Formulation of subcutaneous implantable drug delivery system of ibuprofen using biodegradable polymers

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ABSTRACT

Background: The purpose of this study was to formulate subcutaneous implantable drug delivery system of ibuprofen using biodegradable polymers and to evaluate the formulated implants using *in vitro* and *in vivo* models.

***Methods*:** The solvent casting technique was used in the formulation of the implants with gelatin-hydroxypropyl methylcellulose (HPMC) admixture (80:20) as the polymer blend. The plasticizing agent used was glycerin. The physicochemical properties of the implants were evaluated. The implants *in vivo* analgesic effect on acetic acid-induced mouse writhing in mice was also investigated.

Results: The implant pellets were similar in appearance with minimal variation from batch to batch. The mean diameter/thickness of the implants ranged from 2.60 ± 0.10 - 2.85 ± 0.20 mm, the mean percentage drug content was 96.40 ± 0.10% and the swelling index values were 2.98 ± 0.12 – 4.86 ± 0.11%. In comparison to the control, the *in vivo* analgesic effect of the ibuprofen implants significantly reduced acetic acid-induced writhing in mice.

Conclusion: The results of this study demonstrated that the solvent casting technique can be used in the formulation of ibuprofen biodegradable implants that can be used in the management of chronic diseases such as arthritis.

Keywords: Biodegradable, HPMC, ibuprofen, implant, Subcutaneous

1. INTRODUCTION

Pharmaceutical implants are small sterile solid masses usually cylindrical or rod-shaped consisting of a highly potent and purified active pharmaceutical ingredient intended to be subcutaneously implanted beneath the skin by suitable special injector or by surgical incision for the purpose of providing the continuous release of the active medicament over a prolonged period of time [1]. The advantages of implantable drug delivery systems include convenience, improved drug delivery, increased patient adherence to therapy, potential for zero order controlled release, potential for bio-responsive release and flexibility in termination of therapy [2]. Implants have been used therapeutically as ocular drug delivery systems in the treatment of some ocular diseases such as glaucoma (e.g. ocular insert containing pilocarpine), they are also used in the formulation of some sustained release contraceptives such as levonorgestrel used in the prevention of pregnancy [3]. The device consists of six silicone membrane capsules each containing about 36 mg of levonorgestrel. The capsules are placed sub-dermally on the inside of the upper arm or the forearm and can deliver the hormonal drug into the systemic circulation for up to a period of five (5) years [4]. Implants have also found useful applications in dentistry were polymeric dental implants have recently been evaluated for various dental applications such as prolonged local administration of fluoride, antibiotics and antibacterial agents to the dental cavities [5]. They have also been used in cancer chemotherapy, for example, a hydrogel reservoir delivery system made from cross-linked copolymer of hydroxypropyl methacrylate, histrelin acetate has been used in the treatment of metastatic prostate cancer [6]. Another available commercial product that has been fabricated for the treatment of prostate cancer is goserelin which is a decapeptide analogue of luteinizing hormone releasing hormone (LHRH) on a polylactic glycolic acid (PLGA) polymer matrix made using hot-melt extrusion method. The implant is distributed in the form of a prefilled syringe and continuously releases the drug over a period of 1 to 3 months [7]. Ibuprofen belongs to the class of drugs known as non-steroidal anti-inflammatory drugs (NSAIDs) and it possesses a good analgesic, anti-pyretic and anti-inflammatory properties. It elicits its pharmacological activity by inhibiting the enzyme,

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cyclooxygenase (COX) which convert arachidonic acid to prostaglandin H_2 (PGH_2) thereby decreasing the synthesis of other prostaglandins which are pain, swelling and inflammatory mediators in the body [8]. From previous studies, ibuprofen have been formulated into various acceptable dosage forms such as capsules, tablets, injectables, syrups, oral suspensions and creams [9]. However, only a few studies have been done on the formulation of implantable drug delivery system of ibuprofen using biodegradable polymers for subcutaneous administration in the management of chronic pain and inflammatory disorders such as rheumatoid arthritis, ankylosis spondylitis, osteoarthritis etc. The aim of this study was to formulate subcutaneous implants of ibuprofen for the management of chronic pain and inflammatory diseases and evaluate its analgesic effect *in vivo* using animal models.

2. MATERIALS AND METHODS

2.1 Materials

2.1.1 Chemicals and Reagents

Ibuprofen reference sample was obtained as a gift from Edo Pharmaceuticals Limited, Nigeria. Gelatin and hydroxypropyl methylcellulose (HPMC) were purchased from Pyrex Chemical Industries, London. Glycerin, acetone and formaldehyde were obtained from Aarti industries Ltd, India. Other chemicals used were of analytical grade.

2.1.2 Biological Materials

Male albino mice weighing 30 to 35 g were bought and maintained at the Animal House Facility of the Department of Pharmacology and Toxicology, Faculty of Pharmacy, University of Benin, Benin City, Nigeria. The animals were housed in standard settings and given two weeks to acclimatize before the studies began. Ethical approval (Reference Number: EC/FP/019/22) was obtained from the Faculty of Pharmacy Ethics Committee, University of Benin, Nigeria. The principles and methods stated in the National Institutes of Health Guide for the Care and Use of Laboratory Animals were followed in all animal research. The animals were fed a typical diet of animal pellets and free access to clean tap water on a regular basis.

2.2 Methods

2.2.1 Preparation of implants

Gelatin (24 g) was weighed and was sprinkled on the surface of water in a beaker and allowed to hydrate for 30 min. After that, HPMC (6 g) was added to the hydrated gelatin (Table 1). With continuous stirring, 20 mL glycerin was added as a plasticizing agent, and the solution was heated over a hot water bath at 60°C until the gelatin was completely dissolved. Ibuprofen (4 g) was dissolved in 5 ml acetone separately before being added to the heated gelatin and HPMC mixture in the beaker. The resultant mixture was poured into a glass petri-dish to a height of 3 mm and allowed to gel for 30 min by placing the petri-dish on an ice pack. In an aseptic cabinet, the congealed mass was allowed to air dry for 72 h at room temperature. The implants were removed from the petri-dish after drying and cut into 4 mm wide and 2 mm long rods using a specially designed stainless-steel cutter [10].

2.2.2 Hardening/cross-linking of implants

In an empty glass desiccator, a petri dish containing formaldehyde solution (37 %v/v) was inserted. The sliced implants were retained on top of the petri dish in a wire mesh and the desiccator was immediately closed. The implants were exposed to formaldehyde vapour for 12 h. They were then taken out of the desiccator and air-dried for 72 h to guarantee that the formaldehyde and gelatin had completely reacted. After that, the implants were stored in an open environment in aseptic settings for a week to ensure that any residual formaldehyde was completely evaporated [11].

Table 1: Formula of implants prepared with gelatin-HPMC admixtures incorporating various quantities of the drug.

Formulation	Drug (g)	Gelatin (g)	HPMC (g)	Glycerin (mL)	Water to 100 mL
H1	16.0	24.0	6.0	20.0	100
FH2	8.0	24.0	6.0	20.0	100
FH3	4.0	24.0	6.0	20.0	100

2.2.3 Evaluation of subdermal implants

2.2.3.1Thickness of implants
A micrometer screw gauge was used to measure the thickness of a sample of three implants from each batch, and the mean value was recorded.

2.2.3.2 Weight uniformity of implants
Implant samples from each batch (n=3) were chosen at random and weighed separately on an analytical scale. The average weight and percentage variation from the mean were calculated.

2.2.3.3 Drug content uniformity
The drug content of implants was determined by randomly selecting three implants from each batch and analyzing them. Each implant was micronized and placed in a 50 mL volumetric flask. After that, 45 mL of 0.1 M NaOH was added and shaken vigorously for 30 min with a flask shaker at 500 rpm. The volume was made up to 50 mL. The solution was diluted with 0.1 M NaOH and the absorbance at 227 nm was measured on a UV spectrophotometer to determine the amount of ibuprofen present. The procedure was repeated three (3) times, and the data was statistically analyzed to check for equal drug distribution within the implants and the mean and standard deviations were calculated [1].

2.2.3.4 Swelling Index
Three (3) samples of cut implants were immersed in a phosphate buffer pH 7.4 swelling solution, and the weight of the individual implants was determined one hour later after the excess fluid was removed by gently wiping the surface with a dry piece of tissue paper. [13] The degree of swelling of each implant formulation at a particular time was calculated using equation 1.

$$H = \frac{W_t - W_o}{W_o} \times 100 - - - - - - eqn\ 1$$

where W_t and W_o are the weight of the implant at any given time and in the dry state respectively and H is the swelling index.

2.2.3.5 Percentage moisture content
Each batch had five (5) samples of cut implants weighed on an electronic scale and placed in a dessicator with activated silica gel as the dessicant. The implants were then withdrawn and weighed on a regular basis until they reached a constant dry weight [13]. The percentage mass loss on drying (moisture content) was calculated using equation 2:

$$mass\ loss(\%) = \frac{initial\ weight - dry\ weight}{initial\ weight} X\ 100 - - - eqn\ 2.$$

2.2.3.6 Moisture sorption studies
The cut implant formulations were tested for stability under various simulated relative humidity (RH) conditions. The experiment included saturated sodium chloride (75% RH), magnesium chloride (45% RH), water (100% RH), and activated silica gel (0% RH). The implant formulations were individually wrapped in aluminum foil paper and stored in relative humidity tanks at 25°C ambient room temperature. The physical characteristics of the implants and weight were documented at predetermined intervals for a maximum of three months. The mean values were taken and plotted against time recorded in days.

2.2.3.7 Preparation of Standard calibration curve
Pure ibuprofen sample (100 mg) was dissolved in sufficient quantity of the dissolution medium (0.1 M NaOH) in a volumetric flask to obtain a 100 mL of solution. The concentration of the resulting stock solution was then calculated to be a 1 mg/mL solution. Serial dilutions of the stock solution were done using the dissolution medium to obtain the following concentrations: 0.5, 1, 2, 4, 6, 8, 10 µg/mL. The UV spectrophotometer was used to measure the absorbance of the standard solutions at a maximum wavelength of 227 nm. The measurements were made in triplicate, and a plot of the mean absorbance against the concentration was generated (Beer-Lambert plot).

2.2.3.8 In vitro drug release studies
The reciprocating disc method was used to conduct the dissolution test (Apparatus 7; ST7, G.B. Caleva Ltd, England). Implants were individually placed in a dissolution basket and inserted into a dissolution medium containing 800 mL of 0.1 M NaOH solution heated to 37 ±0.5°C and agitated at 50 rpm. 5 mL aliquots of the dissolving fluid were extracted with the use of a pipette at various time intervals of 1, 4, 8, 16, 32 h etc., and placed in suitable sample test tubes for testing. By replacing the withdrawn dissolution media with fresh 5 mL of 0.1 M NaOH, sink condition was maintained. After adequate dilution with dissolution media, the drug content in

the collected samples of dissolution fluid was measured spectrophotometrically at a wavelength of maximum absorption (max) of 227 nm.

2.2.3.9 In vitro drug release kinetics

To assess release kinetics, the results from the dissolution rate experiments of the ibuprofen-loaded biodegradable implants were subjected to various drug release models. The zero order, first order, Higuchi square root of time, and Korsmeyer-Peppas release kinetics models were used. For each rate order, the linear regression coefficient (r^2) was determined. If the r^2 value was greater than 0.95, the dissolution release profile was regarded to have followed a certain release order [14, 15].

2.2.3.10 Drug excipients interaction

Fourier transform infrared (FTIR) spectra for ibuprofen and the various formulations were obtained using the potassium bromide pellet method on an FTIR spectrometer (Perkin Elmer, Series model 1615, England) and the spectra were analyzed for any interactions or incompatibilities.

2.2.3.11 In vivo analgesic activity

The analgesic effect of the optimized formulations of the ibuprofen-loaded biodegradable implants was assessed using a modified method for acetic acid-induced mouse writhing experiment developed by Koster *et al*., [16]. The mice were randomly assigned to one of four (4) groups: control (placebo), ibuprofen solution (oral administration), or ibuprofen pellets (subcutaneous implant delivery). Each group comprised five (5) animals that had been fasted for 12 h before administration of the test drug. Each animal's dorsal hair was carefully trimmed and shaved and a skin incision (2 cm) was created on the shaved region of the animals to allow the test device to be implanted. To avoid injuring the skin surface, the procedure was performed under lidocaine local anaesthesia (0.1 mL of 2% intradermal).

The animals in groups I and II were given gelatin-HPMC pellets containing 2.5 and 5 mg ibuprofen, respectively. The incised skin was immediately closed with a stainless-steel surgical clip after the implantation. The same treatment was done for animals in Group III (the negative control group), but with blank pellets that did not contain the test drug. The positive (standard) control group, Group IV, was given ibuprofen solution orally (5 mg). Each mouse received 0.2 mL of 0.6%w/v acetic acid intraperitoneally thirty (30) min after the injection. The number of writhes (stretching movement involving arching of the back, elongation of the body, and extension of the limbs) was counted every 5 min for 30 min [17]. Percentage inhibition was computed from the data that was collected using the following formula:

$$\% \text{ inhibition} = \frac{\text{Mean of writhing test (control)} - \text{Mean writhing test (test)}}{\text{Mean of writhing test (control)}} \times 100 \quad \text{- Eqn 3}$$

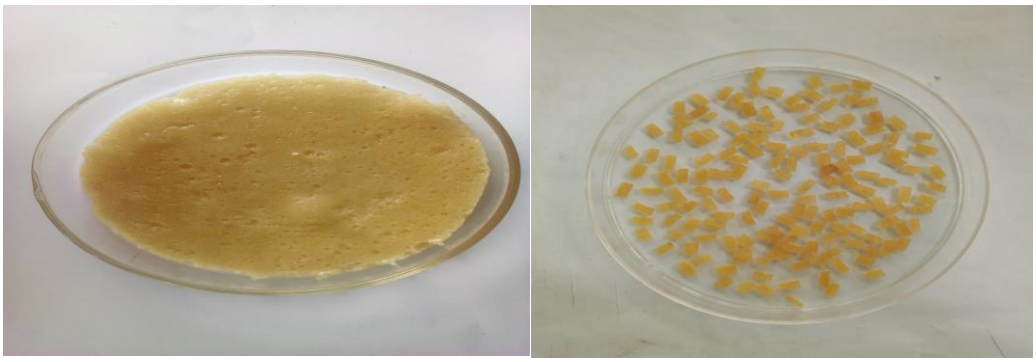
2.3 Statistical Analysis

The results obtained were expressed as mean ± standard deviation (SD). All the data obtained were subjected to GraphPad instat test ($p < 0.05$) to test for significance of difference.

3.0 RESULTS

3.1 Evaluation of physical parameters of implants

Figure 1 shows the physical appearances of the formulated implants. They conformed to the physical characteristics of implants for use in sustained delivery of ibuprofen. The implants made from a gelatin-HPMC polymer combination was yellowish in colour. After 12 h of hardening in formaldehyde solution, the cut implants appeared rigid and smooth.



a **b**

Figure 1: Formed ibuprofen implants (a) with gelatin/HPMC (b) Cut ibuprofen implant.

3.2 Evaluation of the physicochemical parameters of implant formulations

Table 2 shows the findings of the physical properties of the formulated implants. The mean diameter/thickness of the implants was in the range of 2.60±0.10 - 2.85±0.2 mm in all the batches of implant formulations. The average percentage drug content of ibuprofen in the formulated implants was 96.40±0.1% of ibuprofen. However, the results showed a high level of entrapment efficiency and drug loading which were within officially acceptable limits [18]. After 1 h of immersion in a swelling solution of phosphate buffer (pH 7.4), the swelling index of the various implant formulations ranged from 2.98±0.12 - 4.86±0.11%. The percentage mass loss on drying (moisture content) findings show moisture content values ranging from 24.23±0.01% - 28.12±0.01%, which are within approved biodegradable gelatinous polymer moisture content limits.

Table 2: Evaluation parameters of ibuprofen implant formulations

Formulation	Thickness (mm) $\pm S.D$	Weight (mg) ± S.D	Drug content (%)	Swelling index (%)	Moisture content (%)
F1	2.60 ± 0.10	121± 0.2	95.80± 0.11	2.98± 0.01	24.23± 0.01
F2	2.71 ± 0.01	123± 0.1	96.10± 0.10	3.53±0.02	26.48± 0.02
F3	2.85 ± 0.01	124± 0.1	96.40 ± 0.12	4.86±0.01	28.12± 0.01

3.3 Influence of formulation variables on the *in vitro* dissolution profiles of ibuprofen loaded implants

Figure 2 shows the results of *in vitro* drug release studies of the biodegradable ibuprofen implant formulations (FH1 to FH3) in 0.1 M NaOH. The implant formulations all provided an extended release of the active drug throughout a 5-day period, as shown in Figure 2.

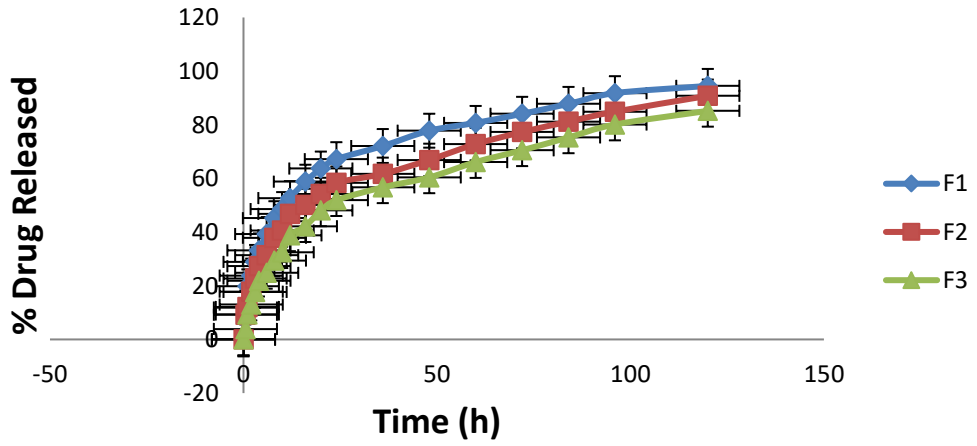


Figure 2: Drug release profiles of ibuprofen implants formulated with gelatin and HPMC. Release kinetics of ibuprofen loaded biodegradable implants

Table 3 shows that the release mechanism of the various ibuprofen implant formulations conformed to the Higuchi model (r^2 = 0.996), indicating that the drug was homogeneously dispersed throughout the polymer matrices and that the kinetics of drug release from the polymer matrices were diffusion controlled [14].

Table 3: Correlation coefficient and Release kinetics of ibuprofen implants formulated using gelatin/HPMC.

Models	Zero		First		Higuchi		Korsmeyer and Peppas	
Formulations	r^2	K_0	r^2	K_1	r^2	K_H	r^2	n
FH1	0.922	4.17	0.956	-0.051	0.991	19.06	0.573	0.58
FH2	0.957	3.96	0.958	-0.028	0.994	17.54	0.625	0.60
FH3	0.957	2.85	0.952	-0.034	0.996	16.82	0.641	0.62

3.4 Drug polymer compatibility studies

The FTIR analysis was used to determine the drug and excipient compatibility. There were no significant changes in the peaks of the pure ibuprofen sample and the various formulations of ibuprofen implants. At the molecular level, there was no difference between the internal structures of the pure ibuprofen sample and the ibuprofen

implant formulations, as shown in the FTIR spectra below (Figure 3). As a result, there were no significant interactions between the drug and the polymers utilized in the formulation of ibuprofen into an implantable drug delivery system.

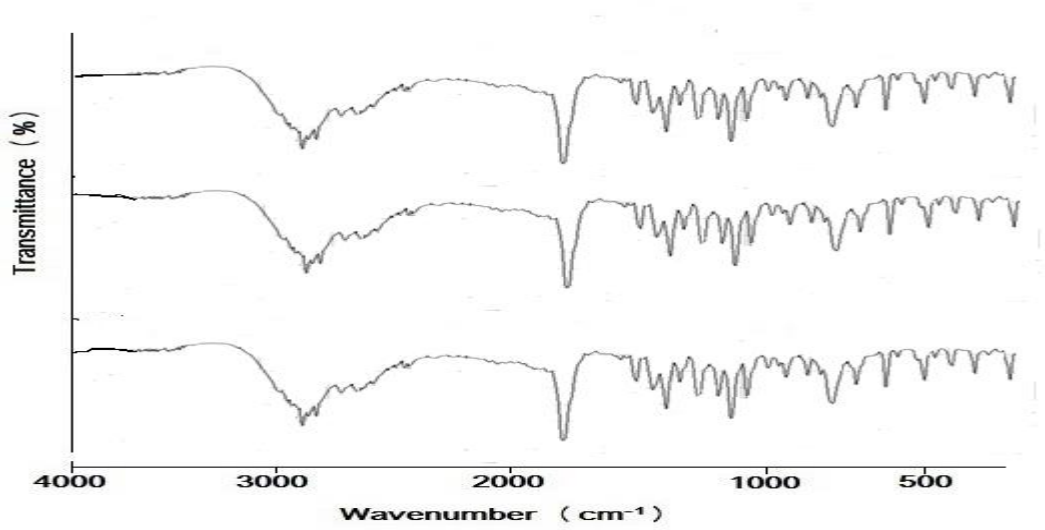


Figure 3: FTIR spectra (a) pure sample of ibuprofen (b) physical mixture of ibuprofen, gelatin and HPMC (c) implant of ibuprofen, gelatin and HPMC

3.5 Influence of relative humidity on the stability profile of the implants

Figure 4 shows the data obtained for the change in implant weights over time under various relative humidity conditions at 30ºC.

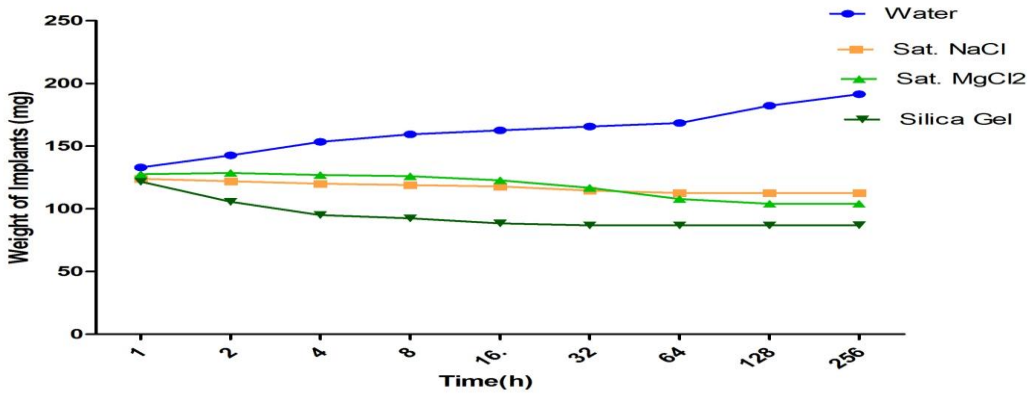


Figure 4: Moisture sorption isotherm of implant formulations under different conditions of relative humidity.

3.6 Acetic acid-induced mouse writhing assay

Table 4 shows the analgesic effectiveness of several ibuprofen implant formulations in a mouse acetic acid-induced abdominal constriction assay. During the 30-minute test period, the number of writhes in control mice was 65.40 ± 1.15.

Table 4: Acetic acid-induced mouse writhing

Treatment	Quantity (mg)	Number of writhes	Inhibition (%)
Blank implant (control)	-	65.40 ± 1.15	-
Gelatin/HPMC	2.5	31.40 ± 2.25*	53.24
Gelatin/HPMC	5.0	24.20 ± 3.12*	67.15
Oral Ibuprofen	5.0	35.20 ± 2.48*	41.37

4.0 DISCUSSION

The interaction of the implants with formaldehyde vapour increased the degree of cross linking of the polymer matrix, thus increasing the tensile strength of the implants. Previous research has shown that the duration of cross

linking affects the rate of drug release from implants hardened with formaldehyde or glutaraldehyde vapour, and that an increase in the duration of cross-linking leads to a corresponding decrease in the rate of drug release due to an increase in the inter-particulate bonding within the polymer matrix, which tends to retard the release of the drug [1, 17]. The weight variation results for all implant formulations showed that the formulated implants passed the weight variation test because the computed % weight variation was within official limits [18]. The weight of the implant formulations was found to be between 121±0.1 and 124±0.1 mg. This is an important characteristic because it indicates the amount of particulate matter compressed within the implant polymer matrix. Swelling, diffusion and degradation are three mechanisms that have been proposed to be responsible for drug release from implants. Firstly, the polymer expands due to the uptake of water when exposed to an aqueous medium. The hydrophobicity of the polymer determines how quickly the implant absorbs water. Secondly, as the implant swells, the encapsulated drug diffuses out through the pores created by the swelling. Under *in vivo* conditions, the third pathway, which involves degradation of the polymer matrix, would occur as a result of enzymatic activity. The diffusion coefficient of water in the implant system could be used to demonstrate the effect of crosslinking agents on the polymer's propensity to swell. Furthermore, the rate of drug release from an implant is influenced by the rate of water diffusion into the formulation. The diffusion coefficient is known to be more sensitive to variations in crosslink density as the molecular size/weight of the medication increases [20]. When biodegradable gelatinous polymers come into contact with a suitable solvent, they are known to form gels. As a result, matrix implants composed of biodegradable gelatinous polymers, which are random network permeated by pores filled with a liquid are known to have high moisture content [1]. In general, the rate of drug release from hydrophilic matrices has been demonstrated to be influenced by factors such as the swelling and dissolution of polymeric drug carriers as well as the dissolution and diffusion of the active drug over a long period of time. Implantable drug delivery systems have been found to successfully sustain the release of drugs held within their matrices for a specified period of time when compared to conventional drug formulations, which are expected to release over 85% percent of their drug content within the first one hour [19]. Ibuprofen has a short biologic half-life of 3 h, which necessitates multiple oral doses per day. However, the implant formulations showed an extended modified release of ibuprofen similar to the zero order release profile based on the *in vitro* dissolution results. The active drug was released from the matrix core in a dose-dependent manner from batches FH1 to FH3 formulated with gelatin-HPMC (80:20) admixture containing 16, 8 and 4 mg of ibuprofen, respectively. However, an early burst release of the active drug was observed, most likely due to surface erosion/leaching of the drug on the implants surface coating, preceding the more effective diffusion-controlled release at a steady rate over a 5-day period and about 91.5 percent of the total payload of the active drug was released [1]. The analysis of the release kinetics indicates that the formulations had a near zero order release profile, which can be attributed to a diffusion mechanism of drug release from the core and partial erosion of the core polymer, resulting in an initial prompt release of the drug from the formulation, followed by a cumulative sustained release over time. Previous studies have shown that diffusion, degradation, or a combination of both often control the mechanism of drug release from biodegradable polymeric implants. The degradation-controlled mechanism occurs when the diffusion rate is less than the erosion rate of the polymer matrix [8]. The results of the Korsmeyer-Peppas diffusion model ($n > 0.5$) show that the diffusion was non-Fickian [15]. The drug release profile from the ibuprofen implant formulations was found to be bi-phasic, with an early burst release followed by a gradual or constant rate of drug release. Burst release is an undesired feature of most monolithic implants since it might cause side effects owing to the fast increase in drug level over a short period of time. However, it can be of medicinal benefit because it can be utilized as a loading dose for some medications if the burst release amount is reproducible [1]. The implants showed a rapid weight gain in water (100% RH) and a significant weight loss in activated silica gel (0% RH), but their weights were rather stable in saturated sodium chloride (75% RH) and magnesium chloride (45% RH) solutions. Stability testing enables recommended storage conditions, retest periods, and shelf-lives to be determined by providing information on how the quality of a drug product fluctuates over time under the influence of a number of environmental factors such as temperature, humidity and light [1]. Based on the results of the moisture sorption isotherm of the ibuprofen implant formulations, there was no appreciable weight gain or change in the organoleptic features of the implants stored at relative humidity of 45 and 75% at a temperature of 30^{o}C over the 3 months test period. It can be concluded that the implants can be safely stored under a similar environmental condition [1]. The animals were pre-treated with rod-like ibuprofen pellets (2.5 and 5.0 mg) mixed with different polymer combinations, which resulted in a significant and dose-dependent reduction in the number of writhes when compared to control. When the implant formulations and the pure ibuprofen were given orally, there was no significant difference in the percentage inhibition of acetic acid-induced mice writhing ($p > 0.05\%$). *In vivo* analgesic effectiveness of the ibuprofen implants showed that they significantly reduced acetic acid-induced writhing in mice, suggesting that the implants may offer an alternative route of administration of the drug [1].

5.0 CONCLUSION

The solvent casting process was used in the formulation of gelatin-HPMC sub-dermal implants of ibuprofen with homogeneous character and minimal batch to batch variation. It was discovered that the rate of drug release from

the ibuprofen-loaded implant pellets was dose-dependent. The implantation procedure helps to improve patient compliance, therapeutic outcome and low incidence of adverse medication reactions and this can be exploited in the development of ibuprofen implants for the management of chronic diseases like rheumatoid arthritis.

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Conflict of Interest
The authors declare no conflict of interest.

Contribution of the Authors
Michael U. Uhumwangho conceived and designed the study and supervised the laboratory works; Collins O. Airemwen co-supervised the laboratory works, analyzed the data and prepared the manuscript; Uchendu P. Adaeze did the animal studies, Emmanuel M. Halilu reviewed the manuscript while Isesele Jude carried out the laboratory work.

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