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Effect of Formulation Variables on the Release of Letrozole from Natural Biodegradable Polymeric Implants

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Authors' contributions

This work was carried out in collaboration between all authors. Author SMH performed the statistical analysis, wrote the protocol, managed the literature searches, and wrote the first draft of the manuscript. Authors SI and MS managed the analyses of the study. Author SI designed the study. All authors read and approved the final manuscript.*

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ABSTRACT

Aim: Letrozole, a non-steroidal aromatase inhibitor, prevents the body from producing its own estrogen. The objective of the present study was to explore the fabrication and evaluation of natural biodegradable polymeric Letrozole implant for long term drug release targeting postmenopausal women with metastatic breast cancer.
Methodology: The effect of different formulation variables i.e. different types of excipients and different hardening times (6 hrs, 12 hrs and 24 hrs) with exposure to formaldehyde vapour was investigated on drug loading efficiency and drug release profile. The result of in-vitro dissolution study was fitted to different kinetic models to evaluate the kinetic data.
Results: Letrozole release was studied for 10 to 19 days with some excipients. The in

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vitro Letrozole release from Gelatin-Sodium Alginate biodegradable polymeric implant was maximum, about 19 days, where Cetyl alcohol was incorporated as excipient. The release kinetics was explored and explained using Higuchi, zero and first order while the mechanism of release was confirmed with Korsmeyer-peppas model. Implants were found to follow Higuchi model the best in most cases. Good correlations were also obtained with Korsmeyere-Peppas model. According to these models, the drug released from implants were of diffusion controlled, where the drug was found to leave the matrix through pores and channels formed by entry of dissolution medium.

Conclusion: The addition of different excipients and variation in hardening times were found to influence the drug loading efficiency and drug release significantly. Further investigation would confirm its potential in breast cancer therapy.

Keywords: Letrozole; biodegradable polymeric implant; gelatin; sodium alginate; DSC; SEM.

1. INTRODUCTION

Breast cancer is the most common cancer in women. It is the leading cause of cancer death in the less developed countries of the world, and is responsible for about 522 000 women deaths in 2012 worldwide. It now represents one in four of all cancers in women [1]. The use of letrozole, which is a more potent suppressor of both plasma and tissue estrogen levels, is an attractive treatment for postmenopausal women with metastatic breast cancer [2]. It is administered to the postmenopausal women who have finished five years of treatment with Tamoxifen [3].

The benefits of Letrozole compared to Tamoxifen were most notable in treating lobular breast cancer compared to ductal breast cancer in improving both disease-free survival (living without the cancer growing), time to distant recurrence and overall survival (living whether or not the cancer grew) in postmenopausal women diagnosed with estrogen-receptor-positive, HER2-negative breast cancer [4,5].

A major challenge in the treatment of metastatic cancer is effective delivery of therapeutics to the tumor lesion. Due to severe side-effects associated with the drug, viz., hot flashes, headache, breast tenderness and a half-life of ≈45 h, this drug appears to be particularly suitable for targeted and controlled release drug delivery system [6]. In order to increase the sustaining capability of Letrozole, means of enhancing its duration of drug release using biodegradable polymers has already been taken into consideration, such as entrapping the drug into nanoparticle technology [7,8] and thermoplastic polymeric drug delivery devices [6]. In this study Letrozole, the third generation of aromatose inhibitor, have been entrapped into Gelatin-sodium alginate biodegradable polymeric implants hardened with formaldehyde vapor for sustained drug delivery. Sodium alginate is included in 20% ration with biodegradable matrix former gelatin as a rate retarding agent [9]. The purpose of exposing the gelatin-sodium alginate implant to formaldehyde vapor is that formaldehyde reacts with gelatin leading to crosslinks between gelatin molecules, resulting in the formation of hardened gelatin [10]. This reaction is of great practical importance, in particular, for preparation of enteric capsules and development of controlled drug delivery systems [11]. Slow release of Letrozole can inhibit estrogen biosynthesis for a prolonged period of time by virtue of increased local concentration of the drug at the receptor site as well as reduce the number of necessary administrations, providing more localized and better use of the active agents.

2. MATERIALS AND METHODS

2.1 Materials

All the chemicals and reagents used in this study were of analytical grade. Letrozole was obtained as a gift from Renata Limited, Bangladesh. Purified Gelatin, Xanthan Gum and Polyethylene glycol (PEG) 4000 were purchased from Merck Specialities Pvt. Ltd, Mumbai. Sodium Alginate, Glyceryl Mono Stearate (GMS), Stearic Acid and Cetyl Alcohol were purchased from Loba Chemie Pvt. Ltd, Mumbai. Cremophor EL was purchased from BASF, Germany. Acetonitrile was purchased from Fischer Chemical, New Jersey (NJ). Suitable storage conditions were maintained to store the working chemicals and reagents.

2.2 Methods

2.2.1 Preparation of Implants

Heating and congealing method is used to prepare biodegradable implants of Letrozole. Implants were prepared using 10% drug load with different excipients to obtain a porous gelatin-alginate matrix to be used as the active substance carrier and getting prolonged drug release action from its implantable form. The excipients used in different formulations are shown (Table 1).

Weighed quantity of Gelatin was sprinkled on the surface of water and kept aside for 30 minutes to hydrate. Sodium Alginate was added in hydrated gelatin. Glycerin, which occurs naturally in human organism, was added as a plasticizing agent with continuous stirring and the solution was heated in a water bath at 60℃ until Gelatin was dissolved. Letrozole was then dispersed separately in acetone and added to the Gelatin and Sodium Alginate solution. The solution was poured in a glass petridish upto 1.45 mm height and allowed to gel by placing the petridish on ice bath for 30 minutes. They were then allowed to set by placing in a refrigerator for 3 days. After 3 days, the implants were placed in a formaldehyde desiccator for hardening. Formulations varied with respect to Gelatin-Sodium Alginate polymer ratios [12,13,14].

Table 1. Excipients used in different formulations

Formulation	Drug	Used excipients
F1	Letrozole	–
F2	Letrozole	Cetyl Alcohol
F3	Letrozole	Stearic Acid
F4	Letrozole	Cremophor EL
F5	Letrozole	GMS
F6	Letrozole	PEG 4000
F7	Letrozole	Xanthan Gum

2.2.2 Hardening of implants

A Petri-dish containing Formaldehyde solution (37% v/v) was placed in an empty glass desiccators. The implants containing petridish was kept on top of the desiccators and was closed immediately. The implants were made to react with formaldehyde vapors for different time interval such as 6, 12 and 24 hours. They were then removed from the desiccator for air

drying for approximately 72 hours, so that the reaction between gelatin and sodium alginate is complete. Implants were then cut into square shapes of 1 cm length and width by an NT cutter. Then the implants were kept in the open air in an aseptic condition for a week to make sure that the residual formaldehyde gets evaporated [12].

2.2.3 Characterization of Implants

2.2.3.1 Photographic imaging

The kinetics of drug release is greatly dependent on the morphological characters of implants [9]. Photographs of drug loaded implants (Fig. 1) were taken using Samsung Galaxy S4, 12.0 Mega Pixel Camera.

Fig. 1. Photographic images of gelatin - sodium alginate polymeric implant

2.2.3.2 Measurement of implant thickness

The thickness of the implants was measured by picking three samples of implants for a particular formulation and exposure time, and measuring their thickness with slide calipers. The average thickness of implants hardened with formaldehyde is shown (Table 2).

2.2.3.3 Weight variation of implants

Weight variation of implants was checked by weighing three implants of a particular formulation and exposure time individually [12]. The average weight of implants hardened with formaldehyde is shown (Table 2).

2.2.3.4 Scanning electron microscope (SEM)

The internal morphology of the samples was evaluated by a SEM Philips XL30, (Netherlands). The implants were initially spread on a carbon tape glued to an aluminum stub and coated with Au using a Sputter Coater under vacuum in a closed chamber. The Au layer was coated to make the implant surface conductive to electrons in the SEM. The implants were then observed under SEM in varying magnifications and micrographs recorded.

2.2.3.5 Differential scanning calorimetry (DSC)

The DSC measurement was performed on a DSC-60 (SHIMADZU) differential scanning calorimetry with a thermal analyzer (TA-60WS). Precise amounts of 7.5 mg of Letrozole + gelatin + Na Alginate sample were placed in a sealed aluminium pan, before heating under nitrogen flow (300 ml/min) at a scanning rate 10ºC min^{-1} from 30℃ to 500℃. An empty aluminum pan was used as reference (Dhaka, Bangladesh).

Table 2. Thickness & weight variation of Letrozole loaded implants with different excipients

Sl. no.	Formulation	Thickness of implant (mm) ± S.D.	Weight of implants (mg) ± S.D.
1	F1	1.21±0.01	178.3±0.45
2	F2	1.93±0.01	138.9±0.52
3	F3	1.40±0.01	164.4±0.25
4	F4	1.27±0.01	186.2±0.12
5	F5	1.47±0.01	145.5±0.33
6	F6	1.46±0.01	176.3±0.23
7	F7	1.68±0.01	205.7±0.38

2.2.4 Determination of drug content (loading dose)

The amount of drug that was actually loaded in implants during fabrication process was determined by spectrophotometric analysis. A weighed Letrozole implant was crushed by a porcelain mortar and pestle and dissolved in 1 ml hot phosphate buffer, pH 7.4 by vigorous ultrasonication. 3 ml of acetonitrile was added for precipitating the polymer followed by addition of 7 ml phosphate buffer, pH 7.4 for extracting the drug in buffer. Centrifugation was done at 3000 RPM for 10-12 minutes to separate the solid material. 1 ml of supernatant was withdrawn into a 100 ml volumetric flask. Volume was made with acetonitrile and phosphate buffer (pH 7.4) at the ratio of 30:70. It was then analyzed at 230 nm (λ_{max} of Letrozole) in UV spectrophotometer. Letrozole concentration was calculated from the standard curve.

The % loading efficiency (LE) of implants was determined with the formula:

$$\%\ loading\ efficiency\ (LE) = \left(\frac{LD}{AD}\right) \times 100$$

Where,

LD is the amount of loaded drug in the implant and
AD is the amount of added drug in the formulation [15].

2.2.5 Test for formaldehyde

2.2.5.1 Qualitative test for free formaldehyde

Implants are subjected to pharmacopoeial test for free formaldehyde to ensure the absence of residual formaldehyde in the implants [16].

2.2.5.2 Quantitative test for crosslinked formaldehyde

A 1500 µg/mL stock solution of formaldehyde was prepared by diluting a volume of 0.95 ml of formaldehyde (37%) solution to 250 ml with water. Serial dilution was then done to obtain the concentrations 0.15 µg/ml, 0.30 µg/ml, 0.75 µg/ml, 1.50 µg/ml and 3.00 µg/ml, respectively. The absorbance of the solutions was measured in a Double Beam UV-VIS spectrometer (SHIMADZU) at 412 nm. From the observed absorbances, standard curve was made for the assay for formaldehyde.

50 ml of distilled water was added to 1g of grounded sample of each implant and the mixture was agitated using an ultrasound bath for 10 min at 80°C. This ensures the removal of acetaldehyde if present. The formaldehyde crosslinked with gelatin was obtained by soaking the sample with 4ml sulfuric acid (90%) medium. The solution was left for a few minutes to cool and then filtered. The absobance of the filtered solution was then observed in Double Beam UV-VIS spectrometer (SHIMADZU) at 412 nm. By plotting the absorbance of the solution into the standard curve equation, the concentration of formaldehyde in the implants was measured [17].

2.2.6 In-vitro dissolution studies

The in-vitro release of Letrozole from implants was carried out in static conditions at 37°C. The weighed implants (at least 3 implants) from each formulation and exposure time were kept in rubber capped glass vessels containing 100 ml of Phosphate Buffer, pH 7.4. 10 ml of the release medium was collected at predetermined time intervals and replaced with 10 ml of fresh buffer to maintain the sink condition. The withdrawn samples were then analyzed for determining the percentage of release of drugs by UV spectrophotometer (UV-1700 Pharma Spec, SHIMADZU) at 230 nm (λ_{max} of Letrozole in Phosphate Buffer, pH 7.4), after subsequent dilution of the samples. All data were used in statistical analysis for the determination of mean, standard deviation and release kinetics.

2.2.7 Statistical analysis

Results were expressed as mean ± S.D. Statistical analysis was performed by linear regression analysis. Coefficients of determination (R^2) were utilized for comparison. *In-vitro* release studies were performed under the same conditions for each implant system. The means and standard deviations were calculated at each time interval. The means were graphed for each release profile with the standard deviations included as error bars. Linear regression was performed on cumulative drug release as a function of time and also on fitted curves to different kinetic models.

3. RESULTS AND DISCUSSION

3.1 Observation through Scanning Electron Microscope (SEM)

The SEM micrograph of Cetyl alcohol (as excipient) loaded Letrozole polymeric implant surface before and after drug release is represented (Figs. 2, 3 respectively). They display a 50 times magnified polymeric implant surface.

The more hydrophobic the polymer, the smoother the surface [18]. The rough implant surface as observed in the SEM micrograph (Fig. 2) is indicative of the hydrophilic nature of

the polymer matrix. This hydrophilic nature of gelatin and sodium alginate is supported by Takahashi et al. [19] and Aslani et al. [20], respectively. Fig. 3 displays the implant surface after drug release. The large pores on the surface as seen in the figure are created by the entry of the dissolution media while drug release continues.

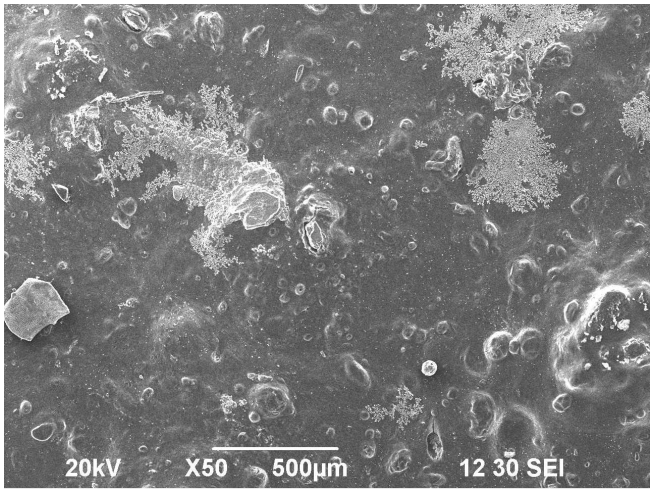

Fig. 2. SEM micrograph of Letrozole biodegradable polymeric implant incorporated with Cetyl Alcohol surface before drug release

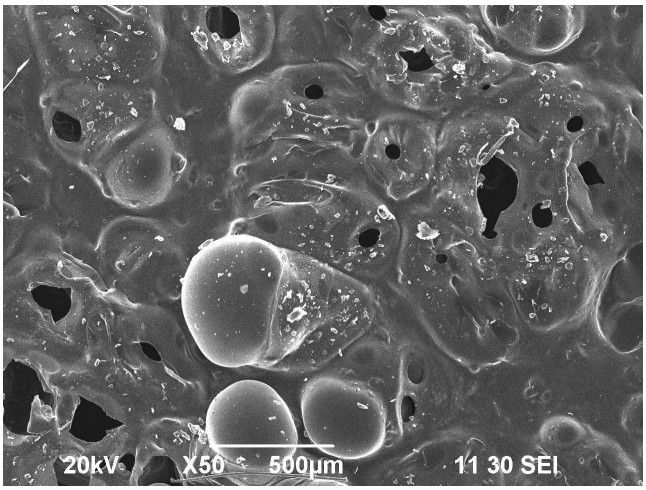

Fig. 3. SEM micrograph of Letrozole biodegradable polymeric implant incorporated with Cetyl Alcohol surface after drug release

3.2 Differential Scanning Calorimetry (DSC) of Drug and Polymer

The DSC scans of pure Letrozole incorporated in Gelatin-Sodium alginate mixture was also performed (Fig. 5). The figure exhibits total four endothermic peaks. Gelatin and Sodium alginate have the first broad endothermic peak corresponding to the onset and offset temperatures 80℃ and 160℃, respectively with the highest peak appearing at 119℃.

Another small and broad endothermic peak is found, which is due to the presence of Letrozole with the onset temperature 199℃ and offset temperature at 226℃ with the highest peak at 221℃ with the ΔH 231.65 J/g. The characteristic endothermic peak of pure Letrozole is at 181℃ (Fig. 4) [21]. There is a little difference found in endothermic peak of Letrozole implant (221℃) which can be attributed to the presence of polymer [22]. The presence of the polymer in the formulation probably raised the melting point of Letrozole causing the shift of endothermic peak to 221℃.

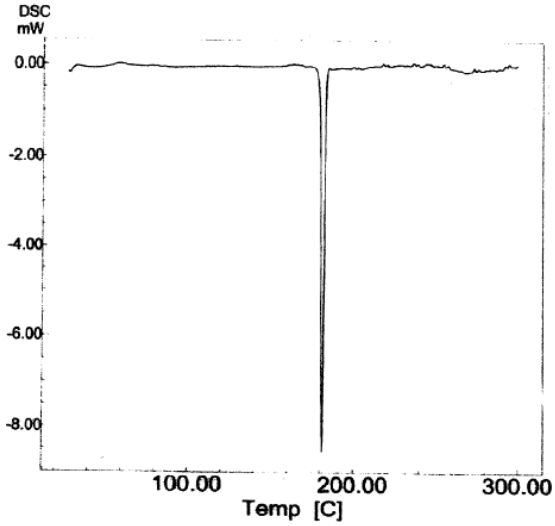

Fig. 4. DSC thermogram of pure crystalline Letrozole [21]

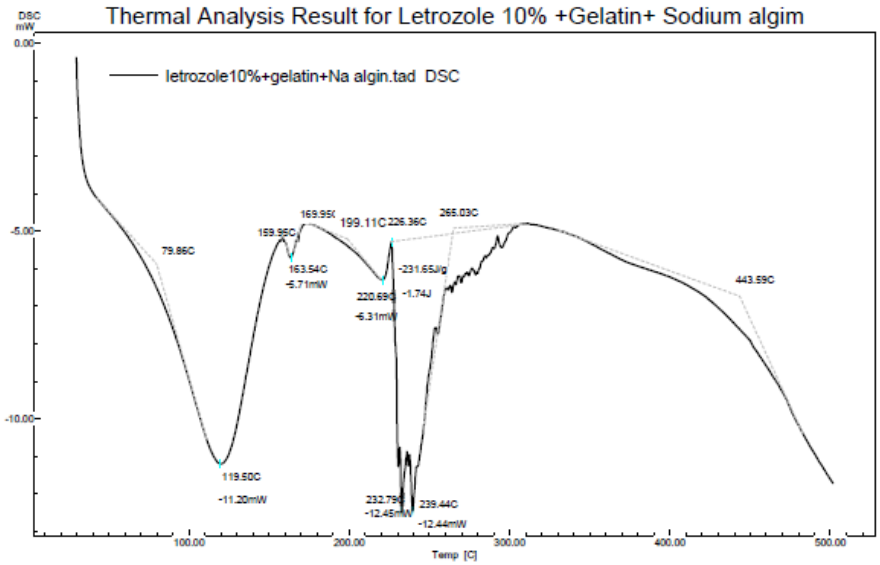

Fig. 5. DSC thermogram of Letrozole incorporated in Gelatin-Sodium Alginate polymeric implant

3.3 Effect of Excipients Loading Efficiency of Gelatin- Sodium Alginate Polymeric Implants

The effect of incorporating different excipients on drug loading efficiency of Letrozole was studied for 10% drug load. The excipient load was the same as the drug load. The changes in the loading efficiency were probably caused by the respective excipients. The data for different excipients with 10% load of Letrozole are represented (Table 3).

Loading efficiency was found to be between 40.19% to 76.93% from different formulations. The highest loading efficiency was found with Stearic Acid (76.93%) and the lowest with Glyceryl monosteareate (40.19%).

The loading efficiency was found to decrease in the following sequence:

Stearic Acid> Cetyl Alcohol> Drug Only> Cremophore EL> PEG 4000> Xanthan Gum> Glyceryl monostearate

Table 3. Effects of excipients on Letrozole loading efficiency (%) of Gelatin- Sodium Alginate polymeric implants

Excipients	Actual drug content (%w/w) Mean ± SD	Loading efficiency (%)
Drug only	8.02±0.077	62.34
Cetyl Alcohol	9.33±0.088	64.32
Cremophor EL	8.56±0.13	59.60
GMS	4.68±0.077	40.19 (minimum)
PEG 4000	9.00±0.282	55.45
Stearic acid	11.07±0.413	76.93 (maximum)
Xanthan Gum	9.62±0.099	55.21

Stearic Acid is practically insoluble in water [23] and thereby decreases the passage for drug which may result in high drug loading efficiency. Glyceryl Monostearate has a HLB value of 3.8, which indicates its hydrophobic nature. It is also practically insoluble in water. Therefore, it probably decreases the dispersibility of the drug [15]. Cetyl Alcohol has been used in matrix- controlled drug delivery system for its hydrophobic property [24]. Therefore, it increases drug loading efficiency. The drug loading efficiency was reduced by adding PEG 4000 as it is a water soluble organic solvent and used as a channeling agent [25,26]. Cremophor EL, a solubilizing agent [27,28], is found to decrease drug loading as compared to the formulation without excipient. This is probably due to its effect in increasing the affinity between the solvent and non solvent.

3.4 Formaldehyde Traces at Implants

The bright yellow colored solution is the standard formaldehyde solution (Fig. 6). The implants, after being subjected to the pharmacopoeial test for free formaldehyde, were observed for color changes against the standard solution. The intensity of yellow color indicates the amount of free formaldehyde in the solution of samples. All the three figures reflect the sample solutions to be colorless. This indicates that these implants did not retain any free formaldehyde. The results of the test for free formaldehyde are shown (Fig. 6).

A human could consume 0.2 mg/kg equivalent to 0.2 ppm of formaldehyde every day, in addition to what their own body produces, without showing any adverse effects [29]. The concentration of crosslinked formaldehyde with gelatin was found to be 0.154 µg/ml equivalent to 0.154 ppm which is within formaldehyde tolerable range in human body.

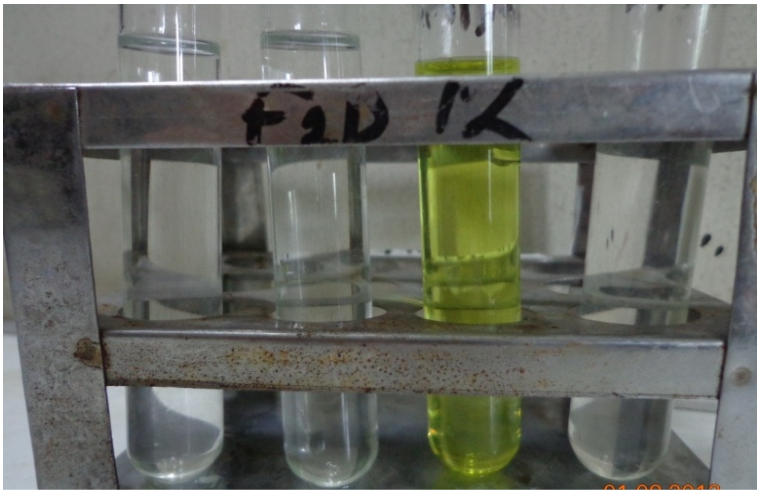

Fig. 6. Test for free formaldehyde at different hardening times of prepared implants

3.5 *In-vitro* Drug Release Studies

A biodegradable polymeric implant can function by releasing a drug in the correct amount of strength over a period of time following one or a combination of mechanisms viz., erosion of the matrix, diffusion through the matrix or combination of both diffusion and erosion mechanisms either enzymatically or non-enzymatically to produce biocompatible or nontoxic by-products [30].

The drug release rate from a polymeric matrix depends on interactions between the active ingredients and polymer [31]. In the literature, plenty of theoretical or empirical release models are described [32,33]. Zero order, First order kinetics, Higuchi and Korsmeyer-Peppas models have been chosen to describe the Letrozole release from Gelatin-Sodium Alginate biodegradable polymeric implants. The zero order rate equation describes the systems where the drug release rate is independent of its concentration. The first order equation describes the release from the system where release rate is concentration dependent. Higuchi describes the release of drugs from insoluble matrix as a square root of time dependent process based on the Fickian diffusion [23]. The Korsmeyer-Peppas equation describes the mode of release of drugs from swellable matrices [34]. Korsmeyer-Peppas kinetic model is applied when the release mechanism deviates from Ficks law [35], assuming perfect sink conditions, rapid surface equilibrium between the polymer and water, symmetric devices, and uniformly dispersed drug in the dry sample [23].

The in vitro release pattern of various excipient-loaded implants is presented (Figs. 7, 10 and 11). Letrozole release from implants with various types of excipients for 6 hr formaldehyde exposure time was continued for 16 days (Fig. 7). The initial burst release was prominent with two formulations, F2 (13.06%) and F5 (11.36%) (Fig. 7). The release gradually decreased and remained constant for 16 days. Formulation F2 containing cetyl alcohol gave

more controlled release of Letrozole as time progressed. As cetyl alcohol [24] is hydrophobic in nature, it decreases the hydrophilicity of the biodegradable implant, which decreases the release of Letrozole from the formulation. This is expected from any hydrophobic excipients as they would prevent the drug from diffusing from the polymer matrix into the aqueous solution. Fig. 10 shows the release curves for implants with 12 hrs formaldehyde exposure time. As the formaldehyde exposure time increased, the relative release rate decreased over 19 days. Initially the drug release increased steadily upto almost 12% in day 1 and then gradually decreased. One reason might be the reaction of formaldehyde with gelatin forming crosslinks between gelatin molecules, resulting in the formation of hardened gelatin [10]. This observation is also supported by Salsa et al. who observed Gelatin crosslinking by FT-IR spectroscopy while monitoring the reaction of an aqueous solution of formaldehyde with gelatin dispersed in a potassium bromide pellet in real time [11].

In accordance with the observations made in the SEM (Fig. 3) studies, the initial burst could be due to the diffusion release of Letrozole distributed near the surface and in the outer portion of the implants. Afterwards, the release rates slowed. Upon contact with the aqueous buffer, cetyl alcohol dispersed in the surroundings caused formation of microporous channels in the polymer matrix through which Letrozole might have leached out. In the present study, 65.08, 64.23 and 65.04% Letrozole was found to be released from the formulation with 6, 12 and 24 hrs formaldehyde exposure time, respectively.

Stearic acid [36], an insoluble compound, probably gives rise to a porous matrix characterised by a series of interconnecting channels developed inside it and hosting the dissolved drug and soluble compound molecules that diffuse outward due to the concentration gradient in formulation F3. Incorporation of PEG 4000 [25,26] in formulaton F6 apparently showed the highest drug release owing to its high aqueous solubility. As GMS is insoluble in water, drug release from GMS incorporated implant F5 is generally achieved by penetration of the release medium into the matrix and dissolution of the drug, followed by the diffusion of the drug solution through the channels and pores of the matrix (R^2 values in Tables 4, 5, 6). Drug solubility plays a significant role in its release duration and kinetics from GMS incorporated implant [37]. A poorly aqueous soluble drug, such as Letrozole, had a longer release duration over 16 days. The rate and extent of drug release increased from the implant with Cremophor EL [27,28] as it is act as a solubilizer.

The release period differed from one formula to another due to the influence of respective excipients as discussed. The time ranged from 10-16 days depending on the excipient characteristics (Fig 7).

Different kinetic models were utilized to analyze the possible drug release mechanism (Figs. 7, 8, 9, 12). The release from most of the implants with excipients best fitted to korsmeyer-peppas kinetic model and regression analysis was performed on the fitted curves.

As can be seen, the Higuchi fits for Gelatin-Sodium Alginate implants with different excipients showed the highest R^2 values among all the models (R^2 values in Tables 4, 5, 6). In the present study almost as good correlations were obtained with korsmeyer-peppas model as well. According to these models (Figs. 8, 12), Letozole release from the implants is diffusion controlled with the drug leaving the matrix through pores and channels formed by the entry of dissolution medium [38]. SEM micrograph also supports that Letrozole leaves the matrix through pores and channels (Fig. 2). The roughness and the caves observed on the surface could provide physical evidence of diffusion release mechanism [39].

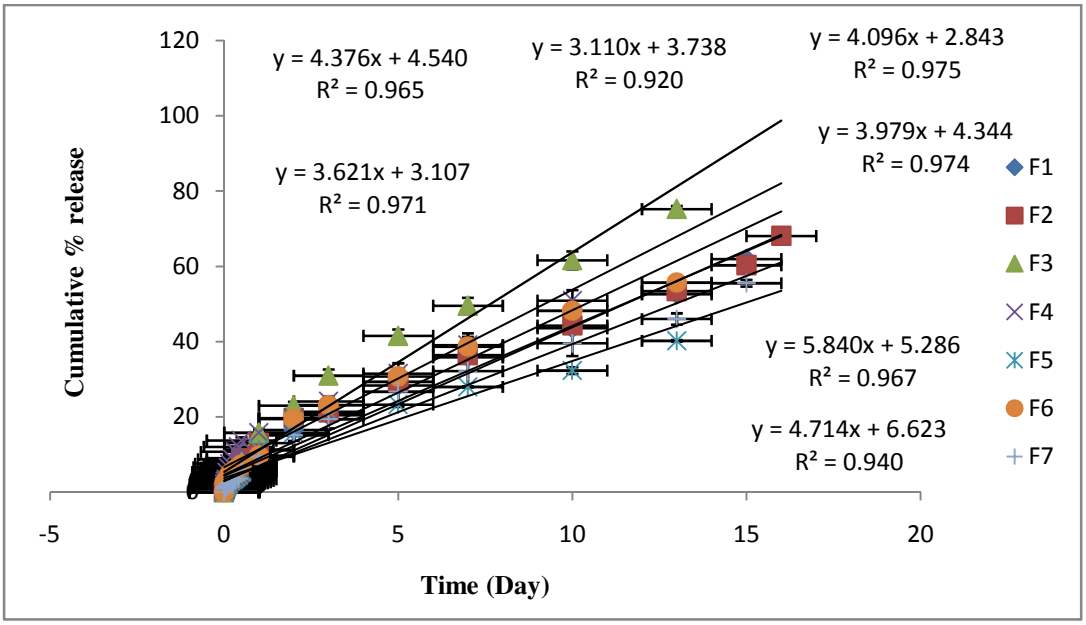

Fig. 7. Zero order plot of Letrozole release from implants with different excipients at 6 hrs hardening time

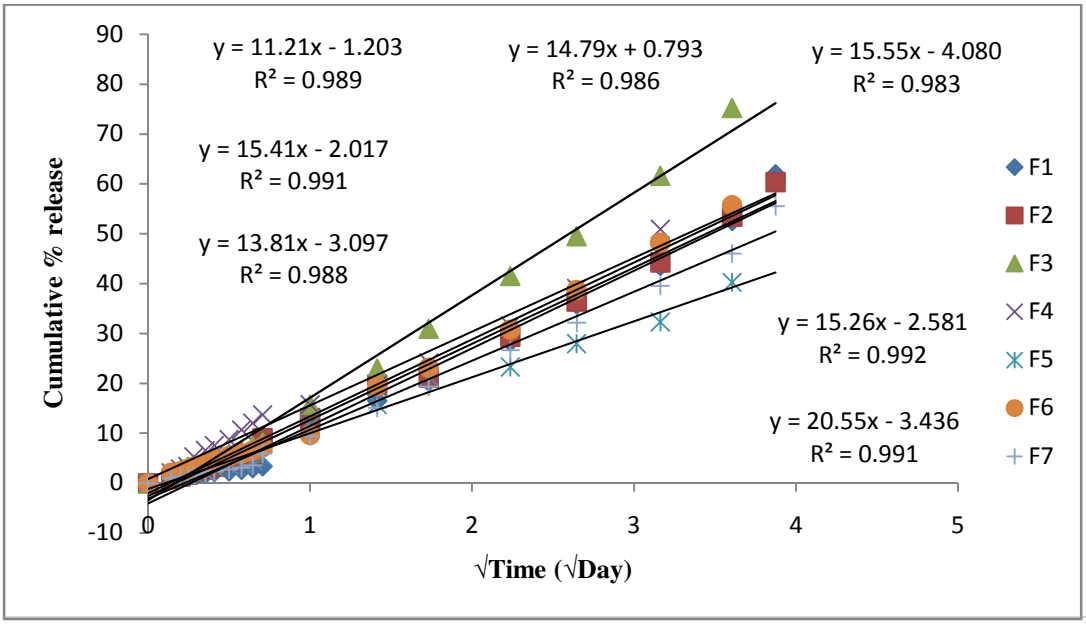

Fig. 8. Higuchi plot of Letrozole release from implants with different excipients at 6 hrs hardening time

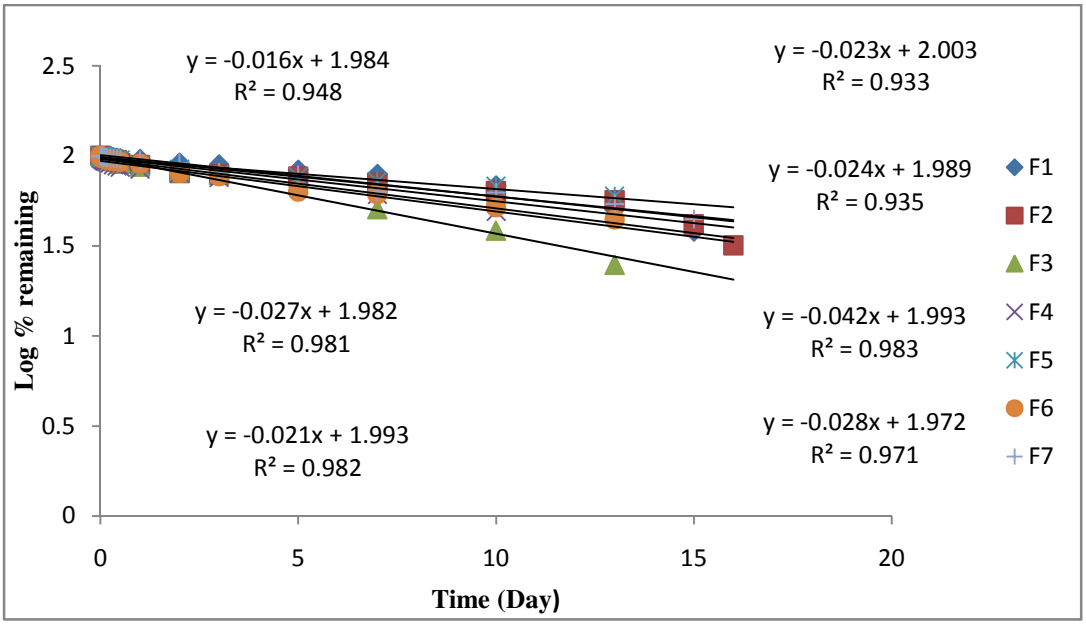

Fig. 9. First order plot of Letrozole release from implants with different excipients at 6 hrs hardening time

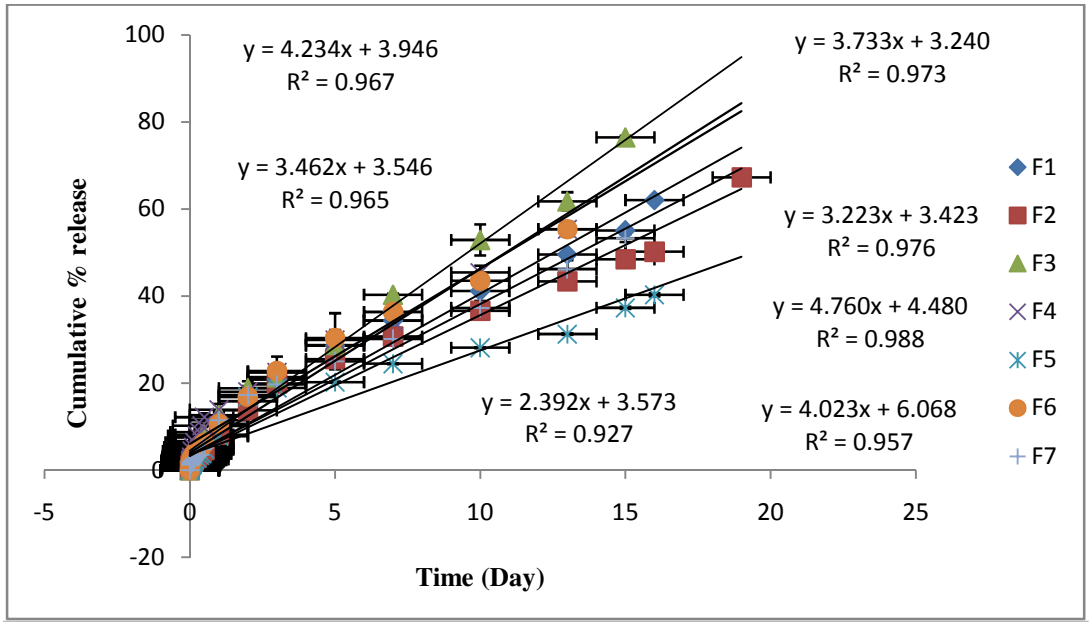

Fig. 10. Zero order plot of Letrozole release from implants with different excipients at 12 hrs hardening time

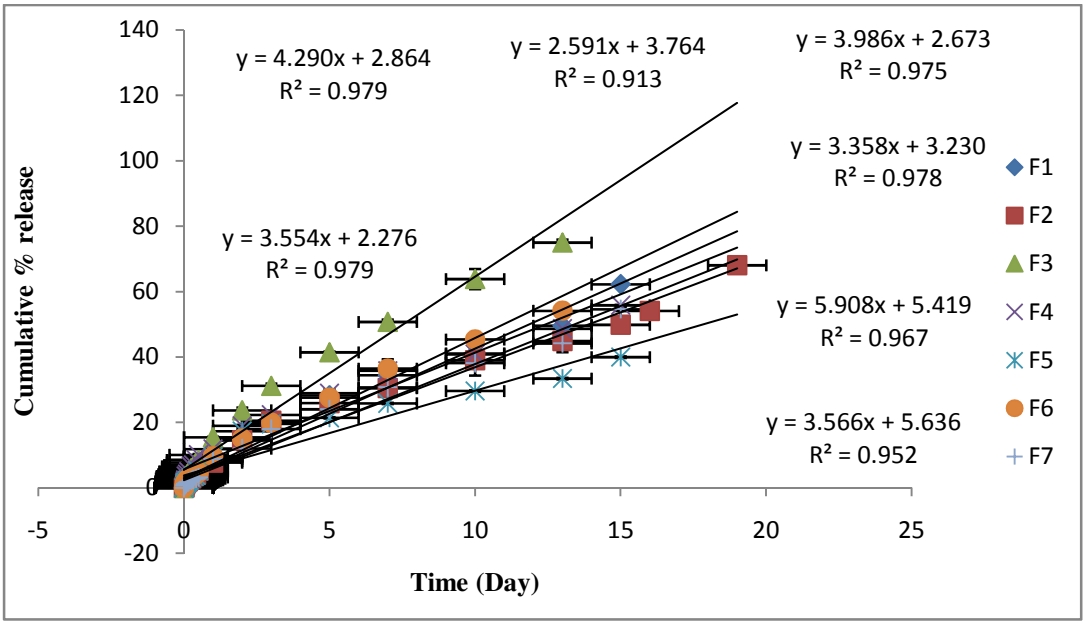

Fig. 11. Zero order plot of Letrozole release from implants with different excipients at 24 hrs hardening time

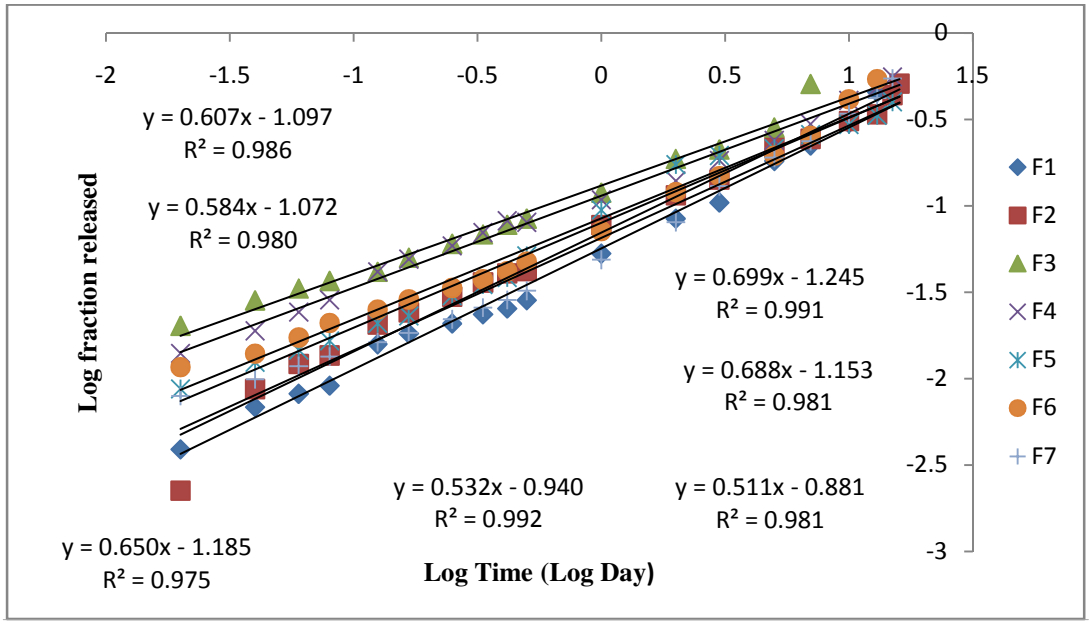

Fig. 12. Korsmeyer-Peppas plot of Letrozole release from implants with different excipients at 24 hrs hardening time

The Korsmeyer-Peppas release rate constant for the implants was found to be within 0.45-0.89 (0.45<n<0.89) which indicates the major mechanism of drug release being nonfickian

diffusion [40] which appears to indicate a coupling of the diffusion and erosion mechanism [41].

Table 4. Fitting comparison of equation of Higuchi, Korsmeyer-Peppas, First order and Zero order for describing Letrozole release from implants with different excipients at 6 hrs hardening time

Formulations	Kinetic model							
	Higuchi		Korsmeyer-peppas		First order		Zero order	
	m value	R^2	n value	R^2	m value	R^2	m value	R^2
F1	15.55	0.983	0.563	0.979	-0.023	0.933	4.096	0.975
F2	15.97	0.987	0.615	0.990	-0.024	0.935	3.979	0.974
F3	20.55	0.991	0.520	0.983	-0.042	0.983	5.840	0.967
F4	14.79	0.986	0.483	0.981	-0.028	0.971	4.714	0.940
F5	11.21	0.989	0.598	0.988	-0.016	0.948	3.110	0.920
F6	15.41	0.991	0.537	0.983	-0.027	0.981	4.376	0.965
F7	14.79	0.988	0.623	0.975	-0.021	0.982	3.621	0.971

Table 5. Fitting comparison of equation of Higuchi, Korsmeyer-Peppas, First order and Zero order for describing Letrozole release from implants with different excipients at 12 hrs hardening time

Formulations	Kinetic model							
	Higuchi		Korsmeyer-peppas		First order		Zero order	
	m value	R^2	n value	R^2	m value	R^2	m value	R^2
F1	15.00	0.988	0.609	0.981	-0.022	0.945	3.733	0.973
F2	13.65	0.977	0.570	0.986	-0.018	0.907	3.223	0.976
F3	17.84	0.970	0.524	0.989	-0.035	0.970	4.760	0.988
F4	14.21	0.988	0.496	0.989	-0.024	0.982	4.023	0.957
F5	9.828	0.985	0.645	0.987	-0.013	0.950	2.392	0.927
F6	14.89	0.989	0.546	0.987	-0.024	0.985	4.234	0.967
F7	13.24	0.988	0.573	0.968	-0.019	0.984	3.462	0.965

Table 6. Fitting comparison of equation of Higuchi, Korsmeyer-Peppas, First order and Zero order for describing Letrozole release from implants with different excipients at 24 hrs hardening time

Formulations	Kinetic model							
	Higuchi		Korsmeyer-peppas		First order		Zero order	
	m value	R^2	n value	R^2	m value	R^2	m value	R^2
F1	15.12	0.980	0.699	0.991	-0.022	0.927	3.986	0.975
F2	14.23	0.981	0.688	0.981	-0.019	0.918	3.358	0.978
F3	20.80	0.992	0.511	0.981	-0.043	0.981	5.908	0.967
F4	13.79	0.996	0.462	0.992	-0.021	0.989	3.566	0.952
F5	10.18	0.985	0.607	0.986	-0.014	0.940	2.591	0.913
F6	15.16	0.991	0.584	0.980	-0.023	0.975	4.290	0.979
F7	13.45	0.980	0.650	0.975	-0.019	0.979	3.554	0.979

4. CONCLUSION

Use of letrozole, which is an attractive treatment option for postmenopausal women with metastatic breast cancer, is recommended for use for a period of 5 years as tablets in most cases. Therefore, this drug appears to be particularly suitable for targeted and controlled release drug delivery system Considerable efforts are being made for sustaining its release for prolonged use and research works have already been reported on entrapping the drug, utilizing nanoparticle technology and thermoplastic biodegradable polymeric drug delivery devices The present study revealed that Letrozole could be entrapped into Gelatin-sodium alginate implants with high drug loading efficiency (40.19-76.93%) and also provide sustained drug release for a period of 10-19 days. Therefore, this work can be taken further to explore its potential in this indication.

CONSENT

Not applicable.

ETHICAL APPROVAL

Not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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