipine in the chromatograms of all eight sample preparations corresponded to that in the chromatogram of the standard preparation at 7.440 min. The average retention time of the sample preparations was 7.469 min, with a percentage RSD of 0.487.

Uniformity of weight

All whole tablet samples, both higher-dose and lower-dose, were within the B.P. 2020 specifications shown in Table 1, hence complied with the compendial acceptance criteria for the uniformity of dosage units. Among the split half-tablets, both the hand-cut and device-cut, only Brand B10 complied with the limits for uniformity of weight, representing 25% of all tested samples as shown in Tables 2 and 3. Pearson's correlation between the average weight and average deviation yielded Pearson's coefficients of -0.712 and -0.939 for the hand-cut and device-cut fragments, respectively. This could account for the compliance of Brand B10 in both cases, considering that it had the highest average weight among the four brands analyzed.

Table 2. Uniformity of weight of hand-cut half-tablets.

Brand	Average weight	Average deviation	Above lower limit	Above upper limit	Inference
A10 B10 C10 D5	0.0975 0.2044 0.1129 0.050	3.56% 3.53% 7.27% 10.21%	4 1 8 5	0 0 2 2	Does not comply Complies Does not comply Does not comply
	Average	6.14%			

Table 3. Uniformity of weight of device-cut half-tablets

Brand	Average weight	Average deviation	Above lower limit	Above upper limit	Inference
A10 B10 C10 D5	0.0949 0.1951 0.1143 0.0536	7.78% 3.66% 9.92% 12.23%	8 2 12 10	3 0 2 4	Does not comply Complies Does not comply Does not comply
	Average	8.40%			

Assay for amlodipine

Calibration curve

The UV-Vis spectrophotometric method for the assay of amlodipine exhibited linearity in the 5-30 ppm concentration range. A linear regression line with the formula: Absorbance = 0.0312(concentration) + 0.0021, and a R^2 value of 0.9998, was obtained upon plotting the absorbance of the standard

solutions against the concentration of amlodipine as shown in Figure 1. The regression formula obtained was used to compute concentration values for the sample test solutions by substituting absorbance in the equation. A dilution factor of four was taken into consideration, and the label claim was normalized.

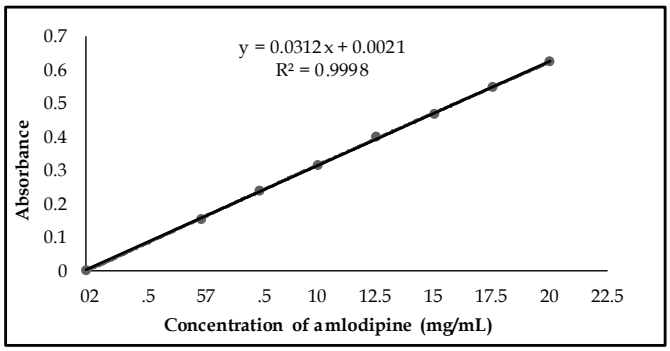

Figure 1. Amlodipine standard calibration curve at 239 nm using distilled water as diluent.

Whole amlodipine tablets

All the whole tablet samples assayed, both higher-dose and lower-dose, complied with the B.P. 2020 specifications for assay of amlodipine. The absorbance measurements were done in triplicate for each sample, and the average absorbance subsequently used in computing content. The error bars in Figure 2 show minimal standard error in the absorbance readings for the higher-dose tablets, implying that reproducibility of measurements by the UV-Vis spectrophotometer could be assumed in all other readings.

Split amlodipine half-tablets

Of the 12 half-tablet amlodipine samples assayed in each case, only five (41.7%) of the hand-cut and three (25%) of the device-cut samples complied with the B.P. 2020 specifications for assay of amlodipine. Pearson's correlation between label claim deviation and average weight deviation of corresponding split fragments yielded Pearson's coefficients of 0.730 and 0.491 for the hand-cut and device-cut half-tablets, respectively.

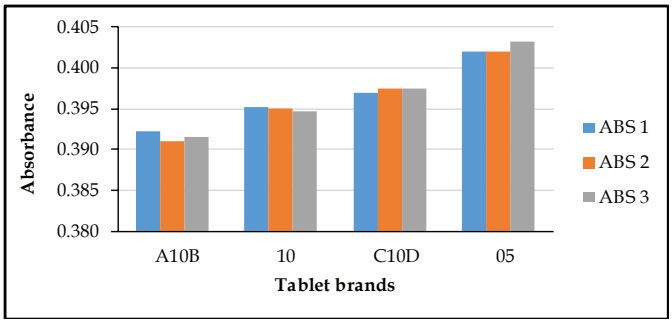

Figure 2. Amlodipine higher-dose tablets absorbance error bars. ABS 1, 2, and 3 represent replicate measurements of absorbance of a 12.5 ppm amlodipine aqueous solution at 239 nm.

Key: ABS 1- Absorbance 1, ABS 2- Absorbance 2, ABS 3- Absorbance 3

Tensile strength

Table 4 shows the tensile strength of whole amlodipine tablets computed from the hardness values using Equation 2. The tensile strengths were correlated with the average deviation of corresponding split fragments to establish any influence the tensile strength of the tablets might have on the weight variation of the split fragments, yielding Pearson's coefficients of 0.479 and 0.695 for the hand-cut and device-cut fragments, respectively.

Table 4. Tensile strength of whole amlodipine tablets

Tablet brand	Hardness (N)	Diameter (m)	Thickness (m)	Tensile strength (mPa)
A10	101.1	0.0074	0.0020	4.35
B10	112	0.0104	0.0037	1.85
C10	68.9	0.0075	0.0024	2.44
D05	105.4	0.0056	0.0024	4.99

Cost savings

Cost savings of between 23% and 44% would be realized by splitting higher-dose amlodipine tablets, as shown in Table 5. Correlation between the unit price of higher-dose tablets and the average deviation of corresponding split half-tablets yielded Pearson's coefficients of 0.996 and 0.869 for the hand-cut and device-cut half-tablets, respectively.

Table 5. Potential cost savings from splitting of amlodipine tablets.

Higher-dose tablet	Unit price	Half-tablet price	Lower-dose tablet	Unit price	Cost-saving
A10	25	12.5	A5	20	38%
B10	27	13.5	B5	24	44%
C10	54	27	C5	35	23%
D5	70	35	D2.5	48	27%

*Prices are in Kenya Shillings.

Discussion

All the whole amlodipine tablets studied complied with the B.P. 2020 acceptance criteria for the uniformity of weight. On the contrary, only one of the four tablet brands split by either hand or tablet cutter complied with the compendial specifications for uniformity of weight. This represents only 25% of the sample size with coincidence of the compliant brand in both cases. The average deviation of device-cut half-tablets was higher (8.40%) than hand-cut fragments (6.14%). Contrary to theoretical expectation, this implies more significant weight loss when splitting the tablets by tablet cutter. Such weight loss could be attributed to crumbling and fragmentation encountered at a much higher degree when the tablet cutter was used. Additionally, tablets with a high degree of tensile strength tend to undergo a high degree of fragmentation when cut using a tablet cutter, contributing to further weight loss as encountered with sample D5, which had the highest tensile strength.

Tablet-specific parameters that affect the ease and accuracy of tablet splitting include size, shape, scoring, and hardness [13]. This study evaluated both average tablet weight and

hardness (tensile strength). Correlation between the average weight of whole tablet samples and the average deviation of the corresponding split half-tablets yielded Pearson's coefficients of -0.712 and -0.939 for the hand-cut and device-cut fragments, respectively. In both instances, the strong negative correlation implies tablet weight is proportional, indirectly, with the average weight deviation of the fragments and directly with dose accuracy. The higher the weight of the whole tablet, the lower the deviation in the weights of the split half-tablets. Therefore, it is no coincidence that Brand B10, whose whole tablet had the largest average weight, was the only sample that produced compliant half-tablets split either by hand or tablet cutter.

Pearson's coefficients between average weight deviation and tensile strength were 0.479 and 0.695 for the hand-cut and device-cut half-tablets, respectively, implying a moderate positive correlation between the two variables and affirming the influence of tensile strength on the ease of tablet splitting [13]. The higher the tensile strength of the tablets, the higher the weight deviation in the split half-tablets hence the lower the dose accuracy. Higher fragmentation, hence greater weight loss, is expected with harder tablets than in tablets with standard tensile strength.

The calibration curve obtained had the formula: Absorbance = 0.0312 (concentration) + 0.0021, and an R2 value of 0.9998 showing a high degree of dependence of the absorbance on the concentration as postulated by Beer-Lambert's law. All the whole tablets analyzed, both higher-dose and lower-dose, met the B.P. 2020 acceptance criteria for the assay of amlodipine. The error bars obtained showed minimal standard errors in the absorbance readings implying high reproducibility of the UV-Vis spectrophotometric technique used in this study.

The half-tablets were assayed in triplicate for each of the four brands, making 12 trials for each method of splitting. Only 41.67% and 25.0% of the half-tablets split by hand and device, respectively, complied with the B.P. 2020 acceptance criteria for the content of amlodipine. Therefore, contrary to theoretical expectation, using a tablet cutter does not necessarily yield better dosing accuracy than splitting tablets by hand. Considering that 25% of all tablets prescribed are split [4], and for several reasons [5], it is worrying that 58.33% and 75% of half-tablets split by hand and device, respectively, may not contain the amount of drug that they ought to.

Correlation between the average weight deviation of the half-tablets and their deviation from the label claim yielded Pearson's coefficients of 0.730 and 0.491 for the hand-cut and the device-cut fragments, respectively. The positive correlation between the weight and content variation of the half-tablets is expected since a loss in mass should translate to a loss in drug content, implying uniform drug distribution within the tablet matrix. It may also imply proper formulation as studies have postulated that elastic binders such as starch exhibit a more uniform distribution of API; hence they are more appropriate for tablets intended to be split [14].

The predicted cost savings ranging between 23% to 44% are compelling incentives for patients and HCPs to split high-dose amlodipine tablets, consistent with existing literature [9]. However, whereas tablet splitting is a simple and effective cost-saving tool that can double the number of people receiving healthcare services with the same financial resources [10], the weight and content variation encountered in this study may offset the cost gains realized. Strong positive correlation between the unit price of the higher-dose tablets and the average weight deviation of the fragments, with coefficients of 0.996 and 0.869 for the hand-cut and device-cut half-tablets, respectively, evidences direct variation between the two. However, this is not of logical relevance to this study. The pricing of a drug is within the purview of the manufacturer. Therefore, it can be extrapolated that the quality of the excipients and the API, the quality of equipment, and personnel qualification, all of which are cost concessions for the manufacturer, directly affect the dose accuracy achieved on splitting a tablet. However, this was not the case when pragmatically tested in this study. The price implications of tablet splitting can be assessed from the perspective that the propensity to subdivide highly-priced tablets is twice that for subdividing cheaper alternatives [5].

Conclusion

For a practice as widely employed as tablet splitting, the findings of this study are quite worrying. Pursuing tablet splitting for dose accuracy is equivalent to speculating on fulfilling health needs. From the findings of this study, neither dosing accuracy nor ideal patient outcomes are assured by the splitting of amlodipine tablets. Gross underdosing or over-dosing could be the case more often than not, posing health risks to the patient with detrimental effects including uncontrolled hypertension, toxicity, and adverse drug reactions. As such, tablet splitting should be avoided as much as possible, and manufacturers should be encouraged to formulate appropriate and demanded dose units for the patients.

Regulatory policies should encourage manufacturers to introduce a broader range of tablet dose units and liquid formulations to avert splitting of tablets as much as possible. Where splitting tablets is completely unavoidable in the healthcare setting, tablet and patient-specific criteria should be met. Only patients with ideal cognitive function and dexterity should be allowed to split tablets. Tablet-specific parameters that should be met include functional score-lines, ideal size, and uniform distribution of the API within the tablet. It is envisaged that this study will provide the impetus for similar case studies on other medicines whose tablet dosage forms are commonly split. This will provide a more detailed understanding of the impact of tablet splitting on drug therapy.

Strengths and limitations of the study

The diverse characteristics of tablets sampled in this study, including tablet shape, size, and tensile strength, are strengths of this study. This widens the scope of tablets within which the results of this study can be extrapolated.

Different designs of tablet cutters exist and may have different influences on the degree of fragmentation encountered; hence the accuracy of weight and content yielded in the final half tablet fragments. This study evaluated one design, the Safe and Sound 3-in-1 tablet cutter (Paul Murray PLC, Southampton, England), possibly excluding other tablet cutting devices developed.

Acknowledgment

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Conflict of interest

The authors declare no conflict of interest.

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The editors reserve the right to reject a manuscript for publication if it does not meet the requirements of the Pharmaceutical Journal of Kenya.

Manuscripts should be submitted to:

The Editor-in-Chief,
Pharmaceutical Journal of Kenya,
P.O. Box 44290 – 00100 GPO,
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