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Preliminary investigation of the properties of diclofenac potassium in SRMS-based tablets

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ABSTRACT

The aims of the study were to formulate sustained release diclofenac potassium tablets based on solidified reverse micellar solution (SRMS) and to evaluate the properties of the tablets and compare with commercial diclofenac potassium tablets for sustained release properties. The SRMS was prepared by fusion using Phospholipon® 90H (P90H) and Softisan® 154 (1:1, 2:1 and 1:2) and characterized using differential scanning calorimetry (DSC). The tablets were prepared using validated plastic mold and analysed by determining the drug content, weight uniformity, tablet hardness, friability test, tablet thickness and diameter. *In vitro* drug release was studied in simulated intestinal fluid (SIF, pH 7.5). The DSC results of the SRMS showed endotherms at 67.0, 75.0 and 62.5 ^{o}C for SRMS 1:1, 2:1 and 1:2 respectively. The tablets exhibited stable thickness of 0.33 ± 0.02 to 0.34 ± 0.02 cm and stable diameter of 1.20 ± 0.01 cm. The tablets' weight showed percentage deviation significantly lower than 5 % ($p < 0.05$) and friability of 0.05 to 0.11 %. The tablet hardness ranged from 5.00 to 5.10 kgf while, erosion time ranged from 36.00 ± 1.10 to 120.00 ± 0.32 min and increased as the concentration of phospholipid increased. The tablets complied with the BP standard for assay of active ingredient. Diclofenac potassium tablet formulations exhibited $T_{100\ \%}$ at 8 -11 h, while the reference tablets showed $T_{100\ \%}$ at 9 h. Therefore, diclofenac potassium tablets based on SRMS had good sustained release properties for once daily administration.

KEYWORDS: Diclofenac potassium, sustained release tablets, SRMS, lipids

INTRODUCTION

Diclofenac potassium is one of the routinely prescribed anti-inflammatory agents available for the management of pain and inflammation. It is marketed as injections, oral normal release and sustained release tablets and topical formulations. The drug is sparingly soluble in water and almost completely absorbed after oral administration, but it is subjected to approximately 50 % hepatic first pass metabolism. However, diclofenac has a short half life of 1 – 2 hours and like other nonsteroidal anti-inflammatory drugs (NSAIDs), it causes gastrointestinal irritation [1]. Owing to the short biological half life of this NSAID, a sustained action dosage form would be preferable, so as to reduce the frequency of administration, enhance patient compliance, and improve the bioavailability profile of the drug.

SRMS based carriers have been investigated, and successfully employed to achieve controlled release of drugs [2 - 5]. Solidified reverse micellar solution (SRMS) consisting of phospholipid and solid lipid such as Softisan® 154, a completely hydrogenated palm oil transform into a lamellar mesophase after melting on contact with water. This transformation enables controlled release of solubilized drugs. SRMs also offer a high solubilization rate of different types of drugs [4].

Homolipids (waxes, fats, oils) and heterolipids (phospholipids) have gained renewed interests as excipients for oral drug delivery of lipophilic drugs. The reasons for the increasing interest in lipid based systems include an improved understanding of the manner in which lipids enhance oral

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bioavailability and reduce plasma profile variability, better characterization of lipidic excipients, formulation versatility, the choice of different drug delivery systems, an improved ability to address the key issues of technology transfer and production scale up [6]. Lipid excipients are generally regarded as safe (GRAS) and have been proven to be non – toxic. Lipids are relatively cheap and widely distributed in nature. Most lipids do not exert pharmacological effect. They have high stability and high carrier capacity [7]. Lipid-based formulations can be used to influence the absorption of active ingredients through different mechanisms to modify the release of active ingredients thus, improving the bioavailability. They can affect the intestinal environment, stimulate the lymphatic transport of active ingredients, and interact with enterocyte-based transport [8]. For poorly water soluble drug molecules, whose dissolution in water is likely the limiting step of overall oral absorption, the primary role of ingested lipids and their lipolytic products is to impact the drug dissolution step by forming – with bile components – different colloidal particles, which are able to maintain a larger quantity of hydrophobic drugs in solution via micellar solubilization [9]. The primary mechanism of action which leads to improved bioavailability is usually avoidance or partial avoidance of slow dissolution process which limits the bioavailability of hydrophobic drugs from conventional solid dosage forms [10]. Lipid formulations generally provide increased drug solubilization for water insoluble drugs. Lipid-based formulations have been shown to enhance the bioavailability of drugs administered orally [11 -15].

The objectives of the work were to formulate diclofenac potassium sustained release tablets based on SRMS and to evaluate the *in vitro* properties of the tablets *vis-a-vis* commercial brands for sustained release properties.

MATERIALS AND METHODS

Adult wistar rats of both sexes weighing between Diclofenac potassium (Healthy Life Pharma, India), Softisan® 154 (Schuppen, Condea Chemie GmbH, Germany), Phospholipon® 90H (Phospholipid GmbH, Köln, Germany), hydrochloric acid, sodium hydroxide, monobasic potassium phosphate (BDH, Poole, England), distilled water (Lion water, Nsukka, Nigeria). Plastic mould used was constructed in the Faculty of Engineering, University of Nigeria, Nsukka. All other reagents and solvents were analytical grade and were used as supplied.

Preparation of solidified reverse micellar solutions (SRMS)

A 1:1, 1:2 and 2:1 quantity of Phospholipon® 90H, and Softisan® 154, were prepared by fusion. In each case the lipids were weighed, melted together and stirred at a temperature of 70 ^{o}C using a magnetic stirrer, until a homogenous, transparent white melt was obtained. The homogenous mixture was stirred at room temperature until solidification [15].

CHARACTERISATION OF LIPID MATRICES

Differential scanning calorimetric analysis

The DSC thermograms of Phospholipon® 90H, Softisan® 154, diclofenac potassium, SRMS 1:1, 2:1and 1:2, were obtained using differential scanning calorimeter (Netzsch DSC 204 F1, Germany). About 10 mg of each SRMS (1:1, 1:2 and 2:1) was weighed into aluminum pan, hermetically sealed and the thermal behaviour determined in the range 20–400 ^{o}C, at a heating rate of 10 k/min under a 20 ml/min nitrogen flux. The thermal properties of pure Softisan® 154 and Phospholipon® 90H were also determined in the range 34 – 400 C and 20 – 200 ^{o}C respectively. Diclofenac potassium (10 mg) was determined at temperature range of 32 – 400 ^{o}C.

Preparation of diclofenac potassium micellar tablets

The plastic mould employed in formulating the tablets was validated by formulating bland or unloaded tablets using the lipid matrices. Also, the concepts of biopharmaceutics, i.e. absorption, distribution, metabolism and excretion were considered in the design of the sustained release tablets [16]. Based on this, the required dose of diclofenac potassium to achieve daily sustained blood level was calculated. Pharmacokinetic studies showed that a dose of 25 mg of diclofenac potassium produces an effective blood level concentration of 0.7 – 1.5 µg/ml within 1.5 – 2.5 h with a half life of 1.1 – 4.0 h [1,16].

Thus elimination rate constant

$$K = \frac{0.693}{t_{1/2}} \text{------(1)}$$

$$\left[0.693/4 = 0.1732\ mg/h\right].$$

Hence the availability rate $\mathrm{R} = \mathrm{k} \times \mathrm{D}$ ---------- (2)

$0.1732 \times 25 = 4.3\ \mathrm{mg/h}$, where D is the usual dose of the drug.

The maintenance dose $\mathrm{Dm} = \mathrm{R} \times \mathrm{h}$ ---------- (3)

$4.3 \text{ x } 20 = 86 \text{ mg}$, where h is the number of hours for which sustained action is desired.

Thus, $\text{total dose} = D + Dm$ ..... (4)

$25 + 86 = 111 \text{ mg}$

$D\text{corrected} = D - Rtp$ ---------- (5)

$25 - (4.3 \text{ x } 2) = 164 \text{ mg}$,

where t_p is the time period required to achieve a peak plasma level.

Therefore, $\text{total dose corrected} = \text{corrected} + Dm$-------(6)

= 16.4 + 86 = 102.4 mg.

With reference to the average weight of the bland tablets prepared with 1:1, 1:2 and 2:1 w/w of SRMS, the amount of diclofenac potassium to be incorporated into each tablet was calculated.

Each of the SRMS was weighed out and placed in a crucible. This was melted at 70 ^{o}C using a magnetic stirrer hot plate. The required amount of the active ingredient was weighed out and transferred quantitatively into the melted lipid matrix in the crucible with stirring. This was stirred in clockwise manner until a homogenous mix was obtained. The homogenous mix was scooped into the wells of the mould with a clean stainless spoon. It was allowed to solidify, scraped and allowed to dry at room temperature. The tablets were pressed out of the plastic mould and allowed to dry properly at room temperature.

CHARACTERIZATION OF THE TABLETS

Determination of size and surface characteristics of the tablets

The shape, colour and size of the tablets were analyzed using tablets randomly selected from each batch (n = 20). The size was determined by the use of venier caliper to determine the tablet thickness and diameter, while the shape and colour of the tablets were determined visually by placing the tablets on a plain white sheath of paper; also the photographs of the tablets were taken.

Uniformity of weight

Twenty tablets were randomly selected from each batch. The tablets were weighed individually using an electronic balance (Ohaus Adventurer, China) and the individual weights recorded. The mean weight, standard deviation and percentage deviation were calculated [17].

Tablet friability test

The friability test was performed using Erweka friabilator (Erweka GmbH, Germany). Twenty tablets were randomly selected from each batch of the tablets. The tablets were dedusted and weighed. The tablets were placed in the drum of the friabilator and rotated at 25 rpm for 4 min. The tablets were removed from the friabilator, dedusted again and reweighed. The friability loss was calculated from the equation below:

$$\text{Friability loss}\,(\%) = 100\left[1 - \frac{W}{W_o}\right] \quad \text{.... (7)}$$

Where, W_o and W are the initial weight and final weight of the tablets respectively [17,18].

Hardness test

This test was carried out using Monsanto-Stokes hardness tester (Manesty, England). Ten tablets from each batch were randomly selected. Each tablet was placed between the jaws of the hardness tester and force was applied by adjusting the knob of tester until the tablet integrity failed. The results were recorded in kgf.

Erosion time test

A method described in the European Pharmacopoeia was adopted and modified [18]. The test was carried out for each batch of the tablet using a beaker containing 500 ml of distilled water and placed on a magnetic stirrer hot plate (Gallenkamp, England). The medium was maintained at 37 $\pm$ 1 ^{o}C and a thermometer was inserted into the medium to maintain the temperature. An inner compartment containing 3 tablets from each batch was tied with a thermo-resistant thread unto a resort stand, and immersed into the medium. The medium was stirred at 100 rpm with a magnetic stirrer bar. The erosion time was taken as the time taken for the tablet to change in shape and erode appreciably. This test was repeated three times for each batch and the mean erosion time was determined.

Assay of active ingredient

Beer's calibration curve was obtained at a concentration range of 0.1 – 1.0 mg % for diclofenac potassium in distilled water at a predetermined wavelength of 297 nm. Twenty tablets were randomly selected from each batch of

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the tablets. The tablets were weighed together and crushed in a mortar with a pestle. An amount equivalent to the average weight of the crushed tablet was weighed out in an analytical balance and dispersed in distilled water. The dispersion was heated for 30 min at 70 ^{o}C using a magnetic stirrer hot plate, to enhance dispersion. This dispersion was allowed to cool, filtered (Whatman No. 1) and an aliquot of the filtrate was assayed using a spectrophotometer (Jenway 6305, UK) at a predetermined wavelength of 297 nm. The absorbance was recorded and the concentration of diclofenac potassium calculated with reference to the Beer's plot.

***In vitro* release studies**

The USP paddle method was adopted in the study. The dissolution medium consisted of 900 ml of freshly prepared SIF (pH 7.5). The temperature of the medium was maintained at 37 $\pm$ 1 ^{o}C. A tablet from each batch was placed inside a tightly secured basket and the basket was placed in the bottom of the beaker. The paddle was rotated at 100 rpm. At various intervals, 5 ml sample was withdrawn from the dissolution medium, filtered with a non adsorbent filter paper (Whatman No.1) and analysed for the drug content using UV-spectrophotometer (Jenway 6305, UK) at 303 nm. An equal volume of the withdrawn sample was replaced with a fresh medium to maintain sink condition. The amount of drug released at each time interval was determined with reference to the standard Beer's plot for diclofenac potassium.

***In vitro* release kinetics**

The dissolution data for the tablets were analysed to determine the *in vitro* release kinetic mechanism using three kinetic models including the first order equation, Higuchi square root equation and Ritger-Peppas empirical model As follows:

$$\ln Q_t = \ln Q_0 - K_1 t \quad \text{----------} \quad (8)$$

$$Q_t = K_2 t^{1/2} \quad \text{----------} \quad (9)$$

$$M_t/M_\infty = K_3 t^n \quad \text{----------} \quad (10)$$

where Q_t is the amount of drug released or dissolved at time t, Q_0 is amount of drug released or dissolved at time t = 0, K_1, K_2 and K_3 are first-order, Higuchi and Ritger-Peppas release rate constants, M_t/M_∞ is fraction of drug released at time t, n is diffusion exponent and is indicator of the mechanism of transport of drug through the matrix [19-21].

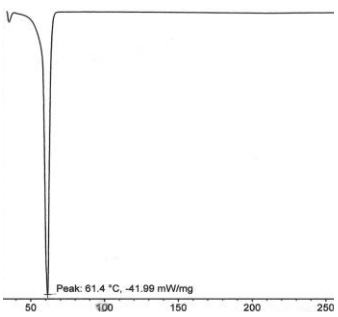
Statistical analysis

Statistical analysis was done using SPSS version 14.0 (SPSS Inc. Chicago, IL.USA). Differences between means were assessed by a two-tailed student's t-test. $P < 0.05$ was considered statistically significant.

RESULTS AND DISCUSSION

Differential scanning calorimetry (DSC)

DSC measurements were carried out in order to determine the thermotropic behaviours of diclofenac potassium, Softisan®, Phospholipon® 90H, SRMS 1:1, 2:1 and 1:2. The results of DSC presented in Fig.1 show that the DSC curve of Softisan® 154 showed a narrow endothermic peak, with melting peak at temperature 61.4 ^{o}C. The narrow melting peak indicated that Softisan®154 is a high purity lipid. Phospholipon® 90H showed endotherm at temperature of 124 ^{o}C. The curve shows that Phospholipon® 90H consist entirely of stable form because of the sharp melting peak seen. From the results, the thermogram of diclofenac potassium pure sample showed a sharp melting peak at 311.4 ^{o}C. The exothermic, sharp melting peak showed that diclofenac potassium used was pure and crystalline, as this is comparable to the melting point reported for diclofenac in BP [17]. The DSC results of the lipid matrices showed that the structuring of Softisan® 154 with P90H generally produced matrices with low enthalpies. Reduction in enthalpy generally suggests less crystallinity of lipid matrices [4,15]. The varied fatty acid contents of these lipids may have interacted in such a manner as to partly disorder the crystal arrangement of the individual lipids [4]. Therefore, SRMS 1:1, 2:1 and 1:2 generated imperfect matrices (due to distortion of crystal arrangement of individual lipids after melting and solidification), which may have created numerous spaces for drug localization [4].



(a)

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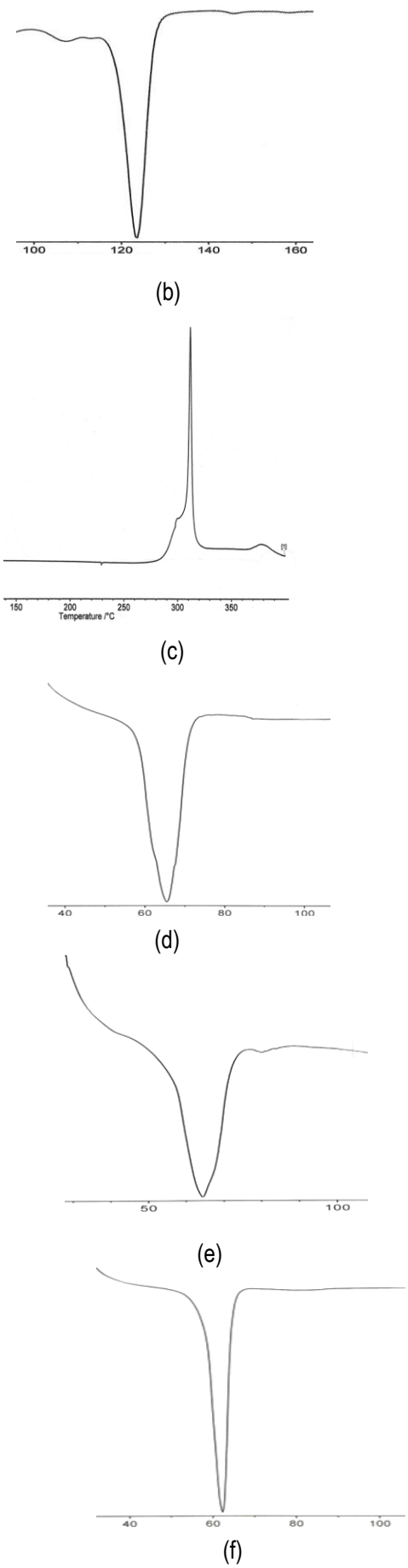

Fig 1. DSC thermograms of: (a) Softisan® 154, (b): Phospholipon® 90H, (c): Diclofenac potassium, (d): SRMS 1:1, (e): SRMS 2:1, (f): SRMS 1:2.

Dimensional properties

The results of the dimensional properties of diclofenac potassium tablets are shown in Table 1. The tablets exhibited stable thickness that ranged from 0.33 ± 0.02 to 0.34 ± 0.02 cm and a stable diameter of 1.20 ± 0.01 cm in all the batches. The tablets were smooth and spherical and were devoid of cracks in all the batches.

Weight uniformity

The results of tablets weight uniformity tests are shown in Table 1. The results show that the tablets weight ranged from 370.0 ± 0.4 to 379.0 ± 0.3 mg. The tablets had percentage deviation significantly lower than 5 % ($p < 0.05$) and therefore, complied with BP specifications for weight uniformity of tablets ≥ 250 mg [17]. Tablets weight uniformity test are important because variation in tablets weight causes variation in drug content and overall bioavailability of the drug. This result also attests to the reproducibility of the formulations and reliability of the production process.

Tablets friability

The results of tablets friability presented in Table 1 show that the tablets exhibited percentage friability of 0.05 to 0.11 % and complied with BP specifications for tablets friability [17]. The tablets could withstand shock and vibrations during handling, packaging, transportation and use.

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Table 1: Properties of diclofenac potassium sustained release tablets

Batch	Diameter (cm)*	Thickness (cm)*	Weight (mg ± CV)*	Hardness (kgf)[a]	Friability (%)*	Erosion Time (min)[a]	Drug content (mg ± CV)*
F1 (1:1)	1.20 ± 0.01	0.34 ± 0.02	370.0 ± 0.4	5.10 ± 0.39	0.08	65.30 ± 0.70	100.00 ± 0.46
F2 (2:1)	1.20 ± 0.01	0.34 ± 0.01	373.0 ± 0.4	5.00 ± 0.47	0.05	120.00 ± 0.32	100.16 ± 0.28
F3 (1:2)	1.20 ± 0.01	0.33 ± 0.02	379.0 ± 0.3	5.00 ± 0.50	0.11	36.00 ± 1.10	100.18 ± 0.32

*Mean for 20 tablets ± SD, [a]Mean for 10 tablets ± SD, CV: coefficient of variation SD: standard deviation, F1-F3: diclofenac potassium tablets.

Tablets hardness

The results of tablets hardness also presented in Table 1 show that the hardness ranged from 5.00 to 5.10 kgf in all the batches. The tablets complied with BP specifications for tablets hardness of 5 – 8 kgf [17]. The results revealed that the mechanical properties of the tablets would not be compromised by long term storage.

Erosion time

The results of erosion time of tablets are also shown in Table 1 and the results show that tablets erosion time ranged from 36.00 ± 1.10 to 120.00 ± 0.32 min for F3 and F2 tablets formulated with SRMS 1:2 and 2:1 (P90H:Softisan® 154). The erosion time of the tablets was therefore, affected by the ratio of the two lipids used. The results indicate that increase in phospholipid concentration increased the erosion time of the tablets. The tablets however, complied with specifications for sustained release tablets. Sustained release preparation and enteric coated tablets are expected to disintegrate or erode appreciably in simulated intestinal fluid within 2 hours [22].

Content of active ingredient

From the results of drug content presented in Table 1, all the tablet batches complied with the BP standard for assay of active ingredient [17]. All the tablets were within the range of 90 % to 110 % of the average value. The result showed that the drug was not lost either by physical or chemical means. The low coefficient of variation of the drug contents also confirms the reproducibility of the formulation and the production process.

***In vitro* release**

The results of release studies presented in Fig 2 show that diclofenac potassium tablets formulated with SRMS 1:1 had maximum release at 8 h (batch F1), while SRMS 2:1 and 1:2 (batches F2 and F3) had maximum drug release at 11 and 10 h respectively. The release rate of diclofenac potassium from tablet formulations was comparable to the release rate of commercial brand of diclofenac potassium sustained release tablets which had maximum release at 9 h. The drug release parameter shown in Table 2 show that at T_{25} (25 min), 13 %, 21 %, and 16 % diclofenac potassium were released from tablets formulated with SRMS 1:1, 2:1 and 1:2 respectively, while 13.1 % was released from the reference drug. At T_{50} (50 min), 17.5 %, 34 %, and 34.5 % diclofenac were released from tablets formulated with SRMS 1:1, 2:1 and 1:2 respectively, while 24 % of diclofenac potassium was released from reference tablets. At 90 min (T_{90}), 23 %, 40 %, 41 % and 30 % diclofenac potassium were released from SRMS 1:1, 2:1, 1:2 and reference drug respectively. Therefore, the ratio of phospholipid in the SRMS affected the rate of drug release. Increase in phospholipid ratio prolonged the rate of drug release. The results indicate that the formulations had good sustained release properties for once daily administration.

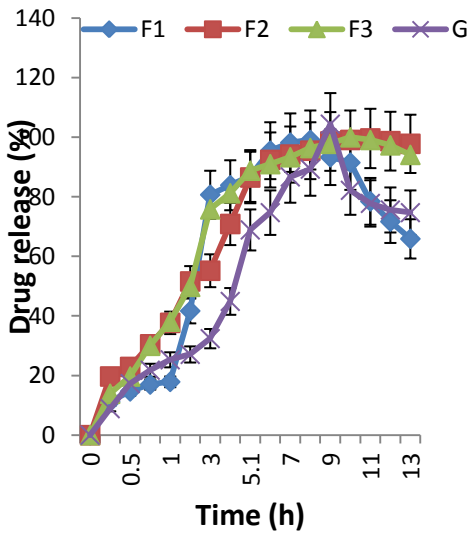

Fig. 2. Release profile of three batches of diclofenac potassium sustained release tablets formulated with SRMS 1:1, 2:1 and 1:2 respectively (F1, F2, F3) and a market brand of sustained release diclofenac potassium (batch G).

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Table 2. Dissolution parameters for sustained release diclofenac potassium tablets

Batch/LM ratio	T_{25} (%)	T_{50} (%)	T_{90} (%)
F1 (1:1)	13.0	17.5	23.0
F2 (2:1)	21.3	31.0	33.0
F3 (1:2)	16.8	24.0	34.0
G (Reference)	13.1	24.0	30.0

Batches F1, F2 and F3 are diclofenac potassium tablets formulated with SRMS 1:1, 2:1 and 1:2 respectively, G represents commercial diclofenac potassium tablets

Drug release kinetics and mechanisms

The drug release kinetics and mechanisms of the tablets were studied using three models including the first order, Higuchi and Ritger-Peppas models. The results presented in Table 3 indicate that the Higuchi plot of amount of drug released against square root of time was linear for all the batches of diclofenac potassium tablet formulations (r^2 = 0.9). However, the plot of the integral form of Higuchi exhibited n value of 0.5 for F2 tablets, which confirmed that diffusion controlled process was the predominant mechanism of drug release [23]. However, F1 and F3 showed n values that were above 0.5, which showed that diffusion controlled process were not the only predominant release mechanism. The first order models were also linear. This showed that the release mechanism was of mixed order. The Ritger – Peppas model for diclofenac potassium showed that the tablet formulations followed a non Fickian release process (anomalous) 0.45 < n < 1.00. Therefore, mechanisms of drug release were by diffusion and erosion from a non swellable matrix [20-21]. These results are in agreement with the report of Schwartz *et al*. [24-25], who reported that the kinetic data from some inert whole wax matrix tablets conformed to both first order and the Higuchi model.

Table 3. Release kinetics of sustained release diclofenac potassium tablets

Batch	Higuchi		First order	Ritger-Peppas	
	(r^2)	(n)	(r^2)	(r^2)	(n)
F1	0.940	0.580	0.9038	0.951	0.740
F2	0.982	0.495	0.9156	0.985	0.496
F3	0.962	1.338	0.9620	0.974	0.580

F1-F3: diclofenac potassium tablets based on SRMS

CONCLUSION

Solidified reverse micellar solution (SRMS) consisting of Phospholipid and triglyceride presented good sustained release matrix for once daily administration of diclofenac potassium. The tablets exhibited good hardness-friability profile and had stable thickness and diameter. The tablets showed higher sustained release properties than the reference tablet. Therefore, further research into this field is highly encouraged in order to further characterize this formulation approach while taking into account the possibilities for scale-up of this formulation.

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