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Formulation and *In Vitro-In Vivo* Evaluation of the Properties of Diclofenac Potassium Suppositories

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Abstract

Background: Diclofenac potassium (DP) is a nonsteroidal anti-inflammatory drug used for the management of pain and inflammation, however, it may cause gastric ulceration when given orally, depending on the nature of the formulation. In order to circumvent this, we explored the formulation of DP rectal suppositories.

Aim: To prepare diclofenac potassium suppositories in order to prevent the gastric ulceration caused by DP when given by oral administration.

Materials and methods: The suppository base were prepared using polyethylene glycol 4000 and Suppocire at varying ratios. Diclofenac potassium suppositories were prepared by fusion. Analysis were made on the suppositories viz physical appearance, weight variation, disintegration study, uniformity content, hardness, in vitro dissolution study and melting point test. The anti-inflammatory properties were studied using Wistar rats.

Results: The suppositories had smooth appearance, suppositories weight ranged from 1.19 ± 0.07 g to 1.31 ± 0.07 g, drug content ranged from 99 to 101 % and melting point of 37.1 ± 0.08 oC was recorded. The suppositories showed stable hardness of 1.2 Kgf and highest disintegration time 24 ± 0.06 min. Drug release was significantly enhanced by the content of Suppocire in the lipid matrix with highest release of 92.60 % at 60 min by formulations containing the highest content of Suppocire®. The anti-inflammatory properties showed that the formulation showed about 49 % 78 % oedema inhibition at 5 h.

Conclusion: Diclofenac potassium suppositories showed good in vitro and anti-inflammatory properties and could be a better delivery system for this drug in order to circumvent gastric ulceration.

Keywords: Anti-Inflammatory Properties; Diclofenac Potassium; NSAIDs; Rectal Suppositories; PEG 4000; Suppocire; Quality Control of Suppositories

Abbreviations: DP: Diclofenac Potassium; NSAID: Non-Steroidal Anti-Inflammatory Drug.

Introduction

Suppositories are solid single unit dosage forms containing active compound usually solubilized or suspended in the base(s), and melts or solubilizes at physiological conditions in order to releases its medicament which may be for local or systemic action [1-3]. Although the oral DDS is considered the most convenient route for drug administration, but some conditions warrant drug administration via other routes like the rectal route which may represent a better alternative route for certain drugs for local and systemic actions [4,5].

In Drug delivery, the rectal route is useful for drugs that are poorly water soluble and have poor permeability and stability following oral administration. It is ideal route of administration when oral ingestion is not feasible especially in patients having nausea and vomiting, in unconscious patients and patients with significant swallowing problems especially some pediatric and geriatric patients. The rectal surface area is smaller than those of the small intestine, however, the rectum relatively stable and have sufficient surface area for drug absorption Jannin V, et al. [6] hence, allows for a constant and reproducible drug absorption with minimal enzymatic activity than other areas of the of the gastrointestinal tract. Also, drugs could be administered in a way as to bypass the liver partly, following systemic absorption, hence, minimizes the hepatic first-pass effect [4]. Hence, rectal suppositories and indeed rectal DDS is utilized and recommended for drugs that undergo high hepatic first-pass metabolism, having limited absorption in the upper GIT, drugs readily degraded and unstable in the GIT, drugs like NSAIDs with significant gastric irritation tendency, and for local action in the distal colon or rectum [7-9].

The suppository would have to be retained in the rectum for some time frame for localized action or systemic absorption to take place [10]. This contact time of drug with the rectal mucosa is vital for the efficacy of drugs in the suppository. For adequate and effective drug efficacy and absorption after administration of rectal suppositories, the drugs would be able to penetrate the mucus layer reaching the rectal epithelial cells lining, bearing in mind that the rectal mucosa is composed majorly of mucins and water forming a fluid layer thickness of range of about 75–250 μm Pullan RD, et al. [11] and Johansson ME, et al. [12] with an estimated turnover time of 3–4 layer which can acts as barriers for the absorption of drugs [4,7]. Hence, adequate selection of bases that would ensure timely and adequate release of drugs from suppositories is vital during pre-formulation processes of suppository development. In this work, a water soluble base PEG 4000 and Suppocire bases were selected for use in other to ensure good stability and effective drug release of diclofenac potassium. Suppocire is hard fat suppository base comprising polyoxylglyceride esters to improve dispersion of hydrophilic APIs in aqueous solutions and enhance absorption [13].

Diclofenac potassium is a non-steroidal anti-inflammatory drug (NSAID) used especially in geriatrics for the management of pain and inflammation. However, like other NSAIDS it could predispose patients to gastric ulceration when given orally [14-16]. Efforts have recently been made to develop gastro intestinally safe NSAIDs on the basis of a reduced ability to interfere with the surface-active phospholipid layer in the gastrointestinal mucus [15,16]. Hence, we report an alternative delivery system for diclofenac potassium by rectal administration in other to avoid gastric irritation posed by oral administration of this drug and to produce drugs that can be used especially when the patient is unable to swallow drugs.

Materials and Methods

Diclofenac potassium, polyethylene glycol 4000 (PEG 4000), sodium hydroxide, potassium dihydrogen phosphate (Merck, Darmstadt, Germany), distilled water (UNN Water Resources, Nsukka, Nigeria), and Suppocire (Gattefosse, Nanterre, France).

Methods

Preparation of Diclofenac Potassium Suppositories

The suppository molds were calibrated using the bases, thereafter, a 100 mg dose of diclofenac potassium suppositories was prepared by fusion method using varying ratios of Suppocire and PEG 4000. The displacement factors were calculated using established procedures and the bases were both melted together at 40°C in a crucible (at different ratios 1:1, 1:2 and 2:1 PEG 4000: Suppocire for batches A, B, and C respectively). The drug was incorporated, mixed properly and after transferred into the wells of the suppository moulds. The suppositories were allowed to solidify at room temperature, removed after cooling and stored in refrigerator.

***In Vitro* Evaluation of Suppositories**

- **Physical Characterization**

The randomly selected suppositories from each formulation were visually examined for colour, shape, and general appearance in terms of the absence of fissuring and pitting.

- **Weight Uniformity Test**

Twenty suppositories were randomly selected from each batch and were subjected to weight variation test where. The selected suppositories were weighed individually using digital electronic balance (Sartious AG, Gottingen, Germany) and the weights of suppositories were noted and average weight was calculated.

- **Hardness Test**

This test was done using Erweka hardness tester (Type SBT, West Germany) where each of the suppository batch formulations were placed between the two gripping ends of the adjusted hardness test instrument and with the application of screwing force, the diclofenac potassium suppositories were broken and thereafter the readings were taken.

- **Disintegration Test**

The disintegration time test of the suppositories was carried out using disintegration time equipment (Erweka GmbH, Germany). Ten suppositories were randomly chosen from

each formulation and placed in the disintegration apparatus and the temperature was maintained at 37°C.

- **Content Uniformity Test**

Ten randomly selected suppositories were individually tested for content uniformity. Each suppository was dispersed in 100 ml of phosphate buffer solution at 37°C, filtered, diluted and analysed in the UV spectrophotometer for drug content at predetermined wavelength of 277nm.

- **Melting Test**

The melting points of the suppositories were determined by using STUART® SMP 30 melting point apparatus. The melting temperature was taken as the temperature when the suppositories started to melt.

In Vitro Dissolution Studies

The *in vitro* dissolution studies of suppositories were carried out by using tablet dissolution tester (Pharm test, Type PTW Germany). In this study 500ml of phosphate buffer pH 7.4 maintained at 37°C was used as dissolution medium. The suppositories were placed in the basket and the rate of stirring at 100 rpm. At time intervals, 5 ml of samples were collected, filtered and analysed in a UV spectrophotometer (UNICO 2102 PC UV/Vis Spectrophotometer, USA). Sink condition was maintained by replacing with 5 ml of fresh dissolution medium.

In Vitro Release Kinetics

Various kinetic models were used to describe the in vitro release kinetics and mechanisms of release of drug from the suppositories. The zero-order kinetics describes the systems where the drug release rate is independent of its concentration (Equation 1). The first order Equation (Equation 2) describes the release from systems where release rate is concentration dependent. Higuchi T [17] described the release of drugs from insoluble matrix as a square root of time dependent process based on Fickian diffusion (Equation 3) [17-20]:

$$Q = k_0 t \quad \text{..... (1)}$$

$$\log Q_0 - \log Q_t = k_1 t / 2.303 \quad \text{..... (2)}$$

$$Q = K_2 t^{1/2} \quad \text{..... (3)}$$

Where Q is the amount of drug released or dissolved at time t, Q0 is the initial concentration of drug, k0, k1, k2 and k3 are zero-order, first-order and Higuchi kinetic constant respectively. Mt/M∝ is fraction of drug released at time t, n is diffusion exponent and is indicative of the mechanism of transport of drug through the matrix. The following plots were made: cumulative drug release versus time (zero-order), log cumulative of % drug remaining vs. time (first order kinetic model), cumulative % drug release vs. square root of time (Higuchi model) and the integral form of Higuchi and log fraction of drug release versus log time [17-20].

Anti-inflammatory Studies

The acute anti-inflammatory activity of the suppositories formulated with varying concentrations of the bases were investigated [21]. All the animal experiments were conducted in accordance with guidelines established by the Institutional Animal Care and Use Committee of University of Nigeria, Nsukka, and adhered to the European Community guidelines for the use of experimental animals (86/609/EEC). The phlogistic agent employed in the study was fresh undiluted egg albumin [22,23]. Adult Wister rats (110– 150 g) of either sex were used for the experiment. The animals were fasted and deprived of water for 12 h before the experiment. The deprivation of water was to ensure uniform hydration and to minimize variability in oedematous response [23]. The rats were divided into five groups of animals (n=5) per group. The control received blank or placebo suppository bases whereas the reference group received commercially obtained suppositories (5 mg/kg). The other three groups received suppository batch formulation of A, B and C containing PEG 4000/Suppocire in a combination ratio of 1:1, 1:2 and 2:1 respectively equivalent to 5 mg/kg diclofenac potassium per body weight was administered rectally to the rats [16]. Acute inflammation was induced by sub-planter injection of 0.1 ml of fresh egg albumin into the right hand paw of each rat. The test drug was administered 60 minutes before the induction of edema. The paw volume was determined by water displacement method using plethysmometer before and at 1, 2, 3, 4 and 5 hours after the injection of egg albumin. The percentage inhibition of edema was calculated using the formula:

$$\%inhibition = \frac{1 - Vt}{Vo} \times 100 \quad \text{..... (4)}$$

Where Vo and Vt are edema volume of control and treated group respectively at the corresponding time [16,24].

Statistical Analysis

Statistical analysis was done using SPSS version 26 (SPSS Inc., Chicago, IL). All values were expressed as mean ± standard deviation (SD). Data were analysed by one-way ANOVA. Differences between means were assessed by a two-tailed student's t-test; $p < 0.05$ was considered statistically significant.

Results and Discussion

Physicochemical Properties

The results of the morphology and physical characteristics of the suppositories showed that white, smooth, and

conical shape suppositories that were devoid of pitting and cracks were formulated. The suppositories were stable at room temperature and hence had good morphological characteristics.

The results of the weight uniformity tests of suppositories are shown in Table 1 and showed that the suppositories had stable weight of 1.2 to 1.3 g and passed the test for weight uniformity with deviations significantly lower ($p<0.05$) than 5 % recommended for suppositories in the compendium. Weight uniformity is an important quality control tests of any dosage form because it affects the overall bioavailability of drugs, determines efficacy and also the treatment outcomes. Weight uniformity affects content uniformity and hence is considered as one of the most important test after drug formulation.

Batch	Weight (g)	Melting point (°C)	Disintegration time (min)	Hardness (KgF)	Drug content (%)
A	1.25 ± 0.09	37.1 ± 0.08	20.40 ± 0.05	1	99 ± 0.075
B	1.20 ± 0.07	37.1 ± 0.05	17.70 ± 0.08	1.1	99 ± 0.095
C	1.30 ± 0.07	37.2 ± 0.04	23.49 ± 0.06	1.2	101 ± 0.057

Batches A, B and C were formulated with PEG4000: Suppocire ratios 1:1, 1:2 and 2:1 respectively.

Table 1: Physicochemical properties of diclofenac potassium suppositories.

The results of the melting range tests of suppositories are also shown in Table 1 and show that the suppositories melted at 37 oC which is the acceptable melting point of rectal suppositories, the reults showed that the formulations would be able to melt in the rectum in order to release the drug contained in it for possible absorption.

The results of the drug content of suppositories are shown in Table 1 and showed that the formulations passed the tests for drug content of suppositories confirmining that the drugs were intact and was not affected by formulation processes nor the materials. The uniform weight obytained per batch of suppository also helped to ensure that each of the formulations had target drug content formulated. The variation within the batches were not significant ($p<0.05$). The unit dose also showed that the suppositories were mint for adults and not children.

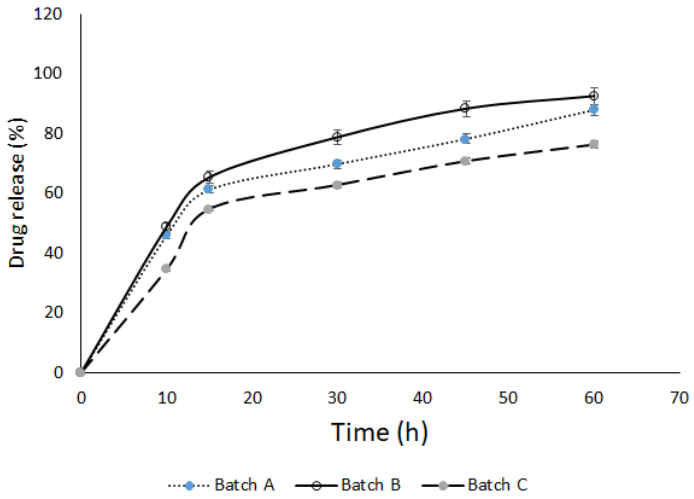
The results of the disintegration time of suppositories are also shown in Table 1 and showed that disintegration time was significantly affected by the combination of the bases used ($p<0.05$). Batch B containing 1: 2 of PEG 4000 to Suppocire had the least disintegration time of 17.7 min, while the batch with higher amount of PEG (2:1 PEG 4000: Sppocire) i.e. Batch C had mean disintegration time of 23.5 min. However, all the formulations passed the tests for disintegration time and were within 30 min for fat base suppositories, and 60 min stipulated for rectal suppositories with water soluble bases like PEG 4000.

The results of hardness or crushing strength of suppositories are also shown in Table 1 and showed that the formulations had sufficient mechanical strength to withstand handling during packaging and use.

In Vitro Drug Release and Release Kinetics

The results of in vitro release kinetics studied in phosphate buffer Ph 7.4 are shown in Figure 1 and show that the formulations had about 62 to 78 % drug release range at 30 min in all the batches. At 60 min, about 76 to 92 % of drug were released from Batches C formulated with PEG4000 and Suppocire ratios 2:1 and batch B formulated with 1:2. Hence, Batch C had more controlled release of drug over time, followed by batch A with ratios 1:1. Hence, the formulation exhibited normal release of diclofenac over time and is therefore, suitable for formulating normal release diclofenac potassium rather than sustained release at concentrations used.

The results of the in vitro release kinetics and mechanisms of drug release from the suppositories shown in Table 2 showed that Higuchi models were suitablly employed and the data showed that this model was adequate as confirmed by the regression values (r^2) obtained from the graphs. Higuchi model comnfirmed that drug release was not solely by diffusion ('n' not equal to 0.5 as shown in Table 2), hence other mechanisms such as erosion and dissolution were implicated as the mechanisms of drug release from the dosage form. However, the kinetics of release studied using zero and first order showed that first order release kinetics were followed, hence, drug release was also dependent on concentration of drug. Zero –order plots were not linear, hence was not further presented, hence the drug release did not follow Zero-order release kinetics.



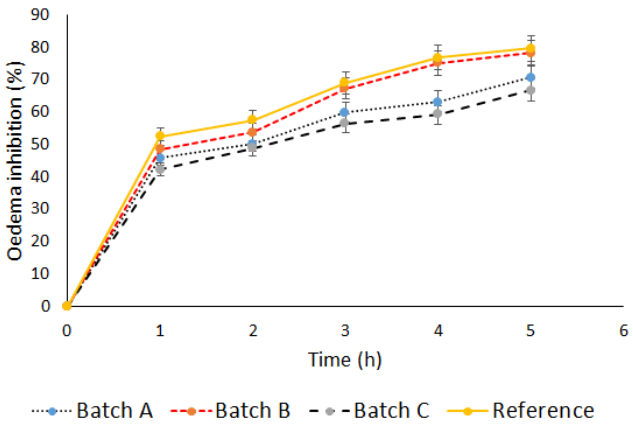
Batches A, B and C were formulated with PEG4000: Suppocire ratios 1:1, 1:2 and 2:1 respectively.
Figure 1: In vitro dissolution rate of diclofenac potassium from suppositories.

Batch	First order (r^2)	Higuchi (r^2)	Higuchi Integral (n)
A	0.97	0.9542	0.3271
B	0.9887	0.9519	0.34
C	0.9293	0.9507	0.3917

Table 2: In vitro drug release kinetic of release of diclofenac potassium from suppositories.

Anti-Inflammatory Properties

The results of the anti-inflammatory properties of diclofenac potassium rectal suppositories are shown in Figure 2 and showed that the formulations had good anti-inflammatory properties comparable to the commercial diclofenac potassium suppository used as the reference ($p< 0.05$). In vivo performance was also comparable to in vitro drug release. Batch B with ratio 1:2 (PEG to Suppocire) had higher anti-inflammatory properties significantly higher than Batch A and B (1:1 and 2:1 PEG to Suppocire). Hence, the formulation could be adopted as a safe and relatively cheap method for formulating diclofenac potassium in order to circumvent the GIT side effects of this drug when taken orally.



Batches A, B and C were formulated with PEG4000: Suppocire ratios 1:1, 1:2 and 2:1 respectively.
Figure 2: Anti-inflammatory properties of diclofenac potassium suppositories.

Conclusion

Rectal suppositories containing diclofenac potassium could be a safer alternative to oral delivery of this drug especially in geriatric for the management of various degrees of pain associated with arthritis. PEG 4000 being water soluble bases combined effectively with fatty base and gave stable formulations that were stable at room temperature. The materials involved in the formulations were relatively inexpensive and the processes involved in formulation and analysis are simple compared to oral dosage forms. Therefore, this formulation has potential of being scaled up easily with minimal equipment, desk space and staff requirement. Hence, a further study on this work is recommended.

Conflict of Interest

The authors state no conflict of interest.

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