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Quantitative analysis of the effects of drug-base ratio on the physical and release properties of paracetamol suppositories

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Abstract
Paracetamol is available in various strengths as rectal suppositories, hence the need to evaluate the effects of drug-base ratio as a formulation variable on the physical and release properties of paracetamol suppositories formulated with a lipophilic base. Suppositories, each containing 60 mg to 500 mg of paracetamol in cocoa butter were prepared by fusion method using 1 g and 2 g capacity moulds. Physical and dissolution properties of the suppositories were determined by established methods. Quantitative effects of the drug-base ratio on physical and release properties of the suppositories were analysed using 2^2 factorial experimental designs. The independent and interaction coefficients of the two variables deviated from zero, indicating significant effects on the physical and release properties of the suppositories. While First-order release kinetics was observed for all the formulations, there was a significant change in the release rate constants with variation in the drug-base ratio. High proportion of base to drug ratio in the suppositories suppressed the release of the drug, suggesting the need to optimize the drug-base ratio when formulating a poor water-soluble drug like paracetamol in fatty bases.

Keywords: Paracetamol suppositories, drug-base ratio, quantitative analysis, physical and release properties

1. Introduction
Paracetamol, an analgesic and antipyretic drug is formulated in the form of suppositories for rectal administration to produce systemic effect at optimum concentration by avoiding the hepatic first-pass effect [1]. Rectal administration of paracetamol has the added advantage of being a substitute where the oral route is not feasible[2], especially in conditions such as nausea, vomiting, convulsion, gastric irritation and difficulty in swallowing [1,2]. Rectal dosage forms of paracetamol for paediatric and geriatric patients are available in doses ranging from 60 mg to 500 mg per suppository [3].

The most commonly used additives in suppository formulations are the bases, which ranged from natural fats like cocoa butter, semi-synthetic fats like Witepsol® to water soluble polyethylene glycol [4-6]. These bases have been reported to influence the release of drugs from the formulations [7-9]. Unlike the tablet formulation of the drug, the base constitutes a greater proportion of the suppository formulation, which could be critical to the release of drugs like paracetamol which have affinity for lipophilic base and limited aqueous solubility [10-12]. While there are enormous research works on the effect of base type and other additives on the physicochemical properties of paracetamol suppositories [2-13] and their bioavailability [10], the effects of the drug-base ratio on these properties have remained largely uninvestigated. The same drug dose embedded in different quantities of suppository base has been reported to produce different therapeutic responses [14]. Therefore, the ratio of the drug to the base in the formulation may become an essential variable that needs to be investigated in situations where the drug has high affinity for the base, and with limited solubility in the dissolution medium or constitute a minute percentage of the physical weight of the formulation.

This study aims at formulating different strengths of paracetamol suppositories using cocoa butter as the base with a view to evaluating quantitatively, the effects of the drug-base ratio on their physical and release properties. The quantitative assessment of formulation variables using factorial experimental design has been used by various researchers in determining the effects and extent of interaction of variables on physicochemical properties of the formulations [7, 8, 15].

2. Experimental

2.1 Materials

Cocoa butter (Starmark Cocoa Processing Company Limited, Ondo, Nigeria), paracetamol powder (gift from Fidson Healthcare Ltd. Sango-Otta, Ogun State, Nigeria), glycerol, sodium hydroxide pellets, potassium dihydrogen orthophosphate (BDH, Poole, England).

2.2 Methods

2.2.1 Preparation of Paracetamol Suppositories

The compositions of each suppository formulation are indicated in Table 1. The quantities of cocoa butter required in a batch of each formula were determined by the drug's displacement value [16] using 20%w/w paracetamol. The suppositories were prepared by fusion method using both 1 g and 2 g metal moulds with six cavities each [17]. Suppositories prepared using 1 g mould were coded A1, A2, A3 and A4, while those with 2 g mould were coded B2 and B4 depending on the amount of paracetamol in the formulation (Table 1). The paracetamol powder was sifted through mesh 120 (125 µm) before it was incorporated into the gently melted cocoa butter followed by thorough mixing to form homogeneous mass, while avoiding air entrapment. The mixture was poured into the lubricated stainless steel mould, allowed to cool, and the excess congealed mass trimmed off. The suppositories were then removed from the mould, packed in a wide-mouthed opaque plastic container and stored in the refrigerator at 4 ± 1 °C.

Table 1: Codes and composition of paracetamol suppositories with different drug-base ratios

Mould size/formulation code	Paracetamol content (g)	Cocoa butter content (g)[a]	Theoretical weight of each paracetamol suppository (g)	Estimated drug-base ratio
1- g Mould				
A1	0.060 (5.9%)	0.966 (94.1%)	1.026	1:16
A2	0.125 (12.1%)	0.907 (87.9%)	1.032	1:7
A3	0.250 (23.9%)	0.795 (76.1%)	1.045	1:3
A4	0.500 (46.8%)	0.569 (53.2%)	1.069	1:1
2-g Mould				
B2	0.125 (6.7%)	1.743 (93.3%)	1.868	1:14
B4	0.500 (26.4%)	1.405 (73.6%)	1.905	1:3

[a] Content based on theoretical weight of paracetamol suppositories obtained from displacement factor of the drug in the base
Figures in parentheses are equivalent%w/w content in the formulation

3. Evaluation of Paracetamol Suppositories

3.1 Weight Uniformity Test

The prepared suppositories were evaluated for uniformity of weight using twenty randomly selected suppositories for each formulation. The mean weight, standard variation, and the% coefficient of weight variation were determined.

3.2 Content Uniformity Test

A suppository taken randomly from each batch was weighed, sliced and placed in a beaker containing 100 ml of phosphate buffer solution (pH 7.2) [6]. The suppository was melted by heating the beaker on a water bath maintained at 45 to 50 ^{0}C. The beaker was shaken gently while the melting proceeded until the suppository had been completely dispersed. The mixture was chilled and the oil layer was removed by filtration, while the aqueous portion was further filtered through Sinter glass number 3 (DURAN Group GmbH, Germany) and 1 ml of the filtrate diluted to 100 ml using the phosphate buffer solution. The absorbance of the diluted solution was measured by UV spectrophotometer (mini-1240 model, Germany) at 244 nm. The concentration of the paracetamol solution was calculated from a standard Beer-Lambert curve in the concentration range of 1.0 x 10^{-3} to 1.0 x 10^{-2}%w/v, and the drug content of each suppository determined. The result was an average of four determinations for each batch of the suppositories.

3.3 Determination of Softening and Melting Points

The softening and melting points of paracetamol suppositories were determined using the modified method of Adebayo and Akala [18]. Each suppository sample was placed in a clean test tube with a thermometer inserted. The tube was clamped vertically, immersed at 8-cm depth in a water bath. Temperature of the water bath was gradually increased (1 °C/ 2 min). The temperature at which the suppository sample began to melt was recorded as the softening point, while the temperature of its complete liquefaction was defined as the melting point [18]. The results obtained were average of four determinations.

3.4 Determination of Mechanical Strength

The hardness of the suppositories was determined using the Monsanto's hardness tester (Copley Erweka, Germany). Six suppositories selected randomly from each formulation were used for the determination. The weight under which the suppository collapsed was taken as measure of hardness of the suppository in kg force [1].

3.5 Determination of Disintegration Time

The disintegration time of six randomly select suppositories from each formulation was determined with the Manesty tablet disintegration apparatus (Manesty Machines ltd., Liverpool, England) using the method for uncoated tablets [19]. The apparatus consists of six cylindrical glass tubes, each filled with 160 ml of distilled water, immersed in a water bath maintained at constant temperature (37 ± 1 °C). For disintegration time testing, one suppository was placed in each glass tube and a metal disc weighing 50 g was added to each tube to prevent the suppository from floating [18]. The time required for complete deformation of each suppository sample was determined.

3.6 *In-vitro* Paracetamol Release from Suppository Formulations

The United States Pharmacopeia basket method [20] was employed for the dissolution studies using tablet dissolution test apparatus (Model VDA-8D, PharmChem Machineries, Mumbai, India). Phosphate buffer solution (900 ml) at pH 7.2 was used as the dissolution medium. A suppository was randomly selected from each batch, its weight determined and placed inside the dissolution basket which was then lowered into a flask containing the dissolution medium maintained at

constant temperature (37.0 ± 0.5 °C). The basket was rotated at the constant speed of 100 rpm [21]. At periodic intervals of 5, 10, 20, 30, 40, 60, 80, 100 and 120 min, 10 ml samples were withdrawn and replaced by equal volume of the buffer solution maintained at 37.0 ± 0.5 °C. The withdrawn solutions were filtered, diluted appropriately with the buffer solution and the absorbance determined by UV spectrophotometer (mini-1240 model, Germany) at 244 nm. The amount of drug released was calculated from a standard Beer-Lambert calibration curve. The mean of four determinations was used in calculating drug release from each batch of suppositories. The percentage released in 60 minutes ($\%D_{60min}$), 120 minutes ($\%D_{120min}$), and the time for 50% release ($T_{50\%}$) were computed.

3.7 Determination of Release Kinetics of Paracetamol from Suppositories

The dissolution data were fitted into four release kinetics models namely: Zero-order (Q vs t), First-order (log ($Q_o - Q_t$) vs t), Higuchi model (Q vs $t^{½}$) and Korsmeyer-Peppas model ($\log Q_t$ vs nlogt) [22,23], where Q is the amount of drug released at time t, Q_o is the initial amount of the drug, Q_t is the amount remaining at the time t and "*n*" is the release exponent from Korsmeyer-Peppas model. Dissolution data were evaluated using Microsoft Excel spreadsheet and DDSolver software [24, 25]. The best-fit dissolution model was identified by Adjusted Coefficient of Determination ($R^2_{adjusted}$) and Model Selection Criteria (MSC), where model with the highest $R^2_{adjusted}$ (≥ 0.950) and MSC (≥ 3.00) values within the set of the models was considered the best fit [24].

4. Factorial Experimental Analysis

The procedures were based on the previous works of Odeniyi and Jaiyeoba [7] and Okubanjo and Odeku [9]. Two variables were used in designing the 2^2 factorial experiments (i.e. 4 factorial levels). The variables, drug concentration (D) and base concentration designated as the size of the mould (M) were employed at "high" level (denoted by subscript, H) and "low" level (denoted by subscript, L). Using the above nomenclatures, the various combinations of variables used in the design were D_HM_H, D_LM_L, D_HM_L and D_LM_H.

D_H = concentration of the drug, 500 mg
D_L = concentration of drug, 125 mg
M_H = mould size, 2 g-mould
M_L = mould size, 1 g-mould

The combinations were grouped into appropriate sets to enable the assessment of each variable on the value of drug release ($T_{50\%}$), uniformity of drug content standard deviation (SD), melting point (MP), mechanical strength (MS) and disintegration time (DT). For example, the effect of changing the mould size (M) from "low" level (1 g) to "high" level (2 g) was determined by summing all the results from samples containing "high" level of M and subtracting the sums of the mould from samples using "low" level of M as in Eq. (1).

$$½[(D_HM_H + D_LM_H) – (D_LM_L + D_HM_L)]. \quad (1)$$

The same procedure was used in calculating the effect of changing the drug concentration (D) from "low" level (125 mg) to "high" level (500 mg). The result of the treatment gave the independent coefficient value which was a quantitative measure of the effect of the variable on the parameter being investigated [9].

To determine whether there was any interaction between the two variables, D and M, the results of the combination in which they appeared together at either "high" or "low" levels were summed and the sum of other combinations subtracted from this to obtain the interaction coefficient [9] as indicated in Eq. (2). For the D and M (D - M);

$$½[(D_HM_H + D_LM_L) – (D_LM_H + D_HM_L)] \quad (2)$$

A result of zero indicated no interaction, but a significant departure from zero implied that the two variables were interacting with each other, with the extent of departure from zero being a measure of the magnitude of the interaction [7,9].

5. Statistical Analysis

The statistically significant differences in the physical properties of the paracetamol suppositories due to the formulation variables (drug-base ratios) were determined with Student *t*-test using Microsoft Excel Software and Analysis of Variance (ANOVA). The minimum level of significance was established at 5%. The level of correlation (r) between the drug concentrations in the formulations and the physicochemical properties of the paracetamol suppositories was determined.

6. Results and Discussion

6.1 Effects of Drug-Base Ratio on Physical Properties of Paracetamol Suppositories

The displacement value of the paracetamol in the base was determined as 1.51 ± 0.05. The mean weights of the suppositories prepared using 1 g mould ranged between 1.019 g and 1.030 g, while those prepared using 2 g mould were found to fall between 1.880 g and 1.942 g, depending on the drug concentration in the formulation (Table 2). All the suppositories were found to meet the BP [19] requirement for weight uniformity test. The physical weights of the suppositories (Table 1) were not significantly different ($P > 0.05$) from their theoretical weights (Table 2).

The drug content of the suppositories ranged from 89.0% to 98.1%, with a corresponding SD between 2.4 and 11.4 (Table 2). All the suppositories were found to meet the BP [19] requirement for content uniformity tests (Table 2). The SD, a measure of content uniformity of the suppositories decreased with increase in the drug concentration of the formulation. Suppositories prepared using 1 g mould showed a significantly ($P < 0.05$) lower SD than the corresponding suppositories prepared using 2 g mould. A quantitative analysis of the effect of drug concentration (D) and mould size (M) as independent variables on SD of drug content uniformity showed that increasing the drug concentration decreased the SD (-4.50), while a change of the mould from 1 g to 2 g increased the SD (+4.50) (Table 3). The interaction coefficient of the two variables (D-M) indicated a decrease (-1.30) in the SD. Such simultaneous increase in the concentration of the drug and the mould size leading to reduction in the SD of the drug uniformity content was typified by formulations B2 and B4 (Table 2). Thus, the correlation between the drug content of the suppositories and their SD indicated the problem that could be encountered in obtaining a homogenous drug distribution within the suppository base when the amount of drug in the formulation is significantly low.

While it has been reported that some drugs could lower the softening point of suppository bases [26], the inclusion of paracetamol in cocoa butter base had no such effect. Rather, there was increase in softening point with increase in the concentration of paracetamol in the formulations (Table 2). The high correlation between the drug concentration and the melting points (r = +0.980) was a confirmation of increase in

the melting points with increase in the concentrations of the drug. The quantitative effect of the drug (D) as an independent variable on the melting point (+2.10) was significantly higher than that of the mould size (M), obtained as +0.10 (Table 3). However, the combined effect of the drug concentration and mould size (D-M) resulted in interaction coefficient of -1.30, an evidence of decrease in the melting point of the suppositories. While an increase in the softening point as a result of addition of paracetamol would improve the handling and storage of the suppositories at room temperature [21, 27], such increase along with the observed increase in melting point (Table 2) could prolong the release of the drug from the suppositories [2].

The mechanical strength of the suppositories showed increased values with increase in the concentration of the drug in the formulations (Table 2). A high correlation was found between the concentrations of the paracetamol in the suppositories and their mechanical strengths (r = +0.949). Some phenolic drugs and essential oils have been reported to repress the mechanical strength of some suppository bases [26]. The finding in this study showed that the paracetamol stiffened the suppositories, hence the increase in the mechanical strength with increase in drug concentration. Previous report [28] showed that drugs like metronidazole could increase the mechanical strength of suppositories formulated with cocoa butter base. The quantitative effects of drug concentration (D) as an independent variable on the mechanical strength of the suppository was calculated as +0.40, which was lower than the effect of the mould size (M) obtained as +1.29 (Table 3). The increase in mechanical strength as a result of a change in the mould capacity from 1 g to 2 g may be related to higher axial force required to deform the more bulky 2 g suppositories. The interaction coefficient obtained as a result of combined effect of the drug concentration and the mould size (D-M) show a minimal effect on the mechanical strength (Table 3).

All the suppositories have disintegration time less than 13 min (Table 2), and therefore met the BP [19] requirement. Using a 1 g mould, a high correlation coefficient (r = +0.997) was obtained between the drug concentration and the disintegration time. This could have been due to the stiffening effect of the paracetamol on the cocoa butter since the drug did not repress the melting point and mechanical strength of the suppositories. The quantitative effect of the drug concentration (D) on the disintegration time (+4.80) was significantly higher than that of the mould size (M) with an independent coefficient of -2.20 (Table 3). However, the values of the interaction coefficient as a result of the combined effect of the two variables (D-M) showed a decrease in the disintegration time (-3.20).

6.2 Effects of Drug-Base Ratio on Drug Release Profile of Paracetamol Suppositories

The dissolution profiles of paracetamol from the suppositories are depicted in Fig. 1, which were characterized by the parameters stated in Table 2. None of the formulations released up to 95% of the paracetamol content within the 120 min duration of the study. The dissolution trend of paracetamol suppositories prepared using 1-g mould was A4 > A3 > A2 > A1, reflecting the variability in the drug-base ratio. The same trend was observed for suppositories prepared using 2 g mould (Table 2). The effect of drug-base ratio on the percentage of paracetamol released in 60 min ($\%D_{60min}$) from the suppositories is depicted in Fig. 2. The profile showed that there was a significant increase ($P < 0.05$) in the drug release with increase in paracetamol content of the suppositories. The highest drug release was observed in formulation A4, with drug-base ratio of 1:1. The release tendency of paracetamol from the suppository is expected to be affected by the insolubility of the cocoa butter in the aqueous dissolution medium. Also lipophilic character of paracetamol with high affinity for fatty bases like cocoa butter, would decrease the tendency of the drug diffuse from the base [29].

At high concentration of the base in the formulation, the solubility of the paracetamol is expected to increase in the base, thus suppressing the release of the paracetamol into the aqueous dissolution medium. Conversely, the base became more saturated with increase in concentration of paracetamol and thus reduced the tendency of the base to suppress the drug release. In formulation of suppositories, not all the drug particles are completely embedded within the base, rather some quantities of the drug particles are located on the surface of the suppositories. Increasing the concentration of the drug in the formulation increases the amount of drug particles that may be localized on the surface of the suppository, and hence the quantity that may be released with ease from the formulation.

The melting of a fatty base and its deformation are prerequisite for drug release [12,30,31]. It is expected that those suppositories with low melting points and short deformation times would release their drug content faster and vice versa. However, the correlation coefficients (r) between the melting point and $T_{50\%}$; and disintegration time and $T_{50\%}$ were -0.711 and -0.630, respectively, indicating that the increase in melting point and disintegration time of the suppositories did not translate to increase in the time taken for 50% of the drug to be released (Table 2). The non-correlation between the deformation time of the suppositories and their release profile may be due to the fact that the deformation times were very low and fell within the BP requirements, and thus played no significant role in the release of the drug. The high release of paracetamol from formulations A3, A4 and B4, despite their high melting points (> 39 °C) indicated that the process of drug release from the bases may not rely solely on melting of the base, rather, other processes like wearing off of the drug particles from the surface of the suppositories might been involved. This assumption is supported by the fact that the quantitative effect of the drug concentration (D) as independent variable on release of the drug ($T_{50\%}$) was the highest (-16.50) among the variables, with the negative value indicating decrease in the time required for 50% drug release. The influence of the mould size (M), with an independent coefficient of +10.40 could be seen in the values of $T_{50\%}$ obtained for formulations A2 and B2 (Table 2). Increasing the base concentration in the formulations decreased the drug release.

Table 2: Physical and release properties of paracetamol suppositories formulated with different paracetamol-cocoa butter ratios.

Formulation code	Combination code for factorial analysis	Mean weight (g)	Mean drug content (%)	Softening point (°C)	Melting point (°C)	Mechanical strength (kg)	Disintegration time (min)	Dissolution parameters	
								D_{120min} (%)	$T_{50\%}$ (min)
A1	(-)	1.019 ± 0.015	89.0 ± 10.4	32.0 ± 0.6	37.1 ± 0.4	1.94 ± 0.24	2.7 ± 0.6	70.5 ± 2.6	65.3 ± 2.6
A2	D_LM_L	1.025 ± 0.018	94.8 ± 5.6	32.3 ± 0.0	37.5 ± 0.6	2.27 ± 0.39	4.7 ± 1.2	78.9 ± 1.8	55.5 ± 1.8
A3	(-)	1.060 ± 0.020	96.5 ± 4.7	34.0 ± 0.0	39.2 ± 0.6	2.28 ± 0.44	6.7 ± 1.5	84.9 ± 2.1	50.5 ± 0.6
A4	D_HM_L	1.103 ± 0.016	98.1 ± 2.4	34.0 ± 0.0	40.9 ± 0.4	2.71 ± 0.39	12.7 ± 2.6	94.5 ± 2.2	44.6 ± 1.3
B2	D_LM_H	1.880 ± 0.055	92.1 ± 11.4	32.7 ± 0.6	38.9 ± 0.6	3.60 ± 0.27	5.7 ± 0.6	68.0 ±1.4	71.5 ± 2.3
B4	D_HM_H	1.942 ± 0.023	96.4 ± 5.6	33.5 ± 0.6	39.7 ± 0.8	3.95 ± 0.99	7.3 ± 0.6	82.1 ±2.1	49.4 ± 1.8

Table 3: Quantitative effects of drug concentration (D) and mould size (M) on the physical and release properties of cocoa butter-based paracetamol suppositories.

Variable	Physical and release properties/coefficient values					
	SD of mean drug content	Softening point	Melting Point	Mechanical strength	Disintegration time	$T_{50\%}$
Independent variable						
D	- 4.50	+ 1.25	+ 2.10	+ 0.40	+ 4.80	- 16.50
M	+ 4.50	- 0.05	+ 0.10	+ 1.29	- 2.20	+ 10.40
Interacting variable						
D-M	- 1.30	- 0.45	- 1.30	- 0.05	- 3.20	- 5.60

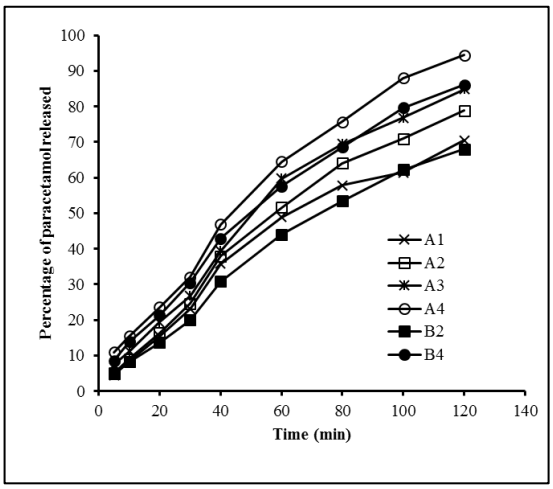

Fig 1: Dissolution profile of paracetamol suppositories formulated with different ratios of paracetamol-cocoa butter combination

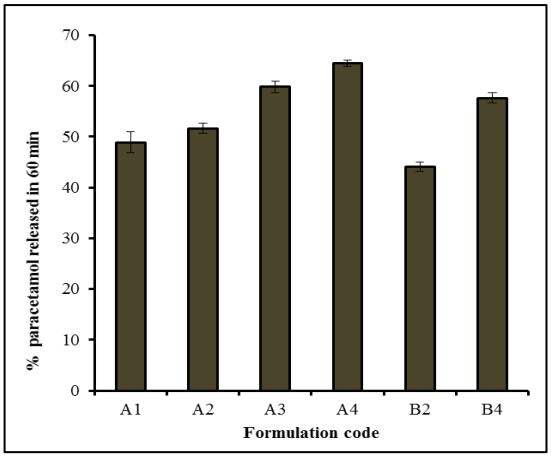

Fig 2: Effect of drug-base ratio on the percentage of paracetamol released in 60 min from the suppository formulations

6.3. Effects of Drug-Base Ratio on Release Kinetics of Paracetamol from Suppositories

The dissolution profiles depicted in Fig. 1 were fitted into the Higuchi square root, Zero-order and First-order release kinetics models with the best fit selection criteria derived from the models indicated in Table 4. The release kinetics of paracetamol from all the formulations was best described with First-order release model ($R^2_{adjusted} \geq 0.975$; MSC ≥ 3.5) (Table 4). There was increase in the release rate constants (K_1) with increase in the concentration of the drug in the formulations i.e. A4 > A3 > A2 > A1. Also the values of K_1 obtained for A2 and B2 demonstrated decrease in the release profile of the paracetamol from the formulations by changing the mould size from 1 g (A2) to 2 g (B2). It also confirmed that a high proportion of cocoa butter base relative to the concentration of the drug in the formulation repressed the release of the drug. The derived $T_{50\%}$ values from the release models (Table 4) showed that only the values derived from the First-order release model were not significantly different ($P > 0.05$) from the experimental values indicated in Table 2. This further confirmed the First-order as the fittest model in characterizing the release mechanism of paracetamol from the suppositories.

The dissolution profiles in Fig. 1 were also fitted into Korsmeyer-Peppas release model using the first 60% drug release data. The derived release constants (K_{kp}), release exponents *n*, and the selection criteria values ($R^2_{adjusted}$ and MSC) are indicated in Table 4. The release exponents *n*, ranged between 0.80 and 1.00, indicating non-Fickian diffusion mechanism [32]. Non-Fickian diffusion release mechanism has been associated with more than one type of release phenomenon from suppository formulations [9], which in the case of cocoa butter-based suppositories would involve melting of the base, partitioning and diffusion of the drug through the molten base to the dissolution medium [30]. In this study, the non-diffusion mechanism could be classified into

two based on the release exponent, *n*, values. Formulation A4 and B4 with release exponents of 0.80 and 0.84, respectively could be classified as Upper Case I non-Fickian diffusion, while formulations A1, A2, A3 and B2 with release exponents greater than 0.89 could be classified as Upper Case II non-Fickian diffusion [32,33]. Thus, the release of paracetamol from the suppositories was of First-order kinetics that involved non-Fickian diffusion release mechanism.

Table 4: Release rate constants and model fitting parameters for release kinetics of paracetamol from suppositories formulated with different paracetamol-cocoa butter ratios

Release Kinetic Model	Release parameter	Formulation code/ release kinetics values					
		A1	**A2**	**A3**	**A4**	**B2**	**B4**
Higuchi	K_H (mg/min$^{1/2}$)	3.539	8.159	17.838	40.250	6.958	36.515
	R^2 adjusted	0.904	0.895	0.904	0.928	0.889	0.930
	MSC	2.1	2.0	2.1	2.4	2.0	2.4
	Derived $T_{50\%}$ (min)	71.9	58.7	49.1	38.6	80.7	46.9
Zero-order	K_o (min^{-1})	0.396	0.919	2.000	4.485	0.785	4.070
	R^2 adjusted	0.934	0.957	0.943	0.929	0.968	0.933
	MSC	2.5	2.9	2.6	2.4	3.2	2.5
	Derived $T_{50\%}$ (min)	75.7	68.1	62.5	55.7	79.6	61.4
First-order	K_1 (mg/min)	0.006	0.015	0.035	0.085	0.011	0.070
	R^2 adjusted	0.991	0.988	0.982	0.975	0.992	0.990
	MSC	4.4	4.2	3.8	3.5	4.6	4.4
	Derived $T_{50\%}$ (min)	67.8	58.1	50.2	40.6	74.4	48.1
Korsmeyer-Peppas	K_{KP} (mg/min^n)	0.708	1.106	2.430	11.555	1.174	9.295
	n	0.90	1.00	1.00	0.80	0.93	0.84
	R^2 adjusted	0.986	0.989	0.990	0.956	0.990	0.991
	MSC	3.8	4.1	4.1	2.6	4.2	4.3
	Derived $T_{50\%}$ (min)	65.1	57.2	50.9	46.6	72.4	50.6

k_o, k_1, k_H = zero-order, first-order and Higuchi release constants, respectively; k_{KP}, *n* = release constant and release exponent in Korsmeyer-Peppas model, respectively; R^2 adjusted = adjusted coefficient of determination; MSC = Model Selection Criterion; $T_{50\%}$ = Time required (min) for 50% of drug content to be released

7. Conclusion

This study has shown that the concentrations of paracetamol and cocoa butter in the suppository formulations as either independent or combined variables affected the physical and release properties of paracetamol as shown by the magnitude of the individual and interaction coefficients obtained for standard deviation of drug content uniformity, softening and melting points, mechanical strength, disintegration time and $T_{50\%}$. The effects of the drug-base ratio were more pronounced on the release parameters than other physical properties of the paracetamol suppositories. Although there was no change in the First-order release kinetics obtained for the formulations by varying the drug-base ratios, the release rate constants (K_1) were significantly different ($P < 0.05$), showing increase with increase in proportion of drug in the formulations. This indicated that high concentrations of the base in the formulations suppressed the release of the drug. The release exponents (*n*) obtained from the Korsmeyer-Peppas model for the suppositories were significantly different ($P < 0.05$) due to variation in the drug-base ratios. In dosage administration, there is tendency to give two-125 mg paracetamol suppositories where a single 250 mg paracetamol suppository is not available. In view of the fact that variation in the drug-base ratios resulted to variability in the physical and release properties of the paracetamol suppositories, such substitution may not yield the desired bioequivalent value. These findings therefore, suggest the need to optimize the drug-base ratio when formulating a poor water-soluble drug like paracetamol in fatty bases. This would require using mould with minimum capacity relative to the drug concentration.

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