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Evaluation of the Kinetics and Mechanism of Piroxicam Release from Lipophilic and Hydrophilic Suppository Bases

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Abstract : Piroxicam rectal suppository offers an alternative in circumventing the side effects associated with oral administration of the drug. Predicting the release profile of piroxicam, a drug with limited aqueous solubility, from suppositories, would require an appropriate release kinetics model, which is dependent on the formulation additives. The objective of this study was to determine the kinetics model that best describes the release of piroxicam from different suppository bases. Suppositories containing 20 mg piroxicam each were prepared in polyethylene glycol (PEG), cocoa butter and Witepsol® H15 and W35 bases by fusion method. Physical and dissolution properties of the suppositories were determined by appropriate methods. The dissolution data were fitted into five release kinetics models and three statistical criteria were used in selecting the most appropriate model. There was complete release of piroxicam from PEG bases, with more than 96.4 ± 6.0 % released within 60 min. Release of piroxicam from the lipophilic bases was poor, and in the order: Witepsol® W35 > Witepsol® H15 > cocoa butter, being significantly influenced by the hydroxyl values of the bases. The kinetics of Piroxicam released from lipophilic bases with or without Tween® 20 was best fitted into Korsmeyer-Peppas model with release exponents between 0.510 and 0.930, while that from PEG bases showed a biphasic pattern which was resolved by Kitazawa equation model.
Keywords: Piroxicam, suppository formulations, suppository bases, release kinetics models.

Introduction

Piroxicam, a potent non-steroidal anti-inflammatory drug (NSAID) with analgesic and antipyretic effects is available for oral, parenteral and topical administration[1,2]. The drug is indicated for use in acute and chronic musculoskeletal and joint disorders, acute gout, dysmenorrheal and pain associated with inflammation[3,4]. Peptic ulceration and severe gastrointestinal bleeding are the major side effects resulting from oral administration of piroxicam[5,6]. Formulating piroxicam as a rectal suppository offers an alternative to circumvent the incidence of gastric irritation associated with oral administration of NSAIDs in general and piroxicam in particular[1,7,8]. Rectal administration of drug could also avoid hepatic first-pass effect and provide relief for patients with swallowing difficulties[9].

Rectal suppositories melt, soften or dissolve in the rectum depending on the nature of the base, prior to releasing the active ingredient[10,11]. Suppository bases and other incorporated additives thus, play important roles in the release rate of the drug from the dosage form and its bioavailability, especially when a poor water soluble drug like piroxicam is incorporated[11-12].

For an accurate characterization of release rate of drug from suppositories, there is need to determine the most appropriate kinetics model that best describe the release of the drug[13]. This involves using

mathematical models to analyse *in vitro* drug release profiles based on defined criteria[14]. Among the models that had been used in defining drug release mechanism from suppositories are; Zero Order kinetics[15], First Order kinetics[16], Higuchi model[17,18], Korsmeyer-Peppas model[19-21], Hixson-Crowell equation[22] and Kitazawa equation[23]. Some of these models had been employed in a previous study[1] to determine the release kinetics of piroxicam from Witepsol® H15 (a semi-synthetic fatty suppository base) to which different additives were incorporated. However, the results did not show a defined kinetics model for the release of piroxicam[1], which could be due to quantitative and qualitative changes in the formulation additives[24], and the statistical criteria used.

This paper therefore, reports thekinetics model that best describes the mechanism of piroxicam release from different suppository bases using three statistical criteria namely; Adjusted Coefficient of Determination ($R^2_{adjusted}$), Akaike Information Criterion (AIC) and Model Selection Criterion (MSC)[14,25,26]. The three selection criteria had been adjudged the most popular in the field of dissolution model identification[14]. The kinetics model of piroxicam release from the suppositories is expected to provide parameters for optimising the formulation factors of the drug and its bioavailability.

Materials and Methods

Materials

Piroxicam powder (Drugfield Pharmaceuticals Ltd, Sango Otta, Nigeria), Cocoa butter (Starmark Cocoa Processing Company Ltd, Ondo, Nigeria), Witepsol® W35 and Witepsol® H15 (AXO Industry International, Chaussee de Louvain 171, Belgium), PEG 1500 and PEG 4000 (Hopkin and Williams, England), Sodium Hydroxide (BDH Laboratory, Poole BH15, England), Potassium dihydrogen orthophosphate (Surechemproducts Ltd, England), Polysorbate 20 (Tween 20®), UV-visible spectrophotometer (Cecil CE 3041 3000series), Digital Tablet Dissolution Test Apparatus Model VDA-8D (PharmaChem Machineries, Mumbai, India), Mettler Toledo PB 153 analytical balance (Switzerland),

Methods

Preparation of Piroxicam Suppositories

The suppositories were prepared by fusion method using a 1g metal mould with six cavities[12]. Lipophilic bases used were cocoa butter, Witepsol® H15, Witepsol® W35, while the hydrophilic base was polyethylene glycol (PEG) (25% PEG4000 and 75% PEG 1500 combination). Suppositories, each containing 20 mg piroxicam were prepared, the quantity of base required in each formula was determined by the drug's displacement value[10,11]. Batches of lipophilic-based suppositories containing 2%w/w Tween 20®were also prepared. The Tween 20®was mixed with the melted bases prior to the addition of piroxicam. The compositions of the formulated suppositories are as in Table 1. The suppositories were stored in a refrigerator (4±1^{o}C) and analysis carried out 24 hours after formulation.

Table 1: Codes and composition of formulated piroxicam suppositories

Code	Formulation
F1	Cocoa butter with 20 mg piroxicam
F2	Cocoa butter with 2%w/w Tween® 20 and 20 mg piroxicam
F3	Polyethylene glycol with 20 mg piroxicam
F4	Witepsol® H15 with 20 mg piroxicam
F5	Witepsol® H15 with 2%w/w Tween® 20 and 20 mg piroxicam
F6	Witepsol® W35 with 20 mg piroxicam
F7	Witepsol® W35 with 2%w/w Tween® 20 and 20 mg piroxicam

Uniformity of Weight Test

Twenty suppositories were randomly selected from each batch of the formulations and weighed individually using a Mettler analytical balance. The mean weight and percentage relative standard deviations

(RSD) were determined. The deviations of the individual weight from the theoretical weight of the suppositories were also calculated.

Determination of Content Uniformity

The method described by Setnikar and Fontani[27] was used. A suppository taken randomly from each batch was weighed and placed in a beaker containing 100 ml of phosphate buffer solution at pH 7.2. The suppository was melted by heating the beaker gradually on a water bath. The beaker was shaken gently while the melting proceeded. When the suppository had been completely dispersed, the mixture was chilled and the oil layer was removed by filtration through a cotton plug. The aqueous portion was further filtered through Sinter glass number 3. The aqueous filtrate (1 ml) was diluted to 100 ml using phosphate buffer solution. The absorbance was measured by UV spectrometer at 350 nm. The concentration of the solution was calculated from a standard Beer-Lambert curve and the drug content was determined. The result was an average of six determinations per batch of suppositories.

Evaluation of Release Profile of Piroxicam from the Suppositories

The United States Pharmacopeia[28] basket method was employed forthe dissolution studies, using digital tablet dissolution test apparatus. The dissolution test conditions are as in Table 2. 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. The dissolution apparatus was set running and samples withdrawn at appropriate predetermined time intervals. The volume of the dissolution medium was kept constant by replacing the volume of the sample withdrawn with an equal volume of fresh buffer solution maintained at the same temperature. The amount of drug in each sample collected was determined spectrophotometrically at 350 nm from a standard Beer-Lambert calibration curve and the percentage calculated. The mean of three determinations was used in calculating drug release from each batch of suppositories. The drug release parameters: percentage of drug released at 180 min, 60 min and the time (min) for 50 % of the drug to be released were calculated.

Table 2: Summary of dissolution test conditions

Parameter	**Material/test condition**
Dissolution medium	Phosphate buffer (pH 7.2)
Dissolution medium volume	900ml
Temperature	37 ± 0.5 ^{o}C
Method	Basket method
Speed	100 rpm
Volume withdrawn	5 ml
Volume replaced	5 ml
Sampling times (min)	5, 10, 15, 20, 30, 40, 50, 60, 80,100, 120, 140, 160, 180

Table 3: Mathematical equations utilized in modeling of piroxicam release

Kinetics model	**Equation**	**Applicable formulation**	**Reference(s)**
Zero-order	$Q_t = Q_o + k_o t$	All formulations	15
First-order	$\ln Q_t = \ln Q_o - k_1 t$	All formulations	16
Higuchi's diffusion model	$Q_t = k_H t^{1/2}$	All formulations	17, 18
Korsmeyer-Peppas	$M_t/M_\infty = k_{KP} t^n$	Lipophilic based	19-21
Hixson-Crowell	$Q_o^{1/3} - Q_t^{1/3} = k_{HC} t$	Lipophilic based	22
Kitazawa Equation	$\ln [Q_o /(Q_o - Q_t)] = kt$	Hydrophilic based	23

Q_t: amount of drug released in time t; Q_o: initial amount of drug in the suppository; Mt/M∞: fractional release of drug;k_o, k_1, k_H:zero-order, first-order and Higuchi release constants, respectively;k_{KP}, k_{HC}, k: release constants in Korsmeyer-Peppas, Hixson-Crowell and Kitazawa models, respectively; *n*: release exponent

Determination of Kinetics of Piroxicam Release

Dissolution data were evaluated using Microsoft Excel spreadsheet and DD Solver software, a specialised program for analysis of dissolution data[14,25]. The data modeling utilised for the release kinetics of piroxicam from the bases are indicated in Table 3. The best-fit dissolution model was identified by $R^2_{adjusted}$, MSC and AIC, where the highest $R^2_{adjusted}$ (≥ 0.99), MSC (≥ 3.00) values and lowest AIC value within the set of the models was considered the best fit[14]. The goodness of fit of the models for each formulation was validated by using the DDSolver package to predict percentage of piroxicam released at 60 min.

Statistical Analysis

All data are given as mean ± standard deviation from at least three determinations. Statistical significant differences were assessed employing GraphPad Prism 5 software with minimum level of significance established at 5 %.

RESULTS

Physical Properties and Release Parameters

The mean weights of piroxicam suppositories were between 1.00 g and 1.28 g with relative standard deviation (% RSD) not greater than 1.0 % (Table 4). The assay of piroxicam content of the suppositories showed that both the mean piroxicam content of the suppositories and their respective % RSD were within the range stipulated by the British Pharmacopoeia[29] (Table 4). The inclusion of 2 %w/w Tween® 20 into the lipophilic bases (cocoa butter, Witepsol® H15, Witepsol® W35) resulted into reduction in their respective % RSD values (F1 vs F2; F4 vs F5; F6 vs F7).

Table 4: Physical and release parameters for formulated suppositories

Formulation code	Mean weight (g)	% Drug content	% Drug released in 180 min	% Drug released in 60 min	$T_{50\%}$ (min)
F1	1.00±0.01 (1.0)	100.8±3.9 (3.9)	12.5±1.7	7.0±1.0	> 180.0
F2	1.00±0.01 (1.0)	102.4±2.8 (2.7)	42.8±4.9	22.7±1.8	.> 180.0
F3	1.28±0.01 (0.8)	100.5±8.6 (8.6)	101.4±0.6	96.4±0.6	< 5.0
F4	1.03±0.01 (1.0)	97.9±4.1 (4.2)	67.2±4.3	30.0±2.8	119.3±5.6
F5	1.03±0.01 (1.0)	96.6±3.2 (3.3)	87.4±0.9	45.0±5.0	71.2±6.3
F6	1.03±0.01 (1.0)	96.3±4.7 (4.9)	84.0±1.0	31.6±1.3	104.9±0.9
F7	1.04±0.01 (1.0)	98.9±3.4 (3.4)	92.1±1.5	36.3±1.8	93.7±2.5

$T_{50\%}$: requiredtime (min) for 50 % release of drug from suppository; values in parentheses are relative standard deviations (RSD) in percentages

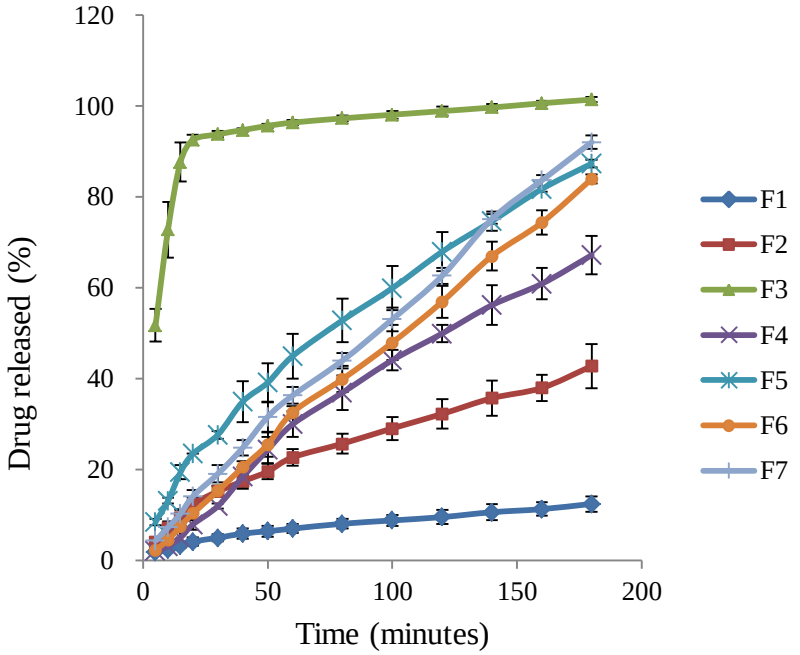

Figure 1: Profile of piroxicam release from different suppository bases

The release profiles of piroxicam from the suppositories are depicted in Fig. 1, which were characterized by parameters stated in Table 4. There was complete release of the drug from PEG base within 180 min, with more than 95 % released within 60 min and 50 % released in less than 5 min. There was very low piroxicam release from cocoa butter base (F1). The release profile of piroxicam from the lipophilic bases without addition of Tween® 20 was in the order of F1 < F4 < F6. The addition of Tween® 20 to the lipophilic bases enhanced the release of piroxicam (F2, F5 and F7). At 180 min, the release of piroxicam from cocoa butter base was enhanced by 242.4 % (F1 vs F2), while those of Witepsol® H15 (F4 vs F6) and Witepsol® W35 (F6 vs F7) were enhanced by 30.1 % and 9.6 %, respectively as a result of addition of 2 %w/w Tween® 20 to the suppository bases. The release of piroxicam from cocoa butter containing 2 %w/w Tween® 20 was significantly lower ($P < 0.01$) than those from Witepsol® bases without Tween® 20 (F4, F6) (Table 4).

Release Kinetics of Piroxicam

The dissolution rate data of piroxicam from the lipophilic bases were fitted to the Korsmeyer-Peppas model, and the resultant release exponents *n* and release constants indicated in Table 5. The *n* values ranged from 0.51 to 0.93 showing both Fickian diffusion and non-Fickian diffusion release mechanism. Addition of Tween® 20 to suppositories formulated with Witepsol® bases led to reduction in the *n* values (F4 vs F5, and F6 vs F7) without altering the release mechanism which was considered to be non-Fickian diffusion controlled. For the cocoa butter based suppositories, addition of Tween® 20 led to an increase in *n* value (F1 vs F2) which resulted to a change in the release mechanism from Fickian diffusion to non-Fickian diffusion controlled (Table 5). The release rate constants of piroxicam from the suppositories using the Korsmeyer-Peppas model (K_{kp}) was in the following order; Witepsol® W35 (F6) > Witepsol® H15 (F4) > cocoa butter base (F1). On addition of Tween® 20 to the suppository bases, there was increase in the release rate constants with Witepsol® H15 having a higher value than Witepsol® W35.

The $R^2_{adjusted}$ and MSC values obtained using the Korsmeyer-Peppas model fell within acceptable predetermined range of values set for good fit for all the lipophilic-based suppositories (Table 5). The two selection criteria ($R^2_{adjusted}$ and MSC) for Korsmeyer-Peppas model were found to be significantly ($P < 0.05$) higher than those of other models for the corresponding formulations except F1 (Table 5). The Korsmeyer-Peppas model also gave significantly ($P < 0.05$) lower AIC values for the formulations except F1.

The $R^2_{adjusted}$, MSC and AIC values obtained when the dissolution data were subjected to Zero-order, First-order, Higuchi, and Hixson-Crowell models showed that release mechanisms of the drug from the

formulations could fit into more than one model (Table 5). For example, F4 could fit either First-order or Hixson-Crowell with $R^2_{adjusted}$value set at ≥0.990. Based on MSC value set at ≥ 3.0, kinetics of drug release from F4 could fit into Zero-order, First-order or Hixson-Crowell models. Combining the three statistical criteria in determination of the best fit release kinetics model for the formulations indicated that F1 is best fitted to Higuchi diffusion model and F2, F4, F5, F6 and F7 to Korsmeyer-Peppas model with resultant $R^2_{adjusted}$values greater than 0.990 and MSC values greater than 5.0 (Table 5, bold cases). The predicted percentage of piroxicam released in 60 min ($\%D_{60\ min}$) (Table 5) using the best fitted release kinetics model compared with the experimental values (Table 4) showed percentage deviations less than 5.0%.

None of the five release kinetics models earlier exploited for the lipophilic bases could adequately characterize the release mechanism of piroxicam from PEG based suppository formulations (Table 5), hence Kitazawa equation was employed. Kitazawa plot showed biphasic release of piroxicam from the suppositories formulated with PEG base (Fig. 2). The two phases of the plot were regressed and their slopes representing the release constants, K_1 and K_2; their coefficients of determination, R^2_1 and R^2_2; and the point of intersection, t_c(min), determined as 0.127 min^{-1}, 0.018 min^{-1}, 0.992, 0.995 and 19.4 min, respectively.

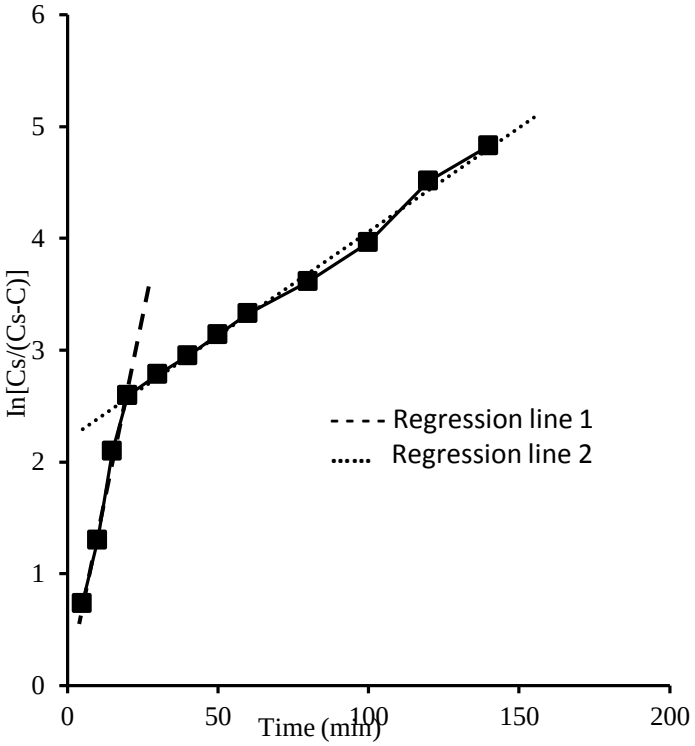

Figure 2: Kitazawa plot for release of piroxicam from polyethylene glycol base

Table 5: Derived values of model fitting parameters from data on piroxicam released for suppository formulations

Model	Parameter	Formulation						
		F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**
Zero-order	K_o (min^{-1})	0.081	0.268	0.842	0.403	0.556	0.477	0.532
	$R^2_{adjusted}$	0.656	0.808	-14.2322	0.979	0.859	0.997	0.990
	AIC	56.9	84.7	149.0	71.1	101.6	51.1	67.9
	MSC	0.9	1.5	-2.9	3.7	1.8	5.5	4.5
First-order	K_1 (mg/min**)**	0.001	0.003	0.135	0.006	0.010	0.007	0.009
	$R^2_{adjusted}$	0.695	0.897	0.9588	0.990	0.985	0.970	0.964
	AIC	55.3	75.9	66.2	62.1	70.0	81.5	86.1
	MSC	1.0	2.1	3.0	4.4	4.1	3.4	3.2
Higuchi's diffusion model	K_H ($mg/min^{1/2}$)	0.901	2.954	10.281	4.270	6.085	5.012	5.638
	$R^2_{adjusted}$	**0.996**	0.984	-4.4288	0.873	0.974	0.856	0.879
	AIC	**-5.9**	50.3	134.5	96.5	77.9	103.4	103.0
	MSC	**5.4**	4.0	-1.8	2.0	3.5	1.8	2.0
	$D_{60min\text{-}Pre}$ (%)	7.0 (0.0)*	NA	NA	NA	NA	NA	NA
Korsmeyer – Peppas	K_{KP} (mg/min^n)	0.861	1.998	Nd	0.799	3.445	0.669	0.985
	n	0.51	0.59	Nd	0.86	0.62	0.93	0.87
	$R^2_{adjusted}$	0.992	**0.997**	Nd	**0.996**	**0.999**	**0.999**	**0.999**
	AIC	-4.2	**29.1**	Nd	**49.7**	**32.4**	**37.2**	**42.3**
	MSC	5.3	**5.5**	Nd	**5.3**	**6.8**	**6.5**	**6.3**
	$D_{60min\text{-}Pre}$ (%)	6.9 (1.4)*	21.9 (3.5)*	Nd	29.2 (2.7)*	44.2 (1.8)*	30.2 (4.4)*	35.2 (3.0)*
Hixson – Crowell	K_{HC} ($mg/min^{1/3}$)	0.000	0.001	Nd	0.002	0.003	0.002	0.002
	$R^2_{adjusted}$	0.682	0.872	Nd	0.992	0.973	0.987	0.984
	AIC	55.8	79.0	Nd	58.0	78.6	69.7	74.8
	MSC	1.0	1.9	Nd	4.7	3.5	4.2	4.0

$R^2_{adjusted}$: adjusted coefficient of determination; AIC: Akaike Information Criterion; MSC: Model Selection Criterion;$D_{60min\text{-}Pre}$ (%): Predicted percentage of drug released in 60 min; Nd: Not determined; NA: Not applicable; Bold case values represent best fit selection criteria per formulation; *Values in parentheses are percentage deviation from experimental values

Discussion

All the suppositories complied with the requirements stated for uniformity of weight and drug content under rectal preparations in the British Pharmacopoeia[29]. The low % RSD obtained for weight uniformity and drug content tests indicated perfect calibration of the suppository mould. The results of the content uniformity helped to assert that the low drug released from formulations F1, F2 and F4 was not due to their drug content being less than the desired 20 mg of piroxicam. The reduction in the RSD of drug content of F2, F5 and F7, an indication of improved content uniformity, may be due to the Tween® 20 facilitating drug dispersion into the bases by reduction of surface tension and making them softer and pliable for the incorporation of the drug[30].

Drug release from suppository bases generally depends upon the drug solubility in the base and chemical composition of the base[31]. Piroxicam is a lipophilic drug with high affinity for fatty bases and low solubility in hydrophilic bases. However, it has a higher tendency to diffuse out of the hydrophilic base (PEG), hence releasing the piroxicam more rapidly than the lipophilic bases. PEG bases are also known to have solubilising effect which in part may explain the higher drug release rates from F3[1,11,20]. Previous studies have shown PEG to be an optimal base for formulation and release of poor water soluble drugs from suppositories[32].

The composition of the lipophilic bases was very significant in the release of piroxicam from them. The presence of monoglycerides in Witepsol® bases, which act as an emulsifier, made them more hydrophilic than

cocoa butter that contains mixture of glyceryl esters and unsaturated fatty acids[7]. Thus, the poor release of piroxicam from cocoa butter compared with other fatty bases (Witepsol®H15 and W35) showed that the cocoa butter has relatively poor miscibility with the dissolution medium. The Witepsol® bases (H15 and W35) have a common melting point range (33.5 – 35.5 ^{o}C) but differ in their hydroxyl values[33]. The higher hydroxyl value 40-45 of Witepsol® W35 imparts a hydro-dispersible character on the base than Witepsol® H15 with lower hydroxyl value of 5-15, hence the higher release rate of piroxicam from F6 formulated with Witepsol® W35.

Incorporating 2 %w/w Tween® 20 that has been shown to be safe for rectal administration inhuman[34] into the lipophilic bases (F2, F5 and F7) improved the release profiles of the formulations significantly ($P < 0.05$) (Fig. 1, Table 4). Similar effects have been reported by several workers[35,36]. Generally, surfactants have been shown to increase the release rate of a number of drugs by changing the lipophilic characteristics of the base to a lipo-hydrophilic nature[34,37], by micellar solubilisation of the drug, and by decrease in the interfacial tension between the suppository and the dissolution medium, that enhanced wettability of the lipophilic drug[37]. The results also indicated that the effectiveness of Tween® 20 in improving the release of piroxicam from the base was in the order of cocoa butter > Witepsol® H15 > Witepsol® W35. The order reflected a decrease in effectiveness of the Tween® 20 with increase in hydroxyl value of the base. This trend indicated that lipophilic base with very high hydroxyl value may not require addition of surfactant, while addition of surfactant to fatty base with low hydroxyl value will enhance the release of the drug.

The release profile of piroxicam from the bases (Fig. 1) showed that the mechanism by which the drug was released from suppositories formulated using PEG base was quite different from the lipophilic bases. While PEG was an optimal base for the release of piroxicam, the release mechanism could only be modeled using the Kitazawa equation that showed biphasic drug release pattern with two release rate constants (Fig. 2). The higher release rate constant (K_1) was associated with the primary phase of rapid release of the drug as the base dissolved in the medium and the drug diffused out of it into the dissolution medium, while the lower release rate constant (K_2) was related to the secondary phase of slow release indicating near saturation of the drug in the medium. The point of intersection of the two phases (t_c) was calculated to be 19.4 min at which 85.6 ± 0.7% of the drug had been released. Under the influence of K_2, it took 140.6 min for the remaining 14.4 % of piroxicam contained in the PEG base to be released, thus confirming that the slow release observed in the second phase of the dissolution profile could be due to saturation of the poor soluble drug in the medium.

The mechanism of piroxicam release from each type of the lipophilic base formulations were best described with Korsmeyer-Peppas model ($R^2_{adjusted} > 0.99$; $0.50 < n < 1.00$), indicating Fickian diffusion and anomalous transport drug release mechanism (Table 5). The Korsmeyer-Peppas release exponent *n* was 0.51 for F1 which confirmed the Higuchi diffusion model as the principal mechanism of drug release. The *n* values in the Korsmeyer-Peppas model for F2, F4-F7 were associated with anomalous transport drug release mechanism, which was an indication of more than one type of release phenomenon facilitating drug release from the formulations[20]. For lipophilic bases, this has been ascribed to the complexity of the drug release process from the suppositories, which involves melting of the base, partitioning and diffusion of the drug through the molten base to the dissolution medium[10,26,38]. The observed increase in *n* value; F6 >F4 >F1 (formulations without Tween® 20) reflected increase in the hydroxyl value of the suppository bases. The hydroxyl values of the fatty bases are known to affect their miscibility with the dissolution medium with resultant change in the original shape of the suppositories with a consequential effect on the release exponent value[39].

The enhancement of piroxicam release from cocoa butter by addition of 2 % w/w Tween® 20 was reflected in the observed change from Fickian diffusion model (F1) to non-Fickian diffusion model (F2) in the release mechanism of the base. While the release of piroxicam from cocoa butter was very low compared with other lipophilic bases, the results showed that Tween® 20 has a great influence in modifying the lipophilic characteristics of cocoa butter as demonstrated by change in its release mechanism.

Most previous studies had involved the use of R^2 and $R^2_{adjusted}$values as selection criteria for the determination of the release model of drugs from solid dosage forms and suppository bases[1,36,40]. The application of$R^2_{adjusted}$values (> 0.990) as selection criterion in this study showed that release of piroxicam from formulations containing lipophilic bases could be classified under more than one release model (Table 5). This finding was confirmed by the values of release exponent *n* obtained using the Korsmeyer-Peppas model, thus implying that the use of $R^2_{adjusted}$value alone may not give an exact measure of the accuracy of a model for the release of piroxicam from the lipophilic bases. As indicated in Table 5 (bold cases), the combined use of the

three statistical criteria i.e., $R^2_{adjusted}$,AIC and MSC provided the best fit model, with the goodness of fit based on model with highest $R^2_{adjusted}$and MSC values, and lowest AIC value. The accuracy (> 95 %) of the predicted percentage of drug released in 60 min was an indication of goodness of fit of the models to the formulations and their suitability in describing the release process of piroxicam from the lipophilic-based suppositories.

It can be concluded that PEG base provided an immediate release of piroxicam from the suppositories with the release kinetics model explained by Kitazawa equation which was analogous to First-Order release mechanism, while the lipophilic bases provided slow release of the drug. Release mechanism of piroxicam from the lipophilic bases with or without Tween® 20 was best described by Korsmeyer-Peppas model with the release exponent *n* dependent on the hydroxyl value of the base. A combination of $R^2_{adjusted}$,AIC and MSC as selection criteria enabled the determination of most suitable release kinetics models that fitted the dissolution data.

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