Trop J Nat Prod Res, February 2019; 3(2):31-36 ISSN 2616-0684 (Print)
ISSN 2616-0692 (Electronic)

Tropical Journal of Natural Product Research

Available online at https://www.tjnpr.org

Original Research Article

Formulation of Paediatric Paracetamol Suppositories Using Shea Butter and Dika Fat as Suppository Bases

Olufunke D. Akin-Ajani*, Oluwatoyin A. Odeku, Yusuf Babalola

Department of Pharmaceutics & Industrial Pharmacy, University of Ibadan, Nigeria.

ARTICLE INFO

Article history:
Received 11January 2019
Revised 08February 2019
Accepted 16 February 2019
Published online 01 March 2019

ABSTRACT

The World Health Organization (WHO) has recognized the use of rectal preparations for certain indications in children as an alternative to parenteral. However, challenges of stability in tropical countries have limited its application. Furthermore, adverse effects arise in the use of some excipients in infants and neonates. In this study, paediatric paracetamol suppositories using two plant-derived fats - shea butter and dika fat - and their combination as suppository bases in comparison with cocoa butter were formulated. Shea butter and dika fat were purified and characterised using acid, iodine and saponification values, refractive index and relative density. Paracetamol suppositories were formulated by fusion method and evaluated using appearance, weight uniformity, melting point range, solidification point, crushing strength, disintegration time and dissolution test. Physicochemical properties showed shea butter and dika fat as stable with minimal susceptibility to oxidation with melting point ranges of 32 - 35°C and 37 - 39°C respectively. Base mixtures yielded melting point ranges of 32 - 39°C. The suppositories had crushing strengths ≤ 31 N and disintegration times ranged between 3 - 21 min. Paracetamol release from the single bases ranked cocoa butter >dika fat > shea butter. Paediatric paracetamol suppositories using these plant-derived fats compared well with cocoa butter. Paracetamol suppositories with mixtures of either shea butter or dika fat with cocoa butter had superior release properties compared to cocoa butter alone. Thus, could serve as an alternative to cocoa butter in the formulation of suppositories.

Keywords: Paediatric, Suppositories, Shea butter, Dika fat, Cocoa butter, Paracetamol.

Introduction

The development of formulations, which are appropriate for children, can present significant challenges to the pharmaceutical scientist.[1] Paediatric practice requires a range of dosage forms that are acceptable at different ages and abilities, and a range of strengths or concentrations allowing administration of the correct age-related dose.[2] Children who are seriously ill will require intravenous drug administration to frequent intramuscular injections. In less serious cases, and where long-term administration is required, the oral route will be preferred but other routes such as rectal, transdermal, buccal and nasal can be useful in some circumstances.[1] However, solid dosage forms also present significant administration challenges in children living with disabilities, bedridden or those who are uncooperative.[3] The WHO has recognised the use of rectal preparations for indications of severe malaria, pain, and infection as an alternative to parenteral preparations for severely ill children, those experiencing nausea and vomiting or children who are unable to swallow.[4] The rectal route of drug administration is useful because it avoids hepatic first-pass effect, decreases gastrointestinal side effects and avoids undesirable effects of meals on drug absorption.[5] Excipients usually form the greater part of the majority of medicines. They serve different functions as fillers, binders, disintegrants, preservatives, antioxidants, sweeteners, and colouring agents.[6] The added challenge for paediatric medicines compared to adult medicines is that the excipients may lead to adverse reactions in children that arenot experienced by adults or are not seen to the same extent.[4] Adverse effects arise with excipients such as propylene glycol, ethanol, benzyl alcohol, propyl paraben, and azo-dyes, in paediatric medicines, especially when used to treat infants and neonates, have been reported.[7] The toxicity of excipients to new-borns and infants have been attributed to the immaturity of their organ and body systems.[8] Therefore, it is essential that paediatric medicines be formulated to best suit a child's age, size, physiologic condition, and treatment requirements. Many existing formulations such as atenolol, albuterol and rifampicin are available in dosage forms and strengths, which are not suitable for children. This often leads to off-label and unlicensed use of adult medicines to extemporaneously prepare the formulation based on the age and weight of the child.[9] The WHO seeing this urgent need, started its initiative to make children size medicines as this would greatly reduce childhood morbidity and mortality particularly in developing countries where treatment of diseases of high burden in childhood with low-resource settings are prevalent.[10, 9] Thus, the ideal paediatric formulation should have flexible dosage increments and minimal excipients, safe and easy to administer, and stable with regard to light, humidity, and heat; and less expensive.[9]

Suppository bases play an important role in the release and bioavailability of the medicaments. One of the prerequisites for a suppository base is that it should remain solid at room temperature but soften, melt, or dissolve readily at body temperature so that the drug is fully available soon after insertion into the rectum. Suppository bases are broadly classified into oleaginous bases, aqueous bases and emulsifying bases.[11] Their ease of formulation and non-irritating, non-sensitizing nature gives the oleaginous bases an advantage over other base types. The main limitation of oleaginous bases in tropical

*Corresponding author. E mail: oakinajani@yahoo.com
Tel: +2348023007412

Citation: Akin-Ajani OD, Odeku OA, Babalola Y. Formulation of Paediatric Paracetamol Suppositories Using Shea Butter and Dika Fat as Suppository Bases. Trop J Nat Prod Res. 2019; 3(2):31-36. doi.org/10.26538/tjnpr/v3i2.2

Official Journal of Natural Product Research Group, Faculty of Pharmacy, University of Benin, Benin City, Nigeria.

climates is of the need for refrigeration due to their melting point ranges. Cocoa butter, one of the most widely used oleaginous bases undergoes polymorphism and therefore has some special requirements of temperature control especially during manufacture. Thus, there is the need to search for new suppository bases with adequate stability and drug release profiles that would be suitable for the tropics.

Shea butter is obtained from seeds of the tree, *Butyrospermum parkii* (G. Don.), or *Vitellaria paradoxa*, family Sapotaceae. The plant grows naturally in West African Savannah and thrives in Southwest Nigeria.[12] In Nigeria, shea butter is primarily used as cooking oil and illuminant and is exported to other countries where it is used in the manufacture of cosmetics, soaps, lubricants, paints and as a substitute for cocoa butter in the production of confectionaries.[13] It is innocuous on human skin,[14] and its water-sorption and rheological properties make it very suitable for ointment preparation.[15] Shea butter has been studied for use in the formulation of pharmaceutical products: as an ointment base for salicylic acid and benzoic acid;[16] and chlortetracycline hydrochloride,[17] and as a component of a suppository base in paracetamol formulation.[18] On the other hand, dika fat – *Irvingia gabonensis*, family Irvingiaceae, commonly known as 'African mango' or 'bush mango' is largely distributed in Africa.[19] The plant is a wild forest tree with dark green foliage, yellow fragrant flowers, spherical fruit with smooth yellow fibrous mesocarp and hard endocarp when ripe.[20, 21] The seed from the plant has been of interest in the food, beverages, cosmetics, medical and pharmaceutical industries.[22-26] The seed of the plant contains lipids and polymeric constituents.[27] The mucilage from the kernel has been used as binding agent in tablet formulation,[26] and as emulsifying and suspending agents.[28] While the lipid has been employed as a lubricant in tableting,[29] sustained release agent,[30] microencapsulating agent,[31] suppository base,[32, 33] and component for film coating operation.[33]

Although both shea butter and dika fat have been used in various pharmaceutical formulations, none of these studies has shown their application as suppository base for paediatric paracetamol suppositories. In the present study, paediatric paracetamol suppositories have been formulated using shea butter and dika fat alone and their combinations as suppository bases in comparison with cocoa butter. Paracetamol the most widely used non-opioid analgesic and antipyretic drug for the treatment of acute or chronic pain with mild to moderate intensity has been used as the model drug.[34]

Materials and Methods

Materials

Paracetamol (a gift from Fidson Pharmaceuticals, Lagos, Nigeria), suppository bases which include cocoa butter (purchased from Showcrown Laboratory Technologists, Ibadan, Nigeria), shea butter, (obtained from a local market in Ibadan, Nigeria) and *Irvingiagabonensis*, (dika nut, obtained from a local market in Ibadan, Nigeria). All other reagents were of analytical grade.

Methods

Extraction and Purification of Base

Shea butter and dika fat were purified using the method of Mital and Dove.[12] This involved the removal of extraneous matter by hot filtration at 60ºC using a silk cloth filter medium placed over a large beaker. The filtrate was allowed to set at the room temperature (28 ± 2ºC) for seven days prior to using the sample for the experiments.

Physicochemical properties of the bases

The acid, saponification and iodine values of the bases were all determined using established procedures.[35]

Relative density

A pycnometer was weighed (W_1 g); filled with the suppository base at laboratory temperature of 26°C and adjusted to the fiducial mark with filter paper and then weighed (W_2 g). The weight of the base in the pycnometer was calculated as ($W_2 - W_1$) g. The base was then removed, and the pycnometer washed and dried and then filled with CO_2 – free water also at the laboratory temperature and adjusted to level and weighed (W_3 g), the weight of water in the pycnometer ($W_3 - W_1$) g.

The relative density of each was the calculated as:

$$RD = \frac{\text{Weight of the oil}}{\text{Weight of water}} = \frac{W2 - W1}{W3 - W1} \qquad (1)$$

Refractive Index

The refractive index of the melted base was measured at 30°C using an Abbe refractometer (Mettler Toledo) with reference to the wavelength of D-line of sodium (λ = 589.3 nm).

Solidification point

The base was melted in a test tube at 45°C and a thermometer was dipped inside the cooling mass and rotated mechanically. The temperature at which the mass first began to adhere to the thermometer was recorded as the solidification point.[36]

Melting point

The melting point range was determined with a Stuart melting point apparatus (model no. 8156/1, England) using the ascending melting point method of Coben and Lieberman.[36] The suppository bases was melted in a water bath and one end of a straight capillary tube was dipped into the molten mass. The molten mass was allowed to rise 5 cm in the capillary tube and stored for 24 h in the refrigerator. The capillary tube was attached to a thermometer graduated in 0.50° increments and lowered into a water bath heated so that the temperature rose at the rate of 1°C per minute. The temperature at which the suppository base began to melt and the temperature when it clarified were recorded as the range for the melting point range.

Preparation of suppository

The displacement value of the suppository bases was determined and suppositories (1 g) containing 200 mg of paracetamol (paediatric dose) were prepared by the fusion method.[37] The mass was then poured into pre-calibrated stainless steel moulds, allowed to cool and the suppositories removed. Suppositories were weighed and kept at room temperature (28 ± 2ºC) for 24 h after removal from the mould to allow for uniform solidification and crystal transformation. The suppositories were wrapped in an aluminium foil and stored in a desiccator in a refrigerator until needed.

Evaluation of Physicochemical properties of formulated suppositories

Test for Appearance

The suppositories were evaluated for appearance according to the British Pharmacopeia method by cutting longitudinally and examining with the eye the internal and external surface of the suppository.[38]

Weight Uniformity

The suppositories were evaluated for uniformity of weight using twenty (20) suppositories according to official specification [38] and the average weight and percent deviation was determined.

Solidification and Melting point

The solidification and melting points of the suppositories were carried out using the method of Coben and Lieberman.[36]

Determination of crushing strength

The hardness of the suppository was determined using the Monsanto Hardness Tester (Monsanto, Cambridge, UK).[37] Six suppositories from each batch selected at random were used for the determination. The force required to break or deform the suppository was recorded.

Disintegration Time

The disintegration time for suppositories in water was determined as the time taken for the suppository to melt or disperse when immersed in a water bath maintained at 37 ± 0.5°C.[38]

In-vitro drug release

In-vitro release test was carried out using the USP XX basket method.[38] The suppository was placed in the basket and lowered into a flask containing 500 mL of phosphate buffer solution, pH 7.2, maintained at 37 ± 0.5ºC. The basket was rotated at a constant speed of 100 rpm. Samples (5 mL) were withdrawn at specified time intervals and the same volume of fresh buffer solution maintained at the experimental temperature was used to replace the withdrawn

samples. The amount of paracetamol was analysed spectrophotometrically at 243 nm. The mean of four determinations was used to calculate drug release from each of the formulation.

Data analysis
All procedures were carried out in triplicate except where stated. Statistical analysis was performed using Analysis of Variance (ANOVA) on a computer software GraphPad Prism® 5 (GraphPad Software Inc., San Diego, USA) at 95% confidence interval, p values ≤ 0.05 (that is 5%) were considered significant.

Results and Discussion

Physicochemical parameters of the suppository bases
The physicochemical properties of the bases presented in Table 1 indicated that shea butter had the highest acid and iodine values and refractive index while cocoa butter had the lowest values. Acid value is dependent on the amount of free fatty acids present or on the degree of hydrolysis of the fat/oil.[39]A high acid value shows unsuitability for use in cooking although it may find usefulness in the production of paints, liquid soap, and shampoos; while a low value indicates stability over a long period of time and protection against rancidity and peroxidation.[40,41] The acid values of all the bases were higher than that stipulated for edible oils, 4 mg/g,[39] thus showing their suitability for industrial purposes rather than cooking oil. Shea butter and dika fat both had significantly ($p < 0.05$) higher acid values than cocoa butter. Thus, indicating that cocoa butter would have a lower susceptibility to rancidity. Iodine value measures the degree of unsaturation in a fat or vegetable oil and determines its stability to oxidation.[42] The iodine values of the bases show that they have a low degree of unsaturation since their values were below 100 gI_2/100 g.[41] Thus indicating that they would be stable with minimal susceptibility to oxidation.
The ranking for saponification value followed the order of cocoa butter > shea butter > dika fat, while melting and solidification points were of the order dika fat > cocoa butter > shea butter. Shea butter and dika fat had similar relative densities of 0.92. Saponification value is inversely proportional to the mean molecular weight of the fatty acid in the glyceride present in the lipid.[39] Though the saponification value of cocoa butter was significantly ($p < 0.05$) higher than the test bases, they all had values that were lower than that indicated for saturated fats, 195–205 mg KOH/g.[42] Thus suggesting that they all contain a high proportion of fatty acids of high molecular weight.
The ranking of the melting point range and solidification point was dika fat > cocoa butter > shea butter. Melting point range of the bases showed that they all would readily melt/dissolve at rectal temperature particularly in conditions of pyrexia when rectal temperature is likely to exceed 37°C.
Refractive index as well as relative density are used to assess purity and check adulteration of fats/oil, making them useful parameters for the acceptance of fats/oils as raw material.[40] The bases had refractive indices less than 1.48 further suggesting that they are non-drying in nature.[43] They all had relative densities < 1, which implies that they are less dense than water. The physicochemical parameters of the suppository bases suggest the suitability of all three bases for the production of the paediatric paracetamol suppositories.

Physical, mechanical and drug release properties of formulated suppositories
The physical, mechanical and disintegration properties of the un-medicated suppositories are presented in Table 2 while the properties of the medicated suppositories are presented in Table 3. The suppositories formulated using the bases singly and in combination as well as the paracetamol suppositories passed, the weight uniformity test i.e. they met the BP specification for weight uniformity, which is a permissible percentage deviation of 5 % and had a good appearance.[38] However, paracetamol suppositories made of shea butter were sticky to touch.
The suppositories had melting points below that of body temperature except un-medicated suppositories containing dika fat and paracetamol suppositories made of dika fat. The primary requirement of a suppository base is that it remains solid at room temperature, but will soften, melt or dissolve readily at body temperature in order to liberate the drug incorporated into the formulation, soon after insertion into the rectum.[44] Melting point range therefore, indicates the temperature limit below which a suppository remains solid. For a fatty base, it is also an indication of the temperature at which the base could release its therapeutic ingredient. A melting point range below 37ºC is thus desirable for such suppositories.[45] The formulated paracetamol suppositories had higher melting point ranges than the suppositories without paracetamol. Paracetamol suppositories made of shea butter and the mix of shea butter and cocoa butter had melting point ranges clearly below body temperature while the melting range for the other paracetamol suppositories started at temperatures below body temperature. This suggests that these suppositories would melt/ dissolve and release their active component.
The crushing strength of the un-medicated suppositories made from the single bases were of the rank order of dika fat > cocoa butter >> shea butter. Suppositories made from the mixture of bases had significantly ($p < 0.05$) lower crushing strengths than suppositories made of dika fat or cocoa butter alone but higher than those made of shea butter alone.

Table 1: Physicochemical Parameters for Suppository Bases (± SD).

Bases	Acid value (mg KOH/g oil)	Iodine value (g iodine)	Saponification value (mg KOH/g oil)	Refractive index at 30°C	Relative density
Shea butter	21.07(0.03)	30.32(0.08)	147.26(0.06)	1.4669	0.92
Dika fat	15.01(0.71)	27.49(0.01)	141.65(0.18)	1.4526	0.92
Cocoa butter	5.75(0.28)	24.32(1.49)	152.87(0.03)	1.4600	0.90

Table 2: Physical and Mechanical Properties; and Disintegration Time of Un-medicated Suppositories (±SD).

Base	Weight (g)	Appearance	Melting point range (°C)	Solidification point (°C)	Crushing strength (N)	Disintegration time (min)
Shea butter	0.994(0.024)	Good	32-35	26.9	4.93(0.611)	1.035(0.021)
Dika fat	1.035(0.012)	Good	37-39	33.7	30.1(2.09)	2.16(0.084)
Cocoa butter	1.008(0.020)	Good	33-35	27.3	27.8(4.45)	1.46(0.487)
Shea butter: cocoa butter (1:1)	1.071(0.027)	Good	32-35.5	32.0	8.9(1.133)	1.21(0.318)
dika fat: cocoa butter (1:1)	1.074(0.019)	Good	33-39	32.0	8.5(0.566)	1.12(0.021)
Shea butter: dika fat (1:1)	1.088(0.032)	Good	33-39	31.0	7.05(0.353)	1.05(0.035)

ISSN 2616-0684 (Print)
ISSN 2616-0692 (Electronic)

Table 3: Physical, Mechanical and Drug Release Properties of medicated Suppositories (±SD).

Base	Weight (g)	Appearance	Feel	Melting point range (ºC)	Solidification point (°C)	Crushing strength (N)	Disintegration time (min)	T_{50} (min)	T_{80} (min)
Shea butter	1.104(0.043)	Good	Sticky to touch	34-36	28.0	1.30(0.383)	2.51(0.024)	32	-
Dika fat	1.078(0.072)	Good	-	37.5-45	29.0	21.5(1.277)	*	25	35
Cocoa butter	1.056(0.012)	Good	-	36-40	29.1	12.10(3.464)	5.16(0.107)	24	34
Shea butter/cocoa butter (1:1)	1.076(0.104)	Good	-	32-35	32.0	2.5(0.141)	7.19(0.126)	23	32
Dika fat/cocoa butter (1:1)	1.127(0.014)	Good	-	37-42	32.0	2.9(0.141)	8.38(0.031)	20	28
Shea butter/dika fat (1:1)	1.132(0.012)	Good	-	37.5-44	31.0	3.8(0.283)	20.92(1.317)	27	39

* Did not disintegrate

Un-medicated suppositories made of shea butter had the least crushing strength. However, the crushing strength of suppositories made of shea butter in mixture with either cocoa butter or dika fat was higher. This was probably due to the greater crushing strengths of suppositories made of dika fat and cocoa butter alone. Conversely, suppositories made from the mixture of dika fat and cocoa butter had significantly lower ($p < 0.05$) crushing strength than those made of dika fat or cocoa butter alone. This suggests interaction amongst the bases as it occurs in co-processing of excipients where the combination of two or more materials using physical methods modify their properties without any chemical alteration.[46] Incorporation of paracetamol into the suppositories lead to a decrease in the crushing strength of all the suppositories. Paracetamol suppositories containing shea butter particularly had low crushing strengths while that containing dika fat alone had higher crushing strengths. The reduction in crushing strength of suppositories made of bases either singly or mixed as a result of incorporation of paracetamol relative to the un-medicated formulations, may be due to the inclusion of the drug (paracetamol) as some drugs have been reported to repress the crushing strength of suppository bases.[44] This effect was more pronounced with shea butter, as the suppositories formed though firm was sticky to touch.

Un-medicated suppositories with mixed bases had lower disintegration time than suppositories containing single bases except for the dika fat: cocoa butter mix. The presence of API in the suppositories prolonged disintegration time with those containing mixed bases having significantly ($p < 0.05$) higher disintegration time than that of un-medicated suppositories made with base mixtures. The un-medicated suppositories had disintegration times less than 3 minutes while the paracetamol suppositories had disintegration times less than 9 minutes except paracetamol suppositories made of shea butter: dika fat, which had a disintegration time of about 21 minutes and paracetamol suppositories made of dika fat, which did not disperse or melt.

Paracetamol suppositories made with dika fat base was probably non-disintegrating due to the melting point of dika fat. The generally short disintegration time of the paracetamol suppositories suggests that most of the suppositories will release their medicaments fast. There appeared to be some correlation between the melting point range, crushing strength and the disintegration times of the suppositories with the exception of paracetamol suppositories made of shea butter: dika fat and that made of dika fat.

The plots of the amount of paracetamol (%) released versus time are presented in Figure 1 while the time taken to release 50% and 80% (t_{50} and t_{80}) of paracetamol from the suppositories is presented in Table 3. Paracetamol release from the suppositories containing the bases alone was of the order cocoa butter > dika fat > shea butter. Paediatric paracetamol suppositories made of shea butter gave the lowest release of paracetamol while that made of cocoa butter gave the highest release. Conversely, paracetamol release from the paediatric paracetamol suppositories made of mixed bases was of the order dika fat: cocoa butter > shea butter: cocoa butter> shea butter: dika fat. Dika fat: cocoa butter had the highest release while shea butter: dika fat gave the lowest release. Drug release from suppositories can be divided into five stages, namely: melting; spreading of the melted mass; sedimentation of the drug particles; movement of the solid particles through the oil/water interface; and dissolution of the drug particles in the rectal aqueous fluid.[47] Although suppositories made from shea butter alone gave the poorest release of paracetamol, shea butter in combination with cocoa butter gave a good release profile that also correlated with its disintegration time. The fastest release of paracetamol was through the mix of dika fat: cocoa butter with t_{50} and t_{80} of 20 and 28 minutes respectively. Thus, showing that paracetamol partitioned through the oil/water interface fastest in the dika fat: cocoa butter mix, which was closely followed by the shea butter: cocoa butter mix with t_{50} and t_{80} of 23 and 32 minutes respectively. Both base mixtures showed superior release properties to the suppositories made from cocoa butter alone thus supporting previous studies that stated that a new suppository base could evolve through the proper handling of these fats.[32, 33] More studies will be required to determine the optimum ratio of these bases mixtures.

ISSN 2616-0684 (Print)
ISSN 2616-0692 (Electronic)

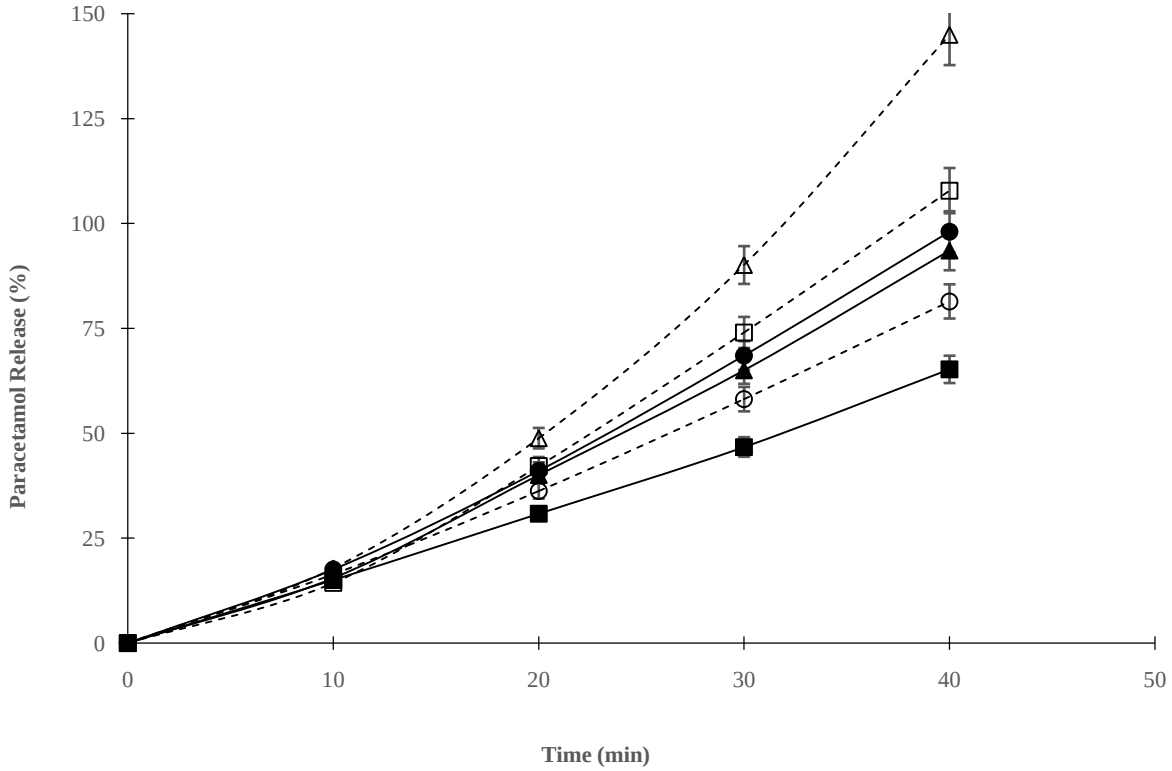

Figure 1:*In-Vitro* Release of Paracetamol from Suppository Formulations (■shea butter, ▲ dika fat, ● cocoa butter, ---- mixed bases, □ shea butter: cocoa butter, Δdika fat: cocoa butter, ○ shea butter: dika fat).

Conclusion

Shear butter and dika fat are stable fats with minimal susceptibility to oxidation making them well suited for the formulation of suppositories. Mixtures of these bases and with cocoa butter yielded melting point ranges that were generally lower than body temperature. The suppositories formed were firm but not hard with disintegration times that were generally less than 9 minutes. Paediatric paracetamol suppositories made from base mixtures of dika fat: cocoa butter and shea butter: cocoa butter had superior release properties compared to suppositories made from cocoa butter alone. Thus, the formulation of suppositories using shear butter and dika fat compared well with cocoa butter and their mixture could substitute cocoa butter in the formulation of suppositories.

Conflict of interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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