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Influence of carnauba wax on the release profile of ibuprofen implants

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Abstract

Pharmaceutical implants are small sterile solid masses usually cylindrical consisting of a highly potent and purified drug 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. The purpose of this study was to evaluate the influence of carnauba wax on the release profile of ibuprofen implants. The implants were prepared with gelatin, hydroxypropyl methylcellulose admixture (80:20) and varying amount of carnauba wax (2.5%, 5%, 7.5%) using the solvent casting technique. Another batch of the implant was formulated without the incorporation of carnauba wax. Glycerin was used as the plasticizing agent. The physicochemical properties and the release kinetics of the implants were evaluated. The implant pellets had a similar appearance with minimal batch to batch variation. The mean diameter/thickness of the implants ranged from 2.46±0.10-2.86±0.03 mm, the percentage drug content was ≤96.92±0.12% and the swelling index values were between 2.68±0.01 – 4.87±0.01%. The rate of drug release from the ibuprofen implants was significantly affected by the incorporation of carnauba wax. The higher the amount of carnauba wax incorporated in the formulation, the more retarded the rate of drug release. This can be exploited in the formulation of sustained release ibuprofen implants for the management of chronic diseases such as arthritis.

Keywords

Carnauba wax, ibuprofen, subcutaneous, implant.

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INTRODUCTION

Pharmaceutical implants are small sterile solid masses containing a highly potent and purified active pharmaceutical ingredient that are intended to be subcutaneously implanted beneath the skin using a suitable special injector or surgical incision to provide continuous release of the active medicament over a long period of time (Wang *et al.,* 2010; Rajgor *et al.,* 2011). Implants have several advantages such as convenience, improved drug delivery, improved adherence to therapy, reduction in the frequency of dosing, potential for zero order controlled release, flexibility in therapy termination, potential for bio-responsive release and flexibility in the choice of polymers as well as the method of manufacture (Alissa *et al.,* 2009; Isesele *et al.,* 2021).

Implants have been used therapeutically in cancer chemotherapy, dental applications, immunization, as ocular drug delivery systems in the treatment of ocular diseases such as glaucoma (e.g., an ocular insert containing pilocarpine) and in the formulation of some long-acting contraceptives such as levonorgestrel, which is used to prevent pregnancy (Tian *et al.,* 2012, Mohammed *et al.,* 2012).

Carnauba wax is a vegetable wax obtained from the fronds of the carnauba tree (*Copernicia cerifera*). It is valued among the natural waxes for its hardness and high melting temperature. It consists primarily of esters of long-chain alcohols and acids. It has a melting point of 85°C and it is normally used pharmaceutically in melt granulation for sustained release of highly soluble tablets (Garcia *et al.,* 2002).

Ibuprofen is an analgesic, antipyretic, and anti-inflammatory drug that belongs to the non-steroidal anti-inflammatory drug (NSAID) class of medications. Its pharmacological activity is elicited by blocking the enzyme cyclooxygenase (COX), which converts arachidonic acid to prostaglandin H_2 (PGH_2), reducing the synthesis of other prostaglandins in the body, which are mediators of pain, swelling and inflammation (Grosser *et al.,* 2010).

It is available as cream, tablet, gel, suppositories and oral suspension. It is used in the treatment of pain associated with sprains, bone fracture, arthritis, dysmenorrhoea and also for the treatment of fever. Isesele *et al.,* (2021) formulated ibuprofen biodegradable subcutaneous implants and investigated the *in vivo* analgesic activities using mice. They found out that the subcutaneous ibuprofen implants significantly inhibited acetic acid-induced writhing in mice as compared to the control.

The aim of this study was to evaluate the influence of carnauba wax on the release profile of subcutaneous implants of ibuprofen (Gisella *et al.*, 2010).

MATERIALS AND METHODS

Ibuprofen sample was obtained as a gift from Edo Pharmaceuticals Limited (Nigeria). Gelatin, carnauba wax 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.

Preparation of implants

Gelatin (24 g) was sprinkled on top of 100 mL of water in a beaker and left to hydrate for 30 min. Hydroxypropyl methylcellulose (HPMC) (6 g) and varying amount of carnauba wax were then added to the hydrated gelatin (Table 1). An extra batch was prepared without the addition of carnauba wax. Glycerin (20 mL) was added as a plasticizing agent while stirring continuously and the solution was heated over a hot water bath at 60°C until the gelatin was completely dissolved. Separately, 4 g of ibuprofen was dissolved in 5 mL acetone before being added to the heated gelatin, HPMC and carnauba wax mixture in the beaker. The resulting liquid was poured into a glass petri-dish and allowed to gel for 30 min while the petri-dish was placed on an ice pack. The congealed mass was allowed to air dry for 72 h at room temperature in an aseptic cabinet. After drying, the implants were removed from the petri dish and cut into 4 mm wide and 2 mm long rods with a stainless-steel cutter (Rajgor *et al.,* 2011).

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 the sliced implants were kept on top of the petri dish in a wire mesh. 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 that the formaldehyde and gelatin had fully reacted. The implants were then stored for one week in an open atmosphere under aseptic conditions to ensure that any leftover formaldehyde was totally evaporated (Rao *et al.,* 2010).

Table 1: Composition formula of ibuprofen implants.

Formulation	Drug (g)	Gelatin (g)	HPMC (g)	Carnauba wax (%)	Glycerin (mL)
IC0	04.0	24.0	6.0	-	20.0
IC1	06.0	24.0	6.0	0.25	20.0
IC2	08.0	24.0	6.0	0.50	20.0
IC3	10.0	24.0	6.0	0.75	20.0

Evaluation of subdermal implants

Thickness of implants

The thickness of a sample of three implants from each batch was measured with a micrometer screw gauge (Begemann GMBH, Germany) and the mean value was recorded.

Weight uniformity of implants

Implant samples were chosen randomly from each batch (n=3) and weighed separately on an analytical scale (Mettler Tolledo, Switzerland). The average weight and the percentage deviation from the mean were calculated.

Drug content uniformity

The drug content of the implants was determined by micronizing three (3) randomly picked implants and transferred to a 50 mL volumetric flask. Then, 45 mL of 0.1 M sodium hydroxide (NaOH) was added and vigorously shaken for 30 min at 500 rpm with a flask shaker, the volume was then made up to 50 mL. To estimate the amount of ibuprofen present, serial dilutions were done and the absorbance was measured using a UV spectrophotometer (UNICO ^{Tm,} 2011, UK). The technique was performed in triplicate. The mean and standard deviations were calculated (Purushotham *et al.*, 2010).

Swelling Index

Three (3) sliced implant samples were immersed in a phosphate buffer pH 7.4 swelling solution and the weight of each implant was calculated 1 h later after the excess fluid was gently wiped away with a dry piece of tissue paper (Kanzaria *et al.*, 2012). 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.

Percentage moisture content

For each batch, five (5) cut implant samples were weighed on a weighing balance and placed in a dessicator with activated silica gel as the dessicant. The implants were removed and weighed on a regular basis until they attained a constant dry weight (Onishi *et al.,* 2005). The percentage mass loss on drying (moisture content) was calculated using equation 2:

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

Moisture sorption studies

Under various simulated relative humidity (RH) conditions, the cut implant formulations were tested for stability. Saturated sodium chloride (75% RH), magnesium chloride (45% RH), water (100% RH) and activated silica gel (0% RH) were used in the experiment. Individually wrapped in aluminum foil paper, the implant formulations were stored

in relative humidity tanks at 30°C ambient room temperature. For a maximum of three months, the physical parameters of the implants and their weight were documented at predetermined intervals. The average values were calculated and plotted against time in days.

Preparation of standard calibration curve

Pure ibuprofen sample (100 mg) was dissolved in sufficient quantity of the dissolution medium (0.1 M NaOH) to yield a 100 mL solution and a stock solution of 1 mg/mL was obtained. Using the dissolution medium, serial dilutions of the stock solution were made to obtain the following concentrations: 0.5, 1, 2, 4, 6, 8, 10 µg/mL. The absorbance of the diluted samples was measured using a UV spectrophotometer at a maximum wavelength of 227 nm. The measurements were carried out in triplicate and a graph of the mean absorbance versus concentration was plotted (Beer-Lambert plot).

***In vitro* drug release studies**

The dissolution test was carried out using the reciprocating disc method (Apparatus 7; ST7, G.B. Caleva Ltd, England). Individual implants were placed in a dissolution basket and immersed into an 800 mL 0.1 M NaOH solution heated to 37±0.5°C and agitated at 50 rpm dissolution medium. Using a pipette, 5 ml aliquots of the dissolving fluid were withdrawn at various time intervals of 1, 4, 8, 16, 32 h, etc. and placed in suitable sample test tubes for testing. Sink condition was maintained by replacing the withdrawn dissolution medium with fresh 5 mL of 0.1 M NaOH. The drug concentration in the obtained samples of dissolution fluid was determined spectrophotometrically at a wavelength of maximum absorption (max) of 227 nm after suitable dilution with the dissolution medium.

***In vitro* drug release kinetics**

The results of the dissolution rate tests of the ibuprofen implants were subjected to several drug release models to analyze the release kinetics and the models used were zero order, first order, Higuchi square root of time and Korsmeyer-Peppas. The linear regression coefficient (r^2) was calculated for each rate order. The dissolution release profile was regarded to have followed a specific release order if the r^2 value was greater than 0.95 (Higuchi, 1963; Korsemeyer *et al.,* 1983).

Drug excipients interaction

The potassium bromide pellet method was used to generate the spectra for ibuprofen and the various formulations on a Fourier transform infra-red (FTIR) spectrophotometer (Perkin Elmer, Series model 1615, England), and the spectra were evaluated for any interactions or incompatibilities.

RESULTS AND DISCUSSION

Evaluation of physical parameters of implants

The physical appearances of the formulated implants are shown in Figure 1. They conform to the physical properties of implants designed for long-term ibuprofen administration. The implants were yellowish in colour. The cut implants appeared firm and smooth after 12 h of hardening in formaldehyde solution. The contact of the implants with formaldehyde vapour improved the degree of cross linking of the polymer matrix, resulting in an increase in the tensile strength of the implants (Oalta *et al.,* 2015).

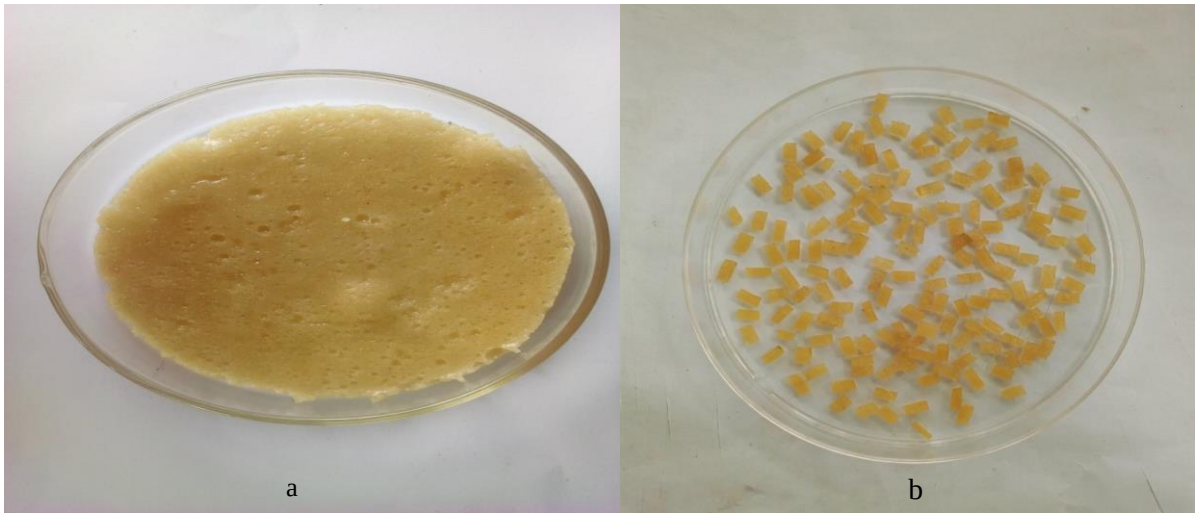

Figure 1: (a) Formulated ibuprofen implants (b) Cut ibuprofen implant.

Evaluation of the physicochemical parameters of implant formulations

The physical parameters of the formulated implants are shown in Table 2. In all batches of implant formulations, the mean diameter/thickness of the implants was between 2.46±0.10 and 2.86±0.03 mm. The computed percent weight variation for all implant formulations was within official limits, indicating that the formulated implants passed the weight variation test (BP, 2012). The implant formulations weighed between 120±0.2 and 126±0.1 mg. This is an important feature since it shows the amount of particulate matter embedded within the implant polymer matrix.

In the formulated implants, the percentage drug content of ibuprofen was ≤96.92±0.12%. The results, however, demonstrate a high level of entrapment efficiency and drug loading and they are within officially permissible limits (BP, 2012).

The swelling index of the various implant formulations ranged from 2.68±0.01 - 4.87±0.01% after 1 h of immersion in a

phosphate buffer swelling solution (pH 7.4). When exposed to an aqueous solution, the polymer expands owing to the uptake of water. The polymer hydrophobicity determines how rapidly the implant absorbs water. The encapsulated drug diffuses out through the pores generated by the swelling of the implant (Michael *et al.*, 2015).

The percentage mass loss on drying (moisture content) data reveal moisture content values ranging from 24.47±0.01% - 28.89±0.02%, which are within the official moisture content limits for biodegradable gelatinous polymers. Gels are formed when biodegradable gelatinous polymers come into contact with a suitable solvent. As a result, matrix implants made of biodegradable gelatinous polymers that form a random network infiltrated by liquid-filled pores are known to have a high moisture content (Satish, 2017).

Table 2: Results of the physical parameters of ibuprofen implant formulations.

Formulation	Thickness (mm) $\pm S.D$	Weight (mg) ± S.D	Drug content (%)	Swelling index (%)	Moisture content (%)
IC0	2.46 ± 0.10	120± 0.2	95.69± 0.11	2.68± 0.01	24.47± 0.01
IC1	2.68 ± 0.01	121± 0.1	96.38± 0.10	3.64±0.02	26.72± 0.02
IC2	2.79 ± 0.02	123± 0.1	96.54 ± 0.12	4.28±0.01	28.64± 0.01
IC3	2.86 ± 0.03	126± 0.1	96.92 ± 0.12	4.87±0.01	28.89± 0.02

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

Figure 2 shows *in vitro* drug release studies of ibuprofen implant formulations (IC0 - IC3) in 0.1 M NaOH. In general, factors such as the swelling and dissolution of polymeric drug carriers, as well as diffusion of the active drug over a long period of time, have been shown to influence the rate of drug release from hydrophilic matrices (Isesele *et al.*, 2021).

Implantable drug delivery systems have been shown to successfully sustain the release of drugs held within their matrices over a long period of time when compared to conventional drug formulations, which are expected to release over 85% of their drug content during the first hour (BP, 2012). As shown in Figure 2, all implant formulations showed a sustained release of the drug over a 6-day period. Ibuprofen has a short biologic half-life of 3 h, hence it must be taken 2-3 times a day. However, based on *in vitro* dissolution studies, the implant formulations revealed a sustained modified release of ibuprofen that was similar to the zero-order release profile.

The rate of drug release was faster for batch IC0 formulated without the incorporation of carnauba wax as compared to formulations IC1-IC3 which showed a sustained release of drug over a long period of time. For example, the maximum drug release for

batch IC0 was 96% and the time to attain maximum drug was 80 h as compared to batches IC1, IC2 and IC3 which had drug released rate of 72%, 64% and 52% respectively in 80 h. Batches IC1-IC3 formulated with the incorporation of carnauba wax had their maximum drug release and were able to sustain the rate of drug release for up to 140 h. The higher the amount of carnauba wax incorporated in the formulation, the more retarded the rate of drug release. Previous studies have reported that the mechanism of drug release from carnauba wax involves the leaching of drug by the dissolution medium and the diffusion of drug from the polymeric matrix (Onyechi and Okafo, 2016). The findings from this research indicate that carnauba wax, a hydrophobic wax was slowly permeated by the dissolution media as a function of time and this delayed the rate of drug release form the implant formulations compared to the formulations that were prepared without the incorporation of carnauba wax which were highly permeated by the dissolution medium leading to the faster release of drug from the formulation. Drug release from the carnauba wax was also diffusion–controlled and simulated the Higuchi's Square root model. There was a significant difference between the drug release rate of the formulations without carnauba wax and those with carnauba wax ($P>0.05$).

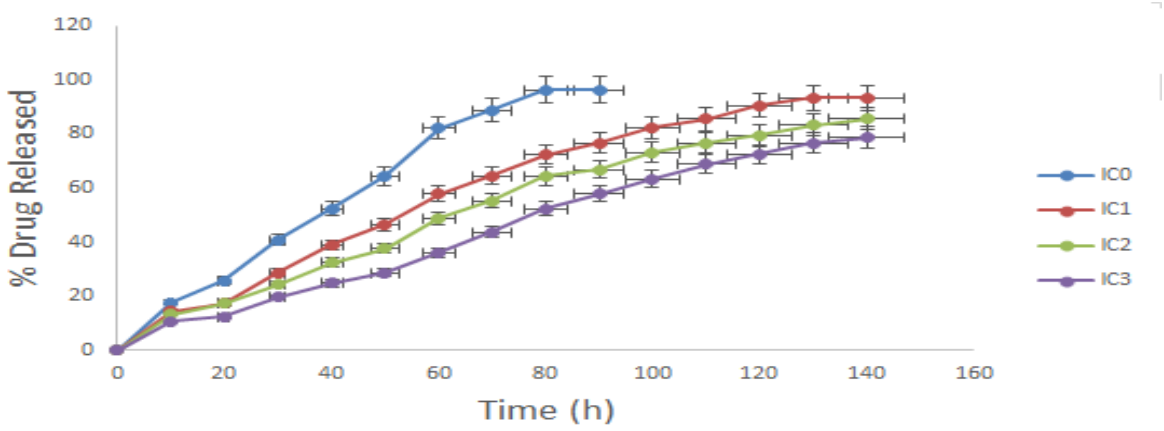

Figure 2: Drug release profiles of ibuprofen implants formulated with gelatin and HPMC.

Release kinetics of ibuprofen implants

The release kinetics analysis shows that the drug initially was released from the formulation rapidly, followed by a sustained release over time. Previous researches have shown that the mechanism of drug release from biodegradable implants is frequently controlled by diffusion, and degradation (Gisele *et al.*, 2010). Table 3 shows that the release mechanism of the various batches of ibuprofen implant formulations simulated the Higuchi model (r^2=0.998), indicating that the drug was homogeneously diffused

throughout the polymer matrices and that drug release kinetics were diffusion controlled (Higuchi, 1963). The results of the Korsmeyer-Peppas diffusion model (n > 0.5) show that the diffusion was non-Fickian (Korsmeyer *et al.*, 1983, Oalta *et al.*, 2015).

Table 3: Correlation coefficient and release kinetics of ibuprofen implants.

Models	**Zero**		**First**		**Higuchi**		**Korsmeyer and Peppas**	
Formulations	r^2	K_0	r^2	K_1	r^2	K_H	r^2	n
IC0	0.926	4.14	0.958	-0.052	0.992	19.28	0.569	0.56
IC1	0.954	3.87	0.959	-0.026	0.993	17.61	0.634	0.62
IC2	0.959	2.68	0.962	-0.037	0.996	16.73	0.652	0.63
IC3	0.964	3.75	0.968	-0.048	0.998	18.92	0.673	0.68

FTIR Analysis

The drug/excipient compatibility was determined using FTIR analysis. The peaks of the pure ibuprofen sample and the various formulations of ibuprofen implants did not differ significantly. The internal structure of the pure ibuprofen sample and the ibuprofen implant formulations were identical at the molecular level, as shown in the FTIR spectra below (Figure 3). As a result, there were no significant interactions between the drug and the excipients used in the formulation of the ibuprofen implants.

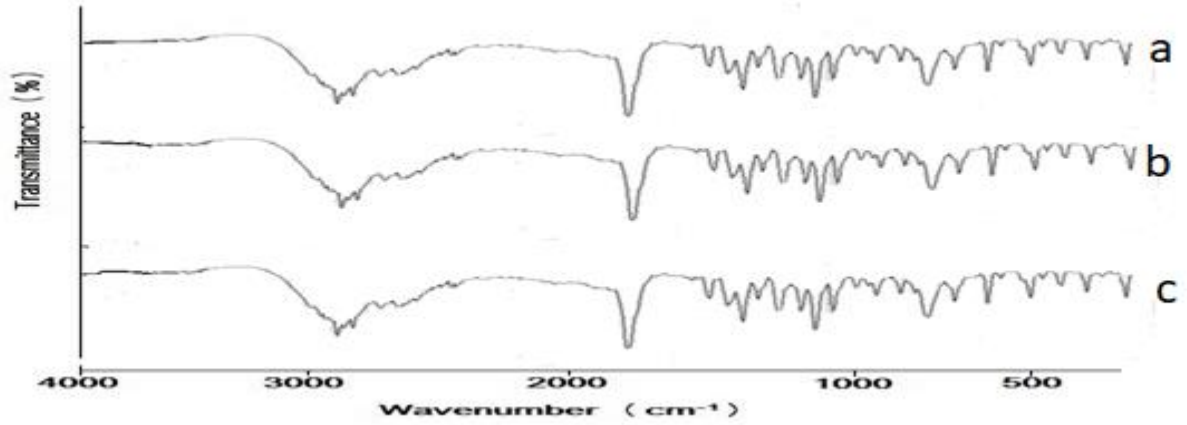

Figure 3: FTIR spectra (a) pure sample of ibuprofen (b) physical mixture of ibuprofen, gelatin and HPMC (c) implant of ibuprofen, carnauba wax, gelatin and HPMC.

Influence of relative humidity on the stability profile of the implants

The data for the change in implant weights over time under various relative humidity conditions at 30^{o}C is shown in Figure 4. In saturated sodium chloride (75% RH) and magnesium chloride (45% RH) solutions, the implants showed a relative stable weight but a rapid weight gain was observed in water (100% RH) and a

significant weight loss in activated silica gel (0% RH). Stability testing enables the determination of recommended storage conditions, shelf-lives and retest periods by revealing how the quality of a drug product changes over time as a result of a variety of environmental factors such as temperature, humidity and light (Isesele *et al.*, 2021).

There was no significant weight increase or change in the organoleptic properties of the implants stored at relative humidity of 45% and 75% at a temperature of 30^{o}C over the 3 months test period, according to the results of the moisture sorption isotherm of the ibuprofen implant formulations. The implants can be safely stored under similar environmental conditions.

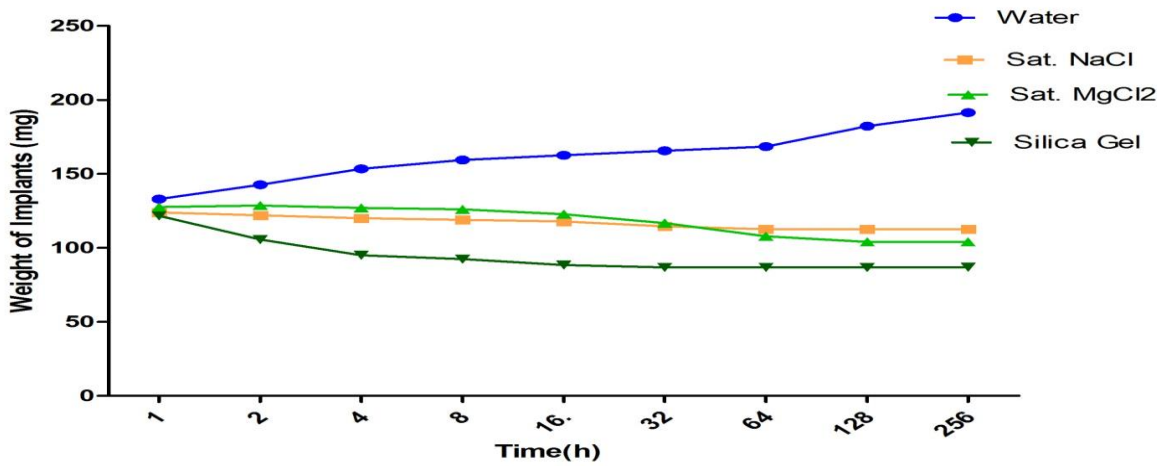

Figure 4: Moisture sorption isotherm of implant formulations under different conditions of relative humidity.

CONCLUSION

The rate of drug release from the ibuprofen implants was significantly affected by the incorporation of carnauba wax. The higher the amount of carnauba wax incorporated in the formulation, the more retarded the rate of drug release. There was a significant difference between the drug release rate of the formulations without carnauba wax and those with carnauba wax ($P>0.05$). This could be exploited in the formulation of sustained release ibuprofen implants for the management of chronic diseases like rheumatoid arthritis.

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