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FORMULATION AND *IN VIVO* STUDIES OF IBUPROFEN BIODEGRADABLE IMPLANTS

Isesele Ejededawe Jude[1], Airemwen Collins Ovenseri[1]*, Uchendu Phina Adaeze[2], Asemwota Iwinosa Osamudiamen[1], Johnbull Aiwaguore Obarisiagbon[3] and Uhumwangho MU[1]

[1]Department of Pharmaceutics and Pharmaceutical Technology, Faculty of Pharmacy, University of Benin, Benin-City, Nigeria.

[2]Department of Pharmacology and Toxicology, Faculty of Pharmacy, University of Benin, Benin-City, Nigeria.

[3]Department of Pharmaceutics and Pharmaceutical Technology, College of Pharmacy, Igbinedion University, Okada, Edo State, Nigeria.

***Corresponding Author: Airemwen Collins Ovenseri**

Department of Pharmaceutics and Pharmaceutical Technology, Faculty of Pharmacy, University of Benin, Benin-City, Nigeria.

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ABSTRACT

The aim of this study was to formulate ibuprofen loaded implants using some biodegradable polymers and to evaluate the analgesic effect *in vivo* using mice. Solvent casting technique was employed for the formulation of ibuprofen loaded implant pellets using gelatin-sodium alginate admixture (80:20) as the polymer blend. Glycerin was used as the plasticizing agent. The cut pellets were evaluated for their physicochemical properties such as weight uniformity, thickness, swelling index, moisture content, moisture sorption, drug content, drug-excipient interactions as well as *in vitro* drug release. The *in vivo* analgesic activity of the implants on acetic acid-induced mouse writhing in mice was also determined. The implant pellets had uniform character with minimum batch to batch variation. The mean diameter/thickness of the implants ranged from 2.91 ± 0.02 - 3.05 ± 0.01 mm, mean weight variation was 123 ± 0.1 to 128 ± 0.1 mg, mean percentage drug content was between 96.75 ± 0.11-98.25±0.12%, mean percentage moisture content ranged from 26.12 ± 0.03 – 31.50 ± 0.01% and swelling index values were between 4.50 ± 0.01 - 5.24 ± 0.02%. *In vivo* analgesic activity of the ibuprofen implants significantly inhibited acetic acid-induced writhing in mice as compared to the control. Ibuprofen biodegradable implants which can be used in the management of chronic disease such as arthritis was successfully formulated using the solvent casting technique.

KEYWORDS: Ibuprofen, implants, biodegradable, sodium alginate.

INTRODUCTION

Generally, implants are medical devices manufactured to replace a missing biological structure (vascular stents that helps to preserve blood flow), support a damaged biological structure (electro-stimulation devices that regulate heart rhythm or blocked spurious signals in the brain) or enhance an existing biological structure (orthopedic devices that mechanically reinforce the spine or restore range of motion of hips and knees).[1] Pharmaceutical implants on the other hand, 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.[2] Implants are developed with a view to transmit drugs and fluids into the blood stream without the repeated insertion of needles.[3] They are particularly suited for the delivery requirements of drugs such as insulin, steroids, chemotherapeutics, antibiotics, analgesics, peptides, proteins and contraceptive hormones.[4] The drug may be dissolved, dispersed or embedded in a matrix of polymers that control release of the drug by dissolution, diffusion or both, bioerosion, biodegradation or an activation process such as osmosis or hydrolysis. The system is generally prepared as implantable flexible/rigid molded or extruded rods, spherical pellets or compressed tablets via compression, injection molding or hot melt extrusion processes.[5] The subcutaneous or intramuscular tissues are ideal locations for implantation of drug-depot devices due to high fat content that facilitates slow drug absorption, minimal innervation, good hemoperfusion and a lower possibility of localized inflammation as a result of antibody reaction to the insertion of foreign materials.[6] In addition to subcutaneous implantation, various other body regions have also successfully served as implantation sites, particularly for delivery to localized tissues such as

intravaginal, intravascular, intraocular,[7] intrathecal,[8] intracranial and intraperitoneal tissues.[9]

Greater therapeutic efficacy of the drug can be achieved by the use of implantable drug delivery systems when compared to conventional oral or intravenous formulations.[2] Unlike in topical drug administration in which percutaneous absorption of most drugs through the skin may be limited due to the physicochemical characteristics of the drugs and the presence of a highly impermeable stratum corneum, absorption of drugs from implants through the subcutaneous route is devoid of such limitations.[6]

Ibuprofen is an analgesic, anti-pyretic and anti-inflammatory agent which belongs to the class of drugs known as non-steroidal anti-inflammatory drugs (NSAIDs). Ibuprofen is a white or almost white, crystalline powder or colourless crystals with a slight characteristic odour. It has a melting point range between 75-78°C. Previous studies have been done to formulate ibuprofen into an acceptable dosage form such as tablet, capsule, syrup, oral suspension, cream and gel. However, only a few studies have been done on formulation of ibuprofen as implants for subcutaneous administration in the management of chronic pain and inflammatory disorders such as arthritis.[10]

The aim of this study was to formulate an implantable drug delivery system of ibuprofen which can sustain the release of the drug for a long period of time thereby reducing the frequency of administration as well improve patient's adherence to therapy in the management of chronic pain diseases. In this study, ibuprofen implants were formulated and its analgesic effect was evaluated *in vivo* using animal models.

MATERIALS AND METHODS

Ibuprofen reference sample was obtained as a gift from Edo Pharmaceuticals Limited, Nigeria. Gelatin and sodium alginate were purchased from Pyrex Chemical Industries, London. Glycerin, acetone and formaldehyde were obtained from Ranbaxy Laboratories Ltd, Mumbai. Other chemicals used were of analytical grade.

Albino male mice (30 - 35 g) was purchased and housed at the Animal House Facility of the Department of Pharmacology and Toxicology, Faculty of Pharmacy, University of Benin, Benin City, Nigeria. Animals were maintained under conventional housing conditions and allowed to acclimatize for 2 weeks before the commencement of the experiments. Ethical approval (Reference Number: EC/FP/019/22) was obtained from the Faculty of Pharmacy Ethics Committee, University of Benin, Nigeria. All animal experiments were conducted in accordance with the principles and procedures outlined in the National Institutes of Health Guide for the Care and Use of Laboratory Animals. The animals were regularly fed a standard diet of animal pellets and clean tap water *ad libitum*.

Preparation of implants

Gelatin (24 g) was weighed and sprinkled on the surface of water in a beaker and kept for 30 min to hydrate. Sodium alginate (6 g) was then added to the hydrated gelatin (Table 1). Glycerin (20 ml) was added as a plasticizing agent with continuous stirring and the solution was heated on a hot water bath held at 60^{o}C until the gelatin was completely dissolved. Ibuprofen (4 g) was dissolved separately in 5 ml of acetone and added to the melted gelatin and sodium alginate mixture in the beaker. The resulting preparation was poured into a glass petri-dish up to 3 mm height and allowed to gel by placing the petri-dish on ice pack for 30 min. The congealed mass was then allowed to air dry at room temperature for 72 h in an aseptic cabinet. After drying, the implants were removed from the petri-dish and cut into rods of 4 mm width and 2 mm length by specially designed stainless steel cutter. [10]

Hardening /cross-linking of implants

A petri-dish containing formaldehyde solution (37%v/v) was placed in an empty glass desiccator. A wire mesh containing the cut implants was kept on top of the petri dish and the desiccator was closed immediately. The implants were made to react with formaldehyde vapour for 12 h. They were then removed from the desiccator and air-dried for 72 h to ensure complete reaction between formaldehyde and gelatin. The implants were thereafter kept in an open atmosphere in aseptic conditions for a week to ensure complete evaporation of residual formaldehyde. [10]

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

Formulation	Drug (g)	Gelatin (g)	Alginate (g)	Glycerin (ml)	Water to 100ml
F1	16.0	24.0	6.0	20.0	100
F2	8.0	24.0	6.0	20.0	100
F3	4.0	24.0	6.0	20.0	100

Evaluation of subdermal implants

Thickness of implants

The thickness of a sample of three implants from every batch was measured with the aid of a micrometer screw gauge and the mean value was recorded.

Weight uniformity of implants

Samples of implants from each batch (n=3) were randomly picked and weighed individually on an analytical balance. The average weight and percentage deviation from the mean were calculated.[11]

Drug content uniformity

Drug content of implants was estimated by removing a sample of three implants from every batch. Each implant was cut into small pieces (micronized) and placed in a 50 ml volumetric flask. Thereafter, 45 ml of 0.1 M NaOH was added and shaken vigorously with the aid of a flask shaker at 500 rpm for 30 min. The volume was made up to 50 ml. The solution was suitably diluted with 0.1 M NaOH and assayed for ibuprofen content by measuring the absorbance at 227 nm on a UV spectrophotometer. The determination was repeated in triplicate and the data was subjected to statistical analysis to test for uniform distribution of the drug within the implants and the mean and standard deviations were calculated.[11]

Swelling Index

Three (3) samples of cut implants were immersed into a swelling solution of phosphate buffer pH 7.4 and the weight of the individual implants were measured after one hour upon removal of excess fluid by gently wiping of the surface with dry piece of tissue paper. The degree of swelling of each implant formulation at the given time was calculated using the following equation:

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

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. [12]

Percentage moisture content

Five (5) samples of cut implants from each batch were individually weighed on an electronic balance and placed in a dessicator containing activated silica gel as dessicant. The implants were then redrawn periodically and weighed until a constant dry weight was obtained. [13] The percentage mass loss on drying (moisture content) was calculated using the equation:

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

Moisture sorption studies

The stability studies of the cut implant formulations were performed at different simulated relative humidity (RH) conditions. Saturated solutions of sodium chloride (75% RH), magnesium chloride (45% RH), water (100% RH) and activated silica gel (0% RH) were utilized for the study. The selected implant formulations were wrapped separately in aluminium foil paper and stored in relative humidity chambers held at ambient room temperature of about 30°C. The physical parameters of the implants such as the change in appearance and weight were taken at specified time intervals for a maximum period of 3 months. The mean scores were taken and plotted against time recorded in days.

Preparation of Standard calibration curve

A stock solution of ibuprofen was prepared by weighing pure ibuprofen sample (100 mg) in a volumetric flask and it was dissolved in sufficient quantity of the dissolution medium (0.1 M NaOH) 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 made with the dissolution medium to obtain the following concentrations: 0.5, 1, 2, 4, 6, 8, 10 µg/ ml. The absorbance of the standard solutions was measured at 227 nm using the UV spectrophotometer. The determinations were performed in triplicate and a plot of the mean absorbance against the corresponding concentration (Beer-Lambert plot) was generated.

***In vitro* drug release studies**

Dissolution test was carried out using reciprocating disc method (Apparatus 7; ST7, G.B. Caleva Ltd, England). Implants were placed separately into a dissolution basket and inserted into a dissolution medium containing 800 ml of 0.1 M NaOH solution thermo-stated at 37 ±0.5°C and stirred at 50 rpm. At different time intervals of 1, 4, 8, 16, 32 h etc., 5 ml aliquots of the dissolution fluid were withdrawn with the aid of a pipette and placed in suitable sample containers for assay. Sink condition was maintained by replacement of withdrawn dissolution medium with fresh 5 ml of 0.1 M NaOH. The drug concentration in the collected samples of dissolution fluid was analyzed spectrophotometrically at a wavelength of maximum absorption (λ_{max}) of 227 nm after suitable dilution with dissolution medium.

***In vitro* drug release kinetics**

The data obtained from the dissolution rate studies of the ibuprofen-loaded biodegradable implants were subjected to different drug release models to determine the nature of their release kinetics. The models used are the zero order, first order, Higuchi square root of time and the Korsmeyer- Peppas release kinetics. The linear regression coefficient (R^2) for each rate order was calculated. The dissolution release profile was considered to have followed a particular release order if the R^2 value was > 0.95. [14]

Drug excipients interaction

The Fourier transform infra-red (FTIR) spectra of ibuprofen and its formulations were obtained by potassium bromide pellet method using Perkin Elmer FTIR series model 1615 Spectrometer and the spectra obtained were compared for possible interactions or incompatibilities.

***In vivo* analgesic activity**

The analgesic activity of the two major formulations of the ibuprofen-loaded biodegradable implants was determined using the modified method of Koster *et al.*, [15] for acetic acid-induced mouse writhing assay. The mice were put in to six (6) different groups of control (placebo), ibuprofen solution (oral delivery) and ibuprofen pellets (subcutaneous implant delivery). Each group had five (5) animals which were fasted for a period of 12 h before administration. The dorsal hair of

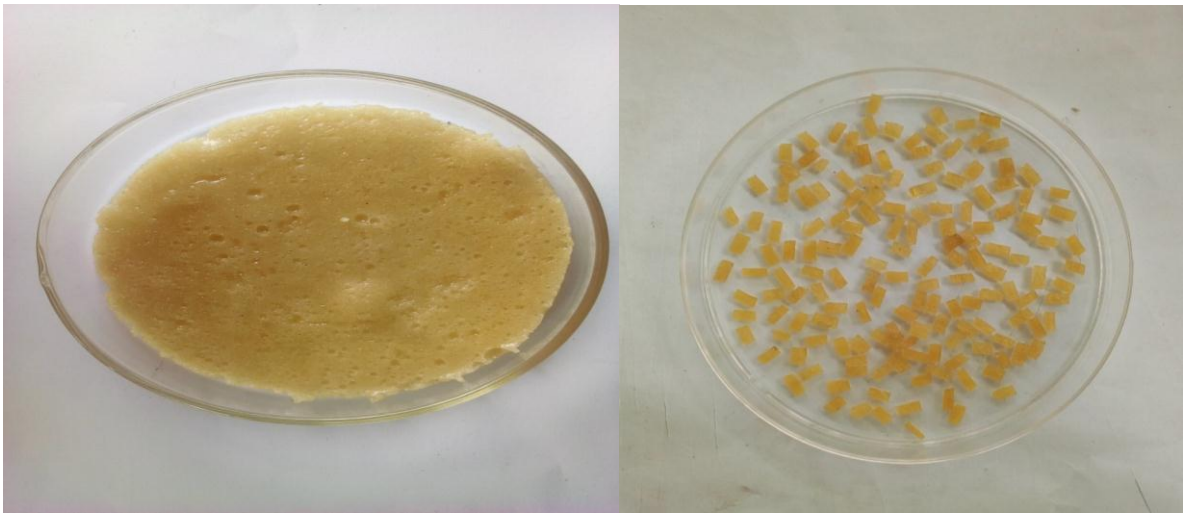
each animal was carefully cut and shaved, a skin incision (2 cm) was made on the shaved portion of the animals to allow the implantation of the test device. This was done under lidocaine local anaesthesia (0.1 ml of 2%, intradermal) to avoid damaging the skin surface. Group I and II animals were administered pellets (gelatin-alginate) containing 2.5 and 5 mg ibuprofen respectively. Immediately after the implantation, the incised skin was closed using stainless steel surgical clip. The same procedure was performed on animals in Group III (negative control group), but with blank pellets not containing the test drug. The Group IV was administered ibuprofen solution orally (5 mg) and was used as positive (standard) control. Thirty (30) minutes after the administration, 0.2 ml of 0.6% w/v of acetic acid was injected intraperitoneally to each mouse. The number of writhes which is the stretching movement (arching of the back, elongation of body and extension of the limbs) was recorded for 30 minutes at the interval of 5 minutes. Percentage inhibition was computed from the data that was collected using the following formula:

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

RESULTS AND DISCUSSION

Evaluation of physical parameters of implants

The physical appearances of the formed and cut implants are shown in Figure 1. They were found to be in accordance with the primary objective of designing and formulating rod shaped matrix type implants for use in prolonged delivering of ibuprofen. Implants obtained from gelatin-sodium alginate polymer admixture had a bright yellowish appearance. The cut implants were found to have a rigid, smooth, polish appearance after hardening with formaldehyde solution for 12 h. The reaction of the implants with formaldehyde vapour was found to increase degree of cross linking of the polymer matrix thus imparting greater rigidity and tensile strength to the formed implants. Previous studies have shown that the rate of drug release from implants hardened with formaldehyde or glutaraldehyde vapour is affected by the duration of cross linking and that an increase in the duration of cross linking leads to a corresponding decrease in the rate of release of the drug due to increase in the inter-particulate bonding within the polymer matrix that tend to retard the release of the entrapped drug held within its 3-dimensional matrix structure.[16]



a **b**

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

Evaluation of the physicochemical parameters of implant formulations

The results of the physical parameters of the formed implants are shown in Table 2. The implants mean diameter/thickness were almost uniform in all batches of implant formulations and were found to be in the range of 2.91 - 3.05 mm. The results obtained for the individual thickness of the formed implants were subjected to statistical analysis and the standard deviation from the mean was obtained.

Results obtained for weight variation for all formulations of implants showed that the formed implants passed the weight variation test as the percentage weight variation computed were within official limits.[17] The weights of all the implant formulations were found to be in the range of 123±0.2 - 128±0.1 mg. This parameter is of utmost importance as it is an indication of the quantity of particulate matter compressed within the implant polymer matrix.

For drug content uniformity, results obtained indicate that, the percentage drug content of ibuprofen in implant

formulations made with gelatin-sodium alginate admixture (F1 to F3) was found to have an average percentage drug content of 98.25±0.12% of ibuprofen. The values however indicate a high degree of entrapment efficiency and drug loading and are found to be within officially acceptable limits.[17]

The values obtained for the swelling index of the various implant formulations upon 1 h immersion in a swelling solution of phosphate buffer (pH 7.4) ranged from 4.5-5.24%. There are three mechanisms postulated to be responsible for the release of drugs from the implants and they include swelling, diffusion and degradation. Upon exposure to an aqueous media, first, the polymer swells due to the uptake of the water. The rate of water uptake by the implant depends on the hydrophobicity of the polymer. Second, when the implant swells, the encapsulated drug is released by diffusion through the pores formed due to swelling. The third mechanism, which involves degradation of the polymer matrix, would occur under *in vivo* conditions as a result of enzyme activity. The effect of crosslinking agents on the swell ability of the polymer could be demonstrated by the diffusion coefficient of water in the implant system. Moreover, the rate of drug delivery from an implant also depends on the rate of diffusion of the waterfront into the device. It is known that the greater the molecular size/weight of the drug, the greater is the sensitivity of the diffusion coefficient to changes in crosslink density.[18]

The percentage mass loss on drying (moisture content) results reveal a moisture content value ranging from 26.12 ± 0.03% - 31.50 ± 0.01% which are within official acceptable limits for biodegradable gelatinous polymers. Biodegradable gelatinous polymers are known to form gels when in contact with a suitable solvent that solvates them. These gels are basically composed of at least two components; the first component being in the solid state built up by a coherent 3-dimensional network in which the second component (usually a suitable solvent) is immobilized. Hence, matrix implants made from biodegradable gelatinous polymers, which may be regarded as a random network permeated by pores that are filled with a liquid medium, are known to have relatively high values for moisture content.[18]

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	3.05 ± 0.01	128± 0.1	98.25± 0.12	5.24± 0.02	26.12± 0.03
F2	2.96 ± 0.02	126±0.2	96.90± 0.11	4.81±0.01	27.57±0.01
F3	2.91 ± 0.02	123±0.1	96.75± 0.11	4.50±0.01	31.50±0.01

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

The results of the *in vitro* drug release studies of the matrix-type biodegradable ibuprofen implant formulations (F1 to F3) in 0.1 M NaOH for 120 h are shown in Figure 2. Generally, rate of drug release from hydrophilic matrices has been shown to be dependent on factors such as swelling and dissolution of the polymeric drug carriers giving rise to mild erosion of the system, concomitantly with dissolution and diffusion of the active drug over a prolonged period of time. When compared with conventional formulations of a drug which are expected to release over 85% of their drug content within the first hour, it has been observed that implantable drug delivery systems successfully sustain and/or prolong the release of drugs held within their matrices for a specified period of time.[10]

From the Figure 2, it can be seen that the implant formulations all had an extended release of the active drug over a 5-day period. Ibuprofen is known to normally have a short biologic half-life of 3 h necessitating several oral doses per day. However, from the *in vitro* dissolution data obtained, it was observed that the implant formulations exhibited an extended modified release of ibuprofen close to the zero order release profile.

The drug release from batches F1 to F3 prepared using gelatin-sodium alginate admixture (80:20) containing 16 mg, 8 mg and 4 mg of ibuprofen respectively exhibited a dose dependent release of the active drug from the matrix core. However, it was observed that there was an initial burst release of the active drug probably due to surface erosion /leaching of the drug on the surface coating of the implants before the more effective diffusion-controlled release at a sustained rate over an extended period of 5 days. It was also observed that about 92.5% of the total payload of the active drug was release at the end of the 5-day study period.

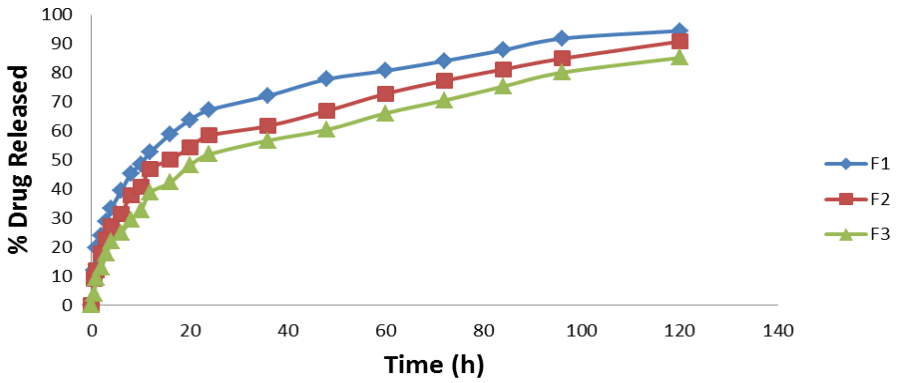


Figure 2: Drug release profiles of ibuprofen implants formulated with gelatin and sodium alginate.

Release kinetics of ibuprofen loaded biodegradable implants

Determination of the release kinetics upon analysis, suggests a near zero order release profile for the formulations which can be attributed to diffusion mechanism of drug release from the core and partial erosion of the core polymer resulting in initial prompt release of the drug from the formulation which was thereafter followed by a cumulative sustained release over time. Drug release mechanisms from biodegradable polymeric systems are usually controlled either by diffusion, degradation or more commonly, a combination of both. The degradation-controlled mechanism occurs when the diffusion rate is less than the degradation or erosion rate of the polymer carrier. From the results obtained for the correlation coefficient and release kinetics of the various ibuprofen implant formulations (Table 3), it can be seen that the release mechanism of the implant formulations conformed with the Higuchi model (r^2 = 0.996) indicating that the drug was homogeneously dispersed within the polymer matrices and that the kinetics of release of the drug from the polymer matrices was diffusion controlled. However, the results obtained for the Korsmeyer-Peppas diffusion model (n > 0.5) indicate that the diffusion was non-Fickian.[18] The drug release profile from the ibuprofen implant formulations was observed to be bi-phasic, starting with an initial burst release followed immediately by a slow release or constant drug release rate. The burst release is an undesirable drawback of most monolithic implants as it may results in the development of side effects due to rapidly increasing drug level within a short period of time. By contrast however, a burst release can also be a pharmaceutical benefit as it can be used as a loading dose for some drugs if the amount of the burst release can be reproducible.[19]

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

Models	Zero		First		Higuchi		Korsmeyer and Peppas	
Formulations	R^2	K0	r2	K1	r2	KH	r2	n
F1	0.902	3.37	0.967	-0.053	0.993	19.09	0.571	0.60
F2	0.937	3.18	0.960	-0.029	0.995	17.70	0.607	0.61
F3	0.947	2.96	0.946	-0.038	0.992	16.36	0.651	0.65

Drug polymer compatibility studies

The drug and excipients compatibility-interaction studies were carried out using the FTIR analysis. The result is presented in Figure 3. The study showed peaks for the corresponding functional groups in ibuprofen. When the spectra were carried out with ibuprofen and the various polymers utilized for the formation of the implants, there were no major changes in the peaks. From the FTIR spectra below, it can be seen that there was no difference between the internal structures of the pure drug (ibuprofen) and the sample formulations at the molecular level. Hence, it can be concluded that there are no major interactions between the drug and the polymers used in the formulation of ibuprofen into an implantable drug delivery device. This will therefore not in any way affect the pharmacological or toxicological activity of the drug (ibuprofen).

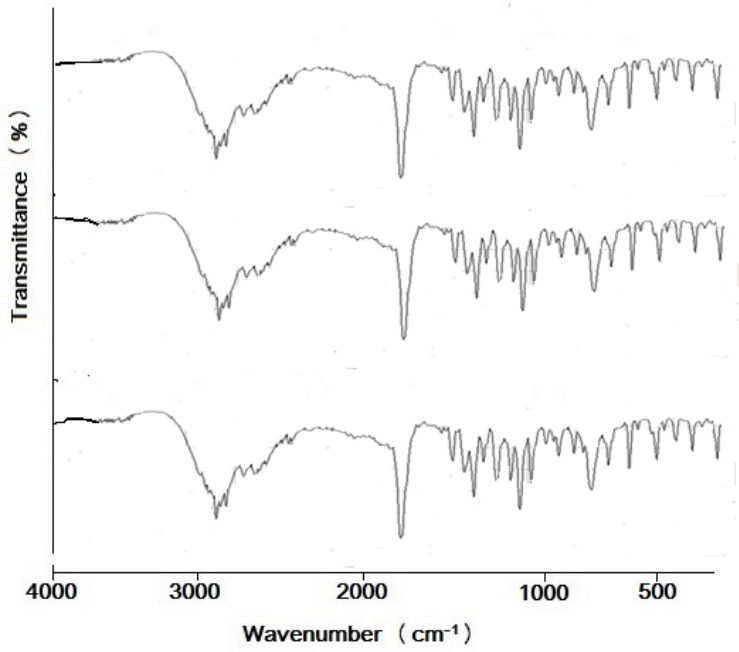


Figure 3: FTIR spectra (a) pure sample of ibuprofen (b) physical mixture of ibuprofen, gelatin and alginate (c) implant of ibuprofen, gelatin and alginate.

Influence of relative humidity on the stability profile of the implants

The results obtained for the change in weights of implants with time under different conditions of relative humidity measured at 30ºC are shown in Figure 4 below. The implants showed a rapid weight gain in water (RH 100%) and an appreciable weight loss in activated silica gel (RH 0%) while the weights remained relatively stable under saturated solutions of sodium chloride (RH 75%) and magnesium chloride (RH 45%). The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity and light, enabling recommended storage conditions, retest periods and shelf-lives.

From the results obtained for the moisture sorption isotherm of the ibuprofen implant formulations, it can be concluded that since there was no appreciable weight gain or change in the organoleptic features of the implants stored at 45% RH and 75% RH held at a temperature of 30^{o}C over the 3 months test period, the implants can be safely stored at a similar environmental condition.

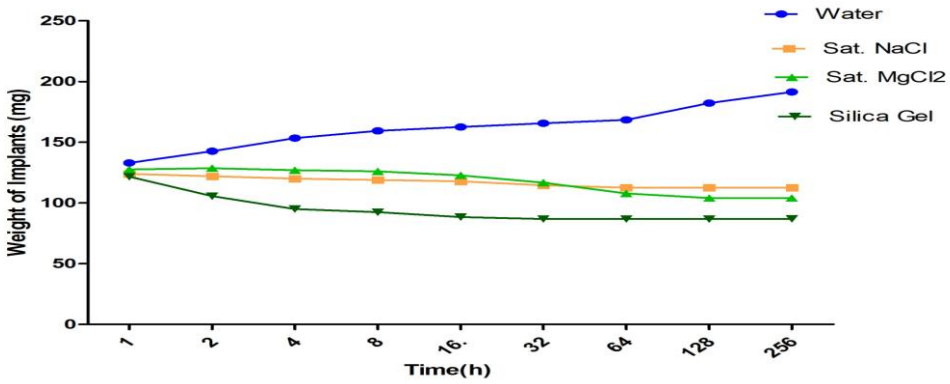


Figure 4: Moisture sorption isotherm of implant formulations under different conditions of relative humidity.

Acetic acid-induced mouse writhing assay

The results for the analgesic activity of the ibuprofen implant formulations on acetic acid-induced abdominal constriction assay in mice are shown in Table 4. In control mice, the number of writhes during the 30 min test period was 69.20 ± 1.25. The pre-treatment of the animals with the rod-like pellets of ibuprofen (2.5 and 5.0 mg) compounded with different polymer combinations produced a significant and dose related reduction in the number of writhes compared to control. There was no significant difference between the values obtained for the percentage inhibition of acetic acid-induced mouse writhing for the implant formulations and the pure drug (ibuprofen) when administered orally (p >

0.05%). *In vivo* analgesic activity of the ibuprofen implants indicates that the implants significantly inhibited acetic acid-induced writhing in mice suggesting that the implants may offer an alternative route of administration of the drug.

Table 4: Acetic acid-induced mouse writhing.

Treatment	Quantity (mg)	Number of writhes	Inhibition (%)
Blank implant (control)	-	69.20 ± 1.25	-
Gelatin/sodium alginate	2.5	33.60 ± 5.41*	51.45
Gelatin/sodium alginate	5.0	21.40 ± 6.26*	69.08
Oral Ibuprofen	5.0	38.00 ± 3.51*	45.09

CONCLUSION

Gelatin-sodium alginate sub-dermal implants of ibuprofen having uniform character can be effectively prepared using the solvent casting technique with minimum batch to batch variation. The rate of drug release from the ibuprofen loaded implant pellets was found to be dose-dependent. The prolongation of the release profile of the drug (ibuprofen) by the implantation process helps to meet the criteria for better patient compliance, improved therapeutic outcome and minimum incidence of adverse drug reaction and this can be exploited in the formulation of ibuprofen implants for the management of chronic diseases such as rheumatoid arthritis.

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