Trop J Nat Prod Res, November 2022; 6(11):1864-1869

ISSN 2616-0684 (Print)
ISSN 2616-0692 (Electronic)

Tropical Journal of Natural Product Research

Available online at https://www.tjnpr.org

Original Research Article

Comparative Study of the Influence of Sodium Alginate and Hydroxypropyl Methylcellulose on the Release Profile of Ibuprofen from Subcutaneous Implant Formulations

Collins O. Airemwen[1,2]*, Jude E. Isesele[1], Johnbull A. Obarisiagbon[3], Michael U. Uhumwangho[1]

[1]*University of Benin, Faculty of Pharmacy, Department of Pharmaceutics and Pharmaceutical Technology, Benin-City, Nigeria*
[2]*Cyprus International University, Faculty of Pharmacy, Nicosia, Cyprus*
[3]*Igbinedion University, College of Pharmacy, Department of Pharmaceutics and Pharmaceutical Technology, Okada, Edo State, Nigeria*

ARTICLE INFO

Article history:
Received 20 August 2022
Revised 23 September 2022
Accepted 10 November 2022
Published online 01 December 2022

ABSTRACT

Pharmaceutical implants are small sterile solid dosage forms consisting of a highly potent drug intended to be subcutaneously implanted under the skin by suitable special injector or surgical incision in order to deliver the active ingredient continuously over an extended period of time. The aim of this study was to compare the influence of sodium alginate and hydroxypropyl methylcellulose (HPMC) on the release profile of ibuprofen from subcutaneous implant formulations. The ibuprofen implants were formulated using the solvent casting technique with either sodium alginate or hydroxypropyl methylcellulose as the synthetic polymer. The formulated ibuprofen implants were then cut into appropriate sizes and their physicochemical properties such as thickness/diameter, moisture content, weight uniformity, drug content, swelling index, moisture sorption, drug-excipient interactions as well as *in vitro* drug release were evaluated. The ibuprofen implants formulated using either sodium alginate or HPMC had uniform physical characteristics with minimum batch-to-batch variation. The mean diameter/thickness of the implants formulated using either sodium alginate or HPMC ranged from 2.45±0.01 – 2.98±0.01 mm and 2.87±0.01 - 3.01±0.01 mm respectively. The mean percentage drug content values for the ibuprofen subcutaneous implants ranged from 95.68±0.11-98.18±0.12%. The implants had moisture content values ranging from 27.64±0.01–28.92±0.01%. The implants formulated using HPMC were found to have sustained the rate of drug release from the formulation better than those formulated using sodium alginate. There was a significant difference between the release rates of ibuprofen from implants formulated using HPMC and sodium alginate ($P<0.05$).

***Keywords*:** Hydroxypropyl methylcellulose, Ibuprofen, Implants, Sodium alginate.

Introduction

Pharmaceutical implants are drug delivery systems that are placed under the skin to release a specific amount of drug into the bloodstream without the repeat insertion of needles.[1] It comprises a rod-shaped polymeric inner matrix with a long cylindrical body and two ends. It is a sterile drug delivery device for subcutaneous implantation with the ability to deliver the drug at a controlled rate over a long period of time.[2,3] Implantation is typically done in intramuscular or subcutaneous tissues with the means of special implantation devices, needles, or the use of a minor surgery.[5] Subcutaneous or intramuscular tissues are usually the best locations for implantation of drug-depot devices, due to high-fat content that promotes sustained drug absorption, good hemoperfusion, minimal innervation, non-sensitization to the insertion of foreign materials and a reduced risk of localized inflammation.[6,7] This drug delivery system has the potential of overcoming some of the disadvantages of oral administration of drugs such as reduced bioavailability, extensive hepatic metabolism, gastric ulceration as well as nausea and vomiting.

*Corresponding author. E mail: collins.airemwen@uniben.edu
Tel: +234 8133737933

Citation: Airemwen CO, Isesele JE, Obarisiagbon JA, Uhumwangho MU. Comparative Study of the Influence of Sodium Alginate and Hydroxypropyl Methylcellulose on the Release Profile of Ibuprofen from Subcutaneous Implant Formulations. Trop J Nat Prod Res. 2022; 6(11):1864-1869. http://www.doi.org/10.26538/tjnpr/v6i11.20

Official Journal of Natural Product Research Group, Faculty of Pharmacy, University of Benin, Benin City, Nigeria.

Implants have several advantages over conventional drug delivery systems such as prolonged duration of action, reduced frequency of dosing, increased patient adherence to therapy and reduced systemic side effects.[8] Implantable drug delivery system is a preferred alternative for a lot of drugs, especially those that cannot be delivered effectively through the oral route, drugs that undergo extensive first-pass effect, drugs that are degraded by the enzymatic action of the stomach or drugs that are poorly absorbed in the gastrointestinal tract.[9,10] Examples of such drugs include steroids, contraceptives, insulin and heparin. Implants should be biocompatible, environmentally stable, relatively easy to sterilize, easy to manufacture, affordable and able to sustain the release of the drug over a long period of time as well as improve patient adherence to therapy by decreasing the frequency of drug administration over the entire period of treatment.[11]

Hydroxypropyl methylcellulose (HPMC)

HPMC can be obtained from the reaction of alkali cellulose with propylene oxide and chloromethane. It is normally available as a whitish, odourless and tasteless granular powder.[12] It is soluble in cold water and insoluble in ethanol, ether and chloroform. It is a common pharmaceutical excipient used in the formulation of oral, ophthalmic, nasal and topical preparations. It is mostly used as a binder and as a matrix former in sustained-release tablet formulations. It is also used as a suspending agent in various liquid oral preparations.[12]

Sodium Alginate

Alginic acid and its calcium, potassium, magnesium and sodium salts are abundantly present in brown algae. Sodium alginate is the sodium

salt of alginic acid. It is insoluble in ether, chloroform and ethanol but sparingly soluble in water in which it forms a viscous colloidal dispersion. It is normally used as a gelling, thickening, suspending and emulsifying agent in the preparation of various liquid and semi-solid pharmaceutical preparations.[13] Ibuprofen is an analgesic, antipyretic and anti-inflammatory agent. It belongs to the class of medications called non-steroidal anti-inflammatory drugs (NSAIDs). It is used in the treatment of fever, pain, migraine and rheumatoid arthritis. It elicits its pharmacological action via the reduction of the production of prostaglandins by decreasing the activity of the cyclooxygenase (COX-1 and COX-2) enzymes. Previous studies have formulated ibuprofen into various dosage forms such as tablets, capsules, syrups, oral suspensions, creams and gels.[14] However, there are limited studies on the formulation of ibuprofen implants hence, the aim of this study was to formulate ibuprofen subcutaneous implants using hydroxypropyl methylcellulose and sodium alginate and to compare the influence of these synthetic polymers on the release profile of ibuprofen from the formulations.

Materials and Methods

Ibuprofen pure sample was a donation from Ranbaxy Pharmaceuticals Limited, India. HPMC, gelatin and sodium alginate were procured from Pyrex Chemical Industries, London. Glycerin, acetone and formaldehyde were purchased from Sigma Aldrich (Germany). The other chemicals used in the research were of analytical grade.

Preparation of implants
Gelatin powder (30 g) was sprinkled on the surface of 200 mL of water in a beaker and allowed to hydrate for 30 min. The hydrated gelatin was then mixed with 10 g of sodium alginate (Table 1). With continuous stirring, glycerin (25 mL) was added as a plasticizing agent and the solution was heated in a hot water bath at 60°C until the gelatin was completely dissolved. Separately, 4 g of ibuprofen was dissolved in 5 mL acetone and added to the melted gelatin and sodium alginate mixture in the beaker. The resultant mixture was poured into a glass petri-dish 3 mm in height 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 constructed stainless steel cutter. Another batch of implants was prepared in the same way using HPMC-gelatin admixture.[3]

Hardening/cross-linking of implants
A petri-dish containing formaldehyde solution (37%v/v) was placed in an empty glass desiccator which was quickly closed after a wire mesh containing the cut implants was placed on top of the petri dish. The implants were exposed to formaldehyde vapour for 12 h. They were then removed from the desiccator and air-dried for 72 h to ensure a complete reaction between formaldehyde and gelatin. The implants were thereafter kept in an open atmosphere in an aseptic condition for a week to ensure complete evaporation of residual formaldehyde.[3]

Evaluation of subdermal implants
Thickness of implants
A micrometer screw gauge was used to measure the thickness of a sample of three implants from every batch of the implant formulations and the mean value was recorded.

Weight uniformity of implants
Three (3) samples of implants from each batch were randomly picked and weighed individually on a digital weighing balance. The mean weight and standard deviation from the mean were calculated.

Drug content uniformity
Three (3) samples of the implants from each batch were used for the drug content uniformity assay. Each implant was cut into small pieces (micronized) using a stainless steel cutter 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 (Model Spectronic 21D, Bausch and Lomvb, USA). 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.[3]

Swelling Index
The cut implants (n=3) were immersed into a phosphate buffer solution of pH 7.4 and the weight of the individual implants was measured after 1 h upon removal of excess fluid by gently wiping off the surface with a dry piece of tissue paper. The degree of swelling of each implant formulation at a given 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.[8]

Percentage moisture content
Five (5) samples of cut implants from each batch were individually weighed on a digital analytical balance and placed in a desiccator containing activated silica gel as a desiccant. The implants were then withdrawn periodically and weighed until a constant dry weight was obtained. 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 cut implant formulations were tested for stability under various simulated relative humidity (RH) conditions such as 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. Physical characteristics of the implants such as the change in appearance and weight were recorded at specified time intervals for a maximum period of three (3) months. The mean values were documented.

Preparation of Standard calibration curve
A standard calibration curve was prepared by weighing a pure ibuprofen sample (100 mg) in a volumetric flask and it was dissolved in a sufficient quantity of the dissolution medium (0.1 M NaOH) to obtain 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, and 10 µg/mL respectively. 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 (Beers-Lambert plot) was generated.

In vitro drug release studies
Dissolution test was carried out using the reciprocating disc method (Apparatus 7; ST7, G.B. Caleva Ltd, England). The 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, 24, 48, 72, 96 and 120 h, 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.

ISSN 2616-0684 (Print)
ISSN 2616-0692 (Electronic)

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

Formulation	Drug (g)	Gelatin (g)	Alginate (g)	HPMC (g)	Glycerin (mL)	Water to 100 mL
FA1	16.0	24.0	6.0	-	20.0	100
FA2	8.0	24.0	6.0	-	20.0	100
FA3	4.0	24.0	6.0	-	20.0	100
FH1	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

In vitro drug release kinetics
The data obtained from the *in vitro* 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 (Higuchi, 1963; Korsemeyer *et al.,* 1983). 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.

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

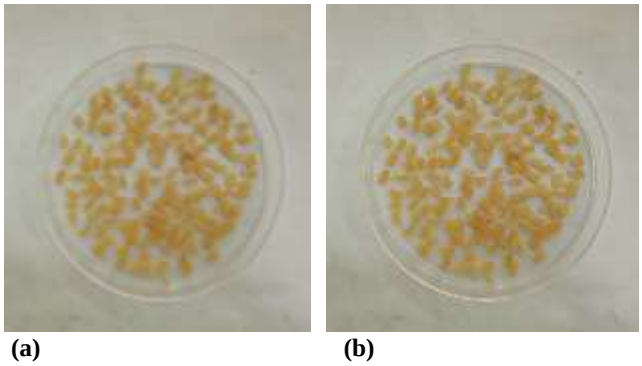
Statistical Analysis
All the data obtained were subjected to the GraphPad Instat test ($p < 0.05$) to test for significance of difference and the results were presented as mean ± standard deviation (SD).

Results and Discussion

Evaluation of physical parameters of implants
The physical appearances of the ibuprofen implants formulated using either sodium alginate or HPMC are shown in Figure 1. The cut implants had a smooth, rigid and polished surface after 12 h of hardening in formaldehyde solution. The interaction of the implants with formaldehyde vapour improved the degree of cross-linking of the polymer matrix thereby increasing the rigidity and tensile strength of the formulated implants. Previous studies also revealed that the duration of cross-linking affects the rate of drug release from implants hardened with formaldehyde or glutaraldehyde vapour and an increase in the duration of cross-linking causes a corresponding decrease in the rate of drug release due to increased inter-particulate bonding within the polymer matrix.[8] The implants formulated using either sodium alginate or HPMC polymer had a similar physical appearance.

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 2.45±0.01-2.98±0.01 mm for implants formulated using sodium alginate and 2.87±0.01-3.01±0.01 mm for those formulated using HPMC. 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. There was no significant difference between the mean diameter/thickness of the ibuprofen implants formulated using either sodium alginate or HPMC ($P>0.05$).
Results obtained for weight variation for all formulations of implants prepared using either sodium alginate or HPMC showed that the formed implants passed the weight variation test as the percentage weight variation computed was within official limits.[15] The weights of all the implant formulations were found to be in the range of 124.2±0.1-127.3±0.1 mg for implants formulated with sodium alginate and 125.2±0.1-126.5±0.2 mg for implants formulated using HPMC. This parameter is of utmost importance as it is an indication of the quantity of particulate matter compressed within the implant polymer matrix. There was no significant difference between the weight variation of the subcutaneous implants formulated using either sodium alginate or HPMC ($P>0.05$).
The results of the drug content showed that ibuprofen implants formulated using sodium alginate had an average percentage drug content of 96.94±0.11% while those formulated using HPMC had an average drug content of 97.27±0.12% of ibuprofen. These values indicate a high degree of entrapment efficiency and drug loading. The values were within officially acceptable limits.[15] The values obtained for the swelling index of the various implants formulated using either sodium alginate or HPMC upon 1 h immersion in a swelling solution of phosphate buffer (pH 7.4) ranged from 4.74±0.02-4.95±0.01% and 4.88±0.02-4.94±0.01% respectively. Drug release from the implants occurred via three mechanisms which are swelling, diffusion and degradation.[1] Upon exposure to an aqueous medium, the polymers swell due to water uptake, the rate of which depends on the hydrophobicity of the polymer. After the swelling of the implants, the encapsulated drug is released by diffusion through the pores formed due to swelling. Another mechanism of drug release from the implants involves the degradation of the polymer matrix, as occurs under *in vivo* conditions as a result of enzyme activity.[3]
The results of percentage mass loss on drying (moisture content) showed a moisture content value ranging from 27.63±0.01% - 28.27±0.02% for implants formulated using sodium alginate and 27.64±0.01% - 28.92± 0.01% for implants formulated using HPMC. Moisture content is the amount of water in a drug product. It influences the physical properties such as weight, viscosity and density of the drug products. It is generally determined by weight loss upon drying and the values obtained are within official acceptable limits for biodegradable gelatinous polymers.[15]

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 ibuprofen implants formulated with sodium alginate (FA1-FA3) and those formulated with HPMC (FH1-FH3) in 0.1 M NaOH for 120 h are shown in Figure 2 (a and b).



(a) **(b)**

Figure 1: Ibuprofen implants formulated using (a) sodium alginate and (b) HPMC

ISSN 2616-0684 (Print)
ISSN 2616-0692 (Electronic)

Table 2: Evaluation parameters of ibuprofen implant formulations

Formulation	Thickness (mm) ± SD	Weight (mg) ± SD	Drug content (%)	Swelling index (%)	Moisture content (%)
FA1	2.98 ± 0.01	127.3 ± 0.1	97.25 ± 0.12	4.95 ± 0.01	28.27 ± 0.02
FA2	2.45 ± 0.01	125.4 ± 0.2	97.90 ± 0.11	4.74 ± 0.02	28.12 ± 0.01
FA3	2.62 ± 0.02	124.2 ± 0.1	95.68 ± 0.11	4.82 ± 0.01	27.63 ± 0.01
FH1	3.01 ± 0.01	126.5 ± 0.1	98.18 ± 0.12	4.91 ± 0.01	28.92 ± 0.01
FH2	2.92 ± 0.02	125.9 ± 0.2	97.28 ± 0.11	4.88 ± 0.02	27.89 ± 0.01
FH3	2.87 ± 0.01	125.2 ± 0.2	96.35 ± 0.12	4.94 ± 0.01	27.64 ± 0.01

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 leading to mild erosion of the system with a concomitant 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 1 h, it has been observed that implantable drug delivery systems successfully sustained the release of drugs held within their matrices for a specified period of time.[3] It can be seen that all the implant formulations had an extended release of the active drug over a 4-day period (96 h) for implants formulated using sodium alginate and 5 days (120 h) for implants formulated using HPMC. 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-release of ibuprofen similar to the zero order-release profile. The drug release from batches FA1-FA3 prepared using sodium alginate exhibited a dose-dependent release of the active drug from the matrix core similar to the drug release pattern for implants formulated using HPMC (FH1-FH3). There was a more effective diffusion-controlled release at a sustained rate over a period of 120 h for implants formulated with HPMC compared to those formulated with sodium alginate. It was observed that the implants formulated using sodium alginate released about 92% of the active drug within a period of 96 h (4 days) whereas the implants formulated using HPMC were able to sustain the rate of drug release from the dosage form for up to 120 h (5 days) i.e. about 88% of the active drug was released at the end of the 5-day study period. The implants formulated using HPMC were found to have sustained the rate of drug release from the formulation better than those formulated using sodium alginate. There was a significant difference between the release rates of implants formulated using either sodium alginate or HPMC ($P<0.05$).

Release kinetics of ibuprofen-loaded biodegradable implants

The release kinetics was determined from the analysis of the dissolution data obtained from the implants formulated with either sodium alginate or HPMC and it showed a near zero order release profile for the formulations which can be attributed to the 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. From the results obtained from the correlation coefficient and release kinetics of all ibuprofen implant formulations (Table 3), it can be seen that the release mechanism of the implant formulations simulated Higuchi release model ($r^2 = 0.998$) which states that the rate of drug release is dependent on the square root of time 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.[16] However, the results obtained for the Korsmeyer-Peppas diffusion model ($n > 0.5$) indicate that the mechanism of drug release was via non-Fickian diffusion.[17] 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.[18]

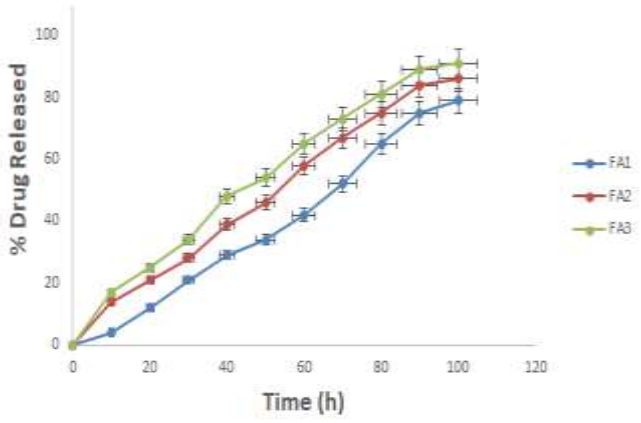


Figure 2a: Drug release profiles of ibuprofen implants formulated with gelatin and sodium alginate.

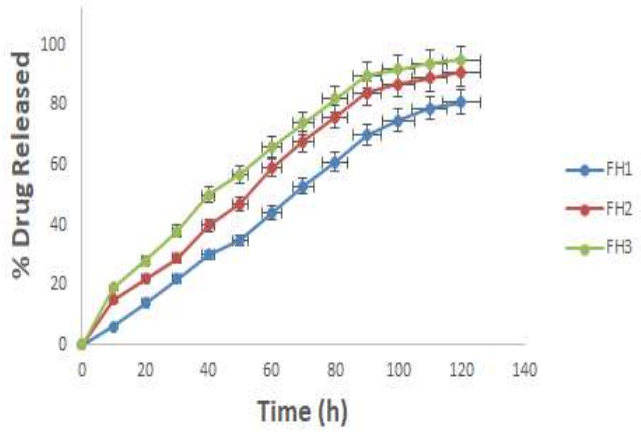


Figure 2b: Drug release profiles of ibuprofen implants formulated with gelatin and HPMC.

Drug polymer compatibility studies

From the FTIR spectra below, it can be seen that there was no significant difference between the internal structures of the pure drug (ibuprofen) and the sample formulations at the molecular level. Hence, it can be concluded that ibuprofen and the excipients used in the formulation of the implants were compatible.

Influence of relative humidity on the stability profile of the implants

The implants showed a significant weight gain in water (RH 100%) and a corresponding significant 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%).

ISSN 2616-0684 (Print)
ISSN 2616-0692 (Electronic)

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

Models	Zero		First		Higuchi		Korsmeyer and Peppas	
Formulations	r^2	K_0	r^2	K_1	r^2	K_H	r^2	n
FA1	0.902	3.37	0.967	-0.053	0.993	19.09	0.571	0.60
FA2	0.937	3.18	0.960	-0.029	0.995	17.70	0.607	0.61
FA3	0.947	2.96	0.946	-0.038	0.992	16.36	0.651	0.65
FH1	0.948	3.92	0.964	-0.047	0.998	17.64	0.589	0.63
FH2	0.945	3.18	0.969	-0.052	0.995	17.59	0.624	0.64
FH3	0.947	3.84	0.971	-0.054	0.994	18.25	0.688	0.65

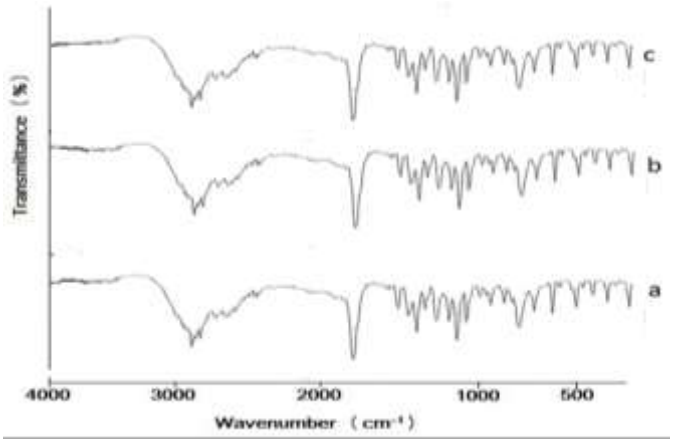


Figure 3: FTIR spectra (a) pure sample of ibuprofen (b) ibuprofen implant formulated using sodium alginate (c) ibuprofen implant formulated using HPMC.

The purpose of stability studies is to provide scientific data on how the quality of a drug product varies with time under the influence of a variety of environmental factors such as temperature, light and relative humidity.[19] Stability studies provide sufficient data for scientists and manufacturers to establish recommended storage conditions, expiration date, retest periods and shelf-lives of foods and drugs.[20,21] From the results obtained for the moisture sorption isotherm of the ibuprofen implant formulated using either sodium alginate or HPMC, it can be concluded that 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 25^{o}C over the three (3) months test period. Hence the implants can be safely stored at a similar environmental condition.

Conclusion

Ibuprofen implants were formulated using sodium alginate and HPMC and their influence on the release profile of the active ingredients from the formulations were compared statistically. The formulated implants were able to sustain the drug release from the formulation for up to the five (5) days study period. HPMC had a better-sustained release profile of the active drug from the implant formulations compared to sodium alginate. There was a significant difference between the rate of drug release from the implant formulated using HPMC and sodium alginate ($P<0.05$). The extended-release action of both polymers in the formulated ibuprofen implants can help to improve patient adherence to therapy, reduced frequency of dosing and better therapeutic outcomes for the management of patients with chronic pain and inflammation.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

References

1. Ovenseri AC, Isesele JE, Obarisiagbon AJ, Halilu ME, Uhumwangho MU. Influence of carnauba wax on the release profile of ibuprofen implants. EMUJPharmSci 2022; 5(1):45-56.
2. Purushotham RK, Jaybhaye SI, Ravindra K, Bhandari A, Pratima S. Designing of Diclofenac Sodium Biodegradable Drug Implant for Speedy Fracture Healing. J Chem Pharm Res. 2010; 3(1): 330-337.
3. Isesele JE, Airemwen CO, Uchendu AP, Asemwota IO, Obarisiagbon AJ, Uhumwangho MU. Formulation and *in vivo* studies of ibuprofen biodegradable implants, Eur J Pharm and Med Res. 2021; 8(7): 58-65.
4. Stewart SA, Domínguez-Robles J, Donnelly RF, Larrañeta E. Implantable polymeric drug delivery devices: classification, manufacture, materials, and clinical applications. Polymers. 2018; 10(12): 1379-1385.
5. Gisele R, Da Silva L, Sílvia LF, Rubens CS, Rodrigo J, Armando-da-Silva CJ. Implants as drug delivery devices for the treatment of eye diseases. Braz J Pharm Sci. 2010; 46(3): 585-595.
6. Airemwen CO, Isesele JE, Obarisiagbon AJ, Uhumwangho MU. Formulation of subcutaneous implantable drug delivery system of ibuprofen using biodegradable polymer. Nig J Pharm and App Sci Res. 2021; 10 (4): 14-21.
7. Aj MZ, Patil SK, Baviskar DT, Jain DK. Implantable drug delivery system: a review. Int. J. Pharm. Tech. Res. 2012; 4 (5): 280-292.
8. Kanzaria R, Kapadia Y, Lalji B, Desai TR. Implant-controlled release medicated formulation. Int J Pharm and Chem Sci. 2012; 1(1):59- 66.
9. Kleiner LW, Wright JC, Wang Y. Evolution of implantable and insertable drug delivery systems. J. Con Rel. 2014; 181(2)104-115.
10. Cole ET, Scott RA, Connor AL, Wilding IR , Petereit HU , Schminke C, Beckert T, Cade D. Enteric coated HPMC capsules designed to achieve intestinal targeting, Int J Pharm. 2002; 231 (2): 83–95.
11. Jain A, Gupta Y, Jain SK. Perspectives of biodegradable natural polysaccharides for site specific drug delivery to the colon. J Pharm and Pharm Sci. 2007; 10: 86-128.

12. Fu Y, Kao WJ (2010). Drug release kinetics and transport mechanisms of non-degradable and degradable polymeric delivery systems. Exp opinion on drug del. 2010; 7(4): 429-444.
13. Korsemeyer RW, Gurny R, Doelker EM, Buri P, Peppas NA. Mechanism of solute release from porous hydrophilic polymers. Int J Pharm. 1983; 15: 25-35.
14. Fumimoto Y, Matsuyama A, Komoda H, Okura H, Lee CM, Nagao A. Creation of a rich subcutaneous vascular network with implanted adipose tissue derived stromal cells and adipose tissue enhances subcutaneous grafting of islets in diabetic mice. Tissue Eng. Meth, 2009; 15: 437-444.
15. British Pharmacopoeia. London, UK: Her Majesty's Stationery Office. 2012; A234.
16. Higuchi T. Mechanism of sustained action medication. Theoretical analysis of rate release of solid drugs dispersed in solid matrices. J. Pharm. Sci, 1963; 52: 1145-1149.
17. Mohammed MI, Sanjeev E, Shanti S. Design and evaluation of subcutaneous implantable drug delivery system of tramadol using natural biodegradable polymer. Annals Phytomed, 2012; 2:30-38.
18. Negrin, CM, Delgado A, Llabres M, Evora C. Methadone implants for methadone maintenance treatment, *in vitro* and *in vivo* animal studies. J Con Release. 2004; 95: 413-421.
19. Oalta R, Grewal Y, Batth S, Singh A. A Survey of analgesic and anti-inflammatory drug prescription for oral implant surgery. Int J Plastic and Aesthetic Res. 2015; 2: 51-55.
20. Onishi HM, Takahashi N and Machinda Y. PLGA implant tablet of ketoprofen: comparison of *in vitro* and *in vivo* releases. Biol Pharm Bull. 2005; 28(10): 2011-2015.
21. Phattanaphakdee W, Ditipaeng C, Uttayarat P, Thongnopkoon T, Athikomkulchai S, Chittasupho C. Development and validation of HPLC method for determination of quercetin in hydrogel transdermal patches loaded with red onion peel extract. Trop J Nat Prod Res, 2022; 6(8):1210-1214.