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Research Article

Effect of Biodegradable Polymer on the Release Pattern of Levothyroxine Sodium Implant

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Graphical Abstract

Gelatin-sodium alginate based levothyroxine sodium implant was prepared by heating and congealing methods. Implants were found to follow both the Higuchi and Korsmeyer-Peppas model of kinetics with variation in polymer ration. The drug release from the implants shows the combination of diffusion and erosion contributes to the control of drug release.

Figure

Abstract

The use of biodegradable polymers as drug carriers increases the drug entrapment efficiency and contributes to the sustained release action of the formulation. The purpose of this study was to prepare and evaluate a sustained release Gelatin-Sodium Alginate biodegradable polymeric implant containing Levothyroxine Sodium as a model drug. Heating and congealing methods were used for the preparation of implants in various ratios of Gelatin and Sodium Alginate (70:30, 80:20 and 90:10 % w/w). The prepared implants were exposed to formaldehyde for different time periods, (6hrs, 12hrs and 24hrs) for hardening. The formulated implants were evaluated for weight variation, thickness, presence of free formaldehyde, and *in vitro* release studies. The interactions between the drug and polymer, good surface integrity, and compatibility have been studied using SEM and DSC. The implant formulated with 80:20 % w/w Gelatin-Sodium Alginate ratio and hardened for 24 hours were found to produce the maximum sustained action for 30 days, and none of the implants contained formaldehyde. The effects of four different excipients with 80:20 ratio were also studied on drug loading efficiency and drug release profile. The drug loading efficiency and drug release were found to be significantly influenced by the addition of different excipients (Stearic Acid > GMS > PEG > Drug only > Cetyl) and variation in hardening times. The results of the *in-vitro* dissolution study were fitted to different kinetic models to evaluate the kinetic data. The kinetic release data were determined by finding the best fit of the release data to these models. Implants were found to follow both the Higuchi model and Korsmeyer-Peppas model of kinetics with the variation in polymer ratio. Therefore, drug release from the implants implies that a combination of diffusion and erosion contributes to the control of drug release.

Keywords: Biodegradable Implant; Gelatin; Sodium Alginate; Levothyroxine Sodium

Introduction

The idea of sustaining or prolonging the release of biologically active agents for extended periods of time has been well perceived and rationalized for decades to overwhelm the drawbacks of fluctuating drug levels associated with traditional dosage forms [1,2]. Polymeric drug delivery systems anticipate the tempting capability of releasing drug formulations in a synchronized manner and sustain the rate over extended periods [3]. Biodegradable implants are sterile solid masses, which consist of a highly purified drug and can be with or without excipients, which are intended for implantation in the body to provide continuous release of the drug for a prolonged period of time [4]. Recently, formulations of implantable drug delivery systems using biodegradable polymers have gained much popularity because of their either hydrolytic or proteolytic characteristics (as they are ruptured into biologically suitable molecules and are assimilated and discarded from the body through normal routes) [5,6]. Thus, these polymeric formulations (implants) alleviate the need for surgical removal of the product after the conclusion of therapy and increases patient acceptance and compliance [7].

Levothyroxine sodium is the sodium salt of the levo isomer of the thyroid hormone thyroxine. These hormones stimulate the oxygen consumption of most cells of the body, which results in increased heat production and energy expenditure, and it possesses a cardiostimulatory effect that may be the result of a direct action on the heart. It also has a complex stability profile and is sensitive to light, temperature, moisture, pH and oxidation [8-11].

The present study was to fabricate Gelatin-Sodium Alginate combination biodegradable implants for sustain release. The active ingredient chosen was Levothyroxine Sodium, an antihypothyroidism drug. The main challenge of this work was to make sustain the release of the drug from the implants because the polymers used (Gelatin and Sodium Alginate) dissolve rather rapidly in an aqueous environment, thus limiting its use in the production of long-term drug delivery. This limitation was alleviated by the use of crosslinking procedures by formaldehyde, reducing gelatin dissolution and drug release at body temperature by the formation of non-soluble networks. Although a few studies on novel delivery systems of Levothyroxine Sodium have been carried out, to our best knowledge no studies have been reported so far on biodegradable implants. Thus, formulating a biodegradable implant with a combination of Gelatin and Sodium Alginate to control drug release and loading the implant with a drug that has found its application in treating many chronic conditions.

Materials and Methods

Materials

Levothyroxine sodium was provided as a generous gift by Renata Limited, Bangladesh. The chemicals and reagents used in this study were of analytical grade.

Methods

Preparation of implants

Levothyroxine Sodium biodegradable implants were prepared by use of two polymers, Gelatin and Sodium Alginate (biodegradable polymers), by heating and congealing method. The implants were prepared using 5% drug with three different polymer ratios (70:30, 80:20 and 90:10) (Table 1).

Ingredients	Formulation		
	70:30	80:20	90:10
Drug	0.25 gm	0.25 gm	0.25 gm
Polymers (Gelatin and Sodium alginate)	4.5 gm	4.5 gm	4.5 gm
Glycerin	2.9 ml	2.9 ml	2.9 ml
Distilled water	15 ml	15 ml	15 ml

Table 1: Formulation of the implants.

Gelatin was made hydrated and Sodium Alginate was added on it. Then, glycerin was added slowly as a plasticizing agent with continuous stirring, and the solution was heated in a water bath at 60°C until gelatin was dissolved. Levothyroxine Sodium was separately dissolved in ethanol and added to the Gelatin-Sodium Alginate mixture. When all the ingredients were mixed properly, the solution was poured in a glass petri dish up to 3 mm height and allowed to gel by placing the petri dish on ice for 30 minutes (Figure 1). After that they were then dried at room temperature for 72 hours in aseptic cabinet. The implants were placed in formaldehyde for hardening [12-14].

Figure 1: Photographic image of levothyroxine implant.

Hardening of implants

Formaldehyde solution (37% v/v) was placed in a petri dish and placed in an empty glass desiccators. A wire mesh containing the implants was kept on top of the petri dish, and the desiccator were closed immediately. Then for a different time interval (3, 6, 12 and 24 hours), implants were made to react with formaldehyde vapors. After that they were removed from the desiccator for air drying for approximately 72 hours. The implants were kept in open air under aseptic conditions for a week to make ensure that the residual formaldehyde was evaporated. This procedure was repeated

for the preparation of all implants containing the composition of 70:30, 80:20, 90:10 w/w gelatin, and sodium alginate [12].

Evaluation of implants

Measurement of thickness and weight variation

A slide caliper was used to measure the thickness of the prepared implants for a particular formulation and exposure time. Weight variation of implants was checked by weighing three implants of a particular formulation and exposure time individually [5].

Scanning electron microscopy (SEM)

The implants were first 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 the electrons in the SEM. The observed SEM micrographs were recorded at varying magnifications. The interior morphology at the cross section of the hot melt extrudates was observed.

Differential scanning calorimetry (DSC)

DSC-60 (SHIMADZU) with a thermal analyzer (TA-60WS) was used for measurements. Precise amounts of 5 mg of the prepared implant samples were placed in a sealed aluminum pan, before heating under nitrogen flow (300 ml/min) at a scanning rate of 10°C min 1 from 50°C to 200°C.

Determination of drug content

Spectrophotometric analysis was used to determine the amount of drug actually loaded in implants during the fabrication process. To determine the drug content of the Levothyroxine Sodium loaded implants was weighed and then crushed. 1 mL phosphate buffer, pH 7.4, was then used to dissolve and was ultrasonicated. 3 mL acetonitrile and 7 mL buffer were added then for precipitating the polymer material. 1 mL of supernatant was withdrawn after centrifuged it at 3000 rpm for about 10 minutes and the volume was made to 100 mL in a volumetric flask with acetonitrile and phosphate buffer, pH 7.4 at a ratio of 30:70. The absorbance was analyzed at 235 nm (λ_{max} of Levothyroxine Sodium) in a UV Spectrophotometer (UV-1601, SHIMADZU). Levothyroxine Sodium concentration was calculated from the standard curve, and the percentage of loading efficiency (% LE) of the implants was determined with the formula [15]:

Percentage Loading Efficiency = (Amount of loaded drug in the implant (LD)/Amount of drug originally added in the formulation (AD) x 100.....(1)

Test of free formaldehyde

To ensure the absence of free formaldehyde, implants were subjected pharmacopoeial test for free formaldehyde (any color change was observed).

In vitro drug release study

After formulation of implants, *in-vitro* dissolution studies of the implants were carried out in static conditions in order to observe the drug release profile for Levothyroxine implants. Three implants from each formulation and exposure time were taken and their weights recorded and were transferred to rubber capped glass vessels containing 100 mL of Phosphate Buffer, p^H 7.4. To ensure uniform distribution of drug throughout the medium, at predetermined time intervals, 10 mL of sample was withdrawn from the dissolution vessels using a 10 mL conventional disposable syringe, after mild stirring of the dissolution vessels for a few seconds. 10 mL of fresh medium (Phosphate Buffer, p^H 7.4) was then added to the dissolution vessels to replace the withdrawn sample to maintain the sink condition. The withdrawn samples were then analyzed for determining the percentage of release of drugs by UV spectrophotometer at 235 nm, after subsequent dilution of the samples. All data were used in statistical analysis for the determination of mean, standard deviation, and release kinetics [16].

Result and Discussion

Measurement of thickness and weight variation

The variations in thickness and weight of the prepared implants at different polymer ratios (70:30, 80:20 and 90:10) hardened with formaldehyde for different exposure times (3 hrs, 6 hrs, 12 hrs, and 24 hrs) are shown in table 2. Thus, it can be said that varying the polymer ratio and hardening time does not affect the average thickness and weight of the implants.

Polymer ratio of Implants	Hardening Time (hrs)	Thickness of Implants (mg) ± SD	Weight of Implants (mg) ± SD
70:30	6	1.512 ± 0.01	185.15 ± 0.13
	12	1.515 ± 0.017	187.25 ± 0.13
	24	1.512 ± 0.015	185.30 ± 0.07
80:20	6	1.511 ± 0.01	182.20 ± 0.12
	12	1.502± 0.02	184.25 ± 0.13
	24	1.500 ± 0.01	185.30 ± 0.15
90:10	6	1.516 ± 0.01	185.32 ± 0.17
	12	1.510 ± 0.01	187.20 ± 0.14
	24	1.514 ± 0.02	185.30 ± 0.14

Table 2: Thickness and weight variation of different implants with respect to polymer ratio.

Scanning electron microscopic (SEM) study

Figure 2 and 3 show SEM micrographs of gelatin-sodium alginate polymeric implants containing levothyroxine sodium before and after drug release.

Before drug release, the implant surface was flaky and porous, but the surface integrity was found to be good (Figure 2). Thereby the entrapping of drug is relatively lower than the 100% entrapping

capability, which also correlates with loading efficiency found from drug content analysis. The loading efficiency was found 71.771% when PEG was incorporated into the implant. Being more porous and rough (Figure 3) indicates that a very low amount of drug remained after drug release, which also complies with the findings of drug release studies.

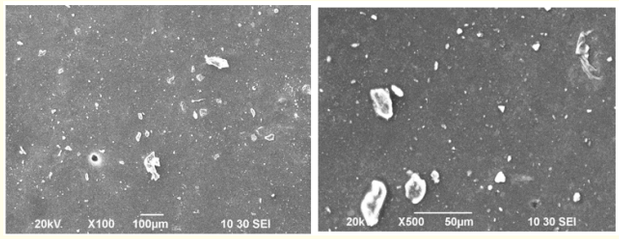

Figure 2: SEM micrograph of levothyroxine sodium polymeric implant (incorporated with PEG as excipient) surface before drug release (100 and 500 times magnification).

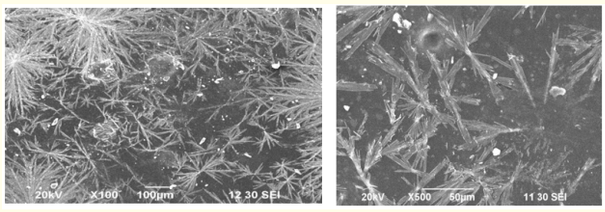

Figure 3: SEM micrograph of levothyroxine sodium polymeric implant (incorporated with PEG as excipient) surface after drug release (100 and 500 times magnification).

Differential scanning calorimetry study (Effect of excipient)

The DSC thermogram (Figure 4) showed that levothyroxine sodium pentahydrate showed two exotherms (at 120°C and 159°C) and an endotherm at 209°C. The two exotherms might correspond to moisture loss from the hydrate form.

Figure 4: DSC thermogram of levothyroxine sodium pentahydrate.

The DSC scan of levothyroxine sodium incorporated in gelatin mixture (Figure 5) exhibits two peaks: one broad endothermic peak, with an onset temperature of approximately 85°C and an offset temperature of 160°C and a maximum peak point at 122°C with a maximum heat flow of 9.5 mW, corresponding to the moisture content in the sample. Another very sharp and distinguished endothermic peak corresponding to the melting of the sample with a melting enthalpy of 296.40 J/g is found at an onset temperature 160°C and an offset temperature of 175°C. This curve is immediately followed by a small broaden curve with 4 mW maximum heat flow and a maximum temperature of 288°C. Further, the sample became unstable above 315°C and the thermograph dropped suddenly at approximately 413°C may be due to boiling/decomposition of the sample. The pure drug shows an endothermic peak at 209°C but in the above figure, it shifted to 236°C due to incorporation of the polymer.

Figure 5: DSC thermogram of levothyroxine sodium with 5% gelatin.

Determination of drug content

The following observation is made from the data obtained from table 3.

Excipients	Actual Drug content (% w/w) Mean ± SD	Loading Efficiency (%)
Drug only	11.283 ± 0.077	66.462
Cetyl alcohol	12.354 ± 0.129	65.665
Stearic acid	11.981 ± 0.413	78.801
Glyceryl monostearate	11.315 ± 0.088	73.254
PEG	11.267 ± 0.282	71.771

Table 3: Effects of excipients on levothyroxine sodium loading efficiency (%) of gelatin-sodium alginate polymeric implants.

Effect of excipients loading efficiency of gelatin-sodium alginate polymeric implants

The effect of incorporation of different excipients on the drug loading efficiency of Levothyroxine Sodium was studied for 5% drug load and was the same for excipients. The changes in the loading efficiency were probably caused by the respective excipients.

Loading efficiency was found in the range of 65.665% to 78.801% from different formulations. The highest loading efficiency was found with Stearic Acid (78.801%) and the lowest with Cetyl alcohol (65.665%). The loading efficiency was found to decrease in the following order: Stearic Acid > Glyceryl mono-stearate > Polyethylene glycol > Cetyl alcohol.

Justification of the effects of excipients on levothyroxine sodium loading efficiency

The excipients added have been found to have variable effects on levothyroxine sodium loading efficiency, which probably depends on their respective lipophilicity/hydrophilicity and solubility in solvent and non-solvent [16].

Glyceryl monostearate (GMS): The drug loading efficiency was found to be 66.462% when GMS was incorporated into the implant as compared to 65.653% for drug-only implants. GMS has an HLB value of 3.8 [17], which indicates its hydrophobic nature [18] and also GMS is practically insoluble in water. GMS is used as a matrix ingredient for a biodegradable, implantable, controlled release dosage form [17].

Stearic acid: The drug loading efficiency was found to be 76.006% when Stearic Acid was incorporated in the implant which is the highest among all the excipients used as compared to 65.653% for drug-only implants. Stearic Acid has a lower acid value: 200 - 212 [19], which indicates its hydrophobic nature [20]. Stearic Acid is also practically insoluble in water, and it has also been suggested that stearic acid may be used in enteric tablet coatings and as a sustained-release drug carrier [19].

Cetyl alcohol: The drug loading efficiency was found to be 73.254% when cetyl alcohol was incorporated in the implant as compared to 65.653% for drug-only implants. Here, cetyl alcohol increased the levothyroxine sodium loading efficiency. Cetyl alcohol is insoluble in aqueous buffer and is widely used in modified release dosage forms. Cetyl alcohol is used because of its emollient, water-absorptive, and emulsifying properties. It enhances stability, improves texture, and increases consistency [21]. The percentage of Cetyl Alcohol that is used in this formulation may act as a water absorptive agent for which it may reduce drug loading efficiency.

Poly-ethylene glycol (PEG): The drug loading efficiency was found to be 71.771% when PEG was incorporated in the implant as compared to 65.653% for drug-only implants. Here, Cetyl Alcohol increased the Levothyroxine Sodium loading efficiency.

Figure 2 and 3 represent the SEM micrograph of Levothyroxine Sodium loaded with PEG (as excipient) polymeric implant surface before drug release and after drug release, respectively.

Test of free formaldehyde

The bright yellow colored solution is the standard formaldehyde solution. The implants, after being subjected to the pharmacopoeial test for free formaldehyde, were observed for color changes against the standard solution. The intense the yellow color of the solution of the samples, the greater the amount of free formaldehyde. Figure 6 reflects that the color of the sample solutions was colorless. This indicates that these implants did not retain any free formaldehyde.

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

Drug release profile of implants based on different hardening time with respect to polymer ratio

It can be seen that almost all the implants of all ratios and hardening times show the same pattern of drug release. In these three formulations, (70:30, 80:20 and 90:10), implants hardened for 6 hours showed less sustained action than those hardened for 12 hours and 24 hours respectively (Figure 7). The following conclusions can be made:

- The formulation containing Gelatin-Sodium Alginate in the ratio 80:20 showed an optimum sustained effect.
- Hardening the implants with formaldehyde sustained drug release, with the optimum hardening time being 24 hours in two ratios of 80:20 and 90:10.
- The formulation containing 80:20 Gelatin-Sodium Alginate hardened for 24 hrs with formaldehyde showed maximum sustained action of drug release.

Figure 7: Percentage (%) release from implants with different hardening times from 11 days.

The formulation containing 80:20 Gelatin- Sodium Alginate hardened for 24 hrs with formaldehyde showed maximum sustained action of drug release.

To analyze the *in-vitro* release data, various kinetic models were used to describe the release kinetics (Table 4). The kinetics of Levothyroxine Sodium from polymer ratios (70:30, 80:20 and 90:10) with different hardening times were fitted to Zero order, First order, Higuchi, Korsmeryer-Peppas plots. The zero order rate equation describes the systems where the drug release rate is independent of its concentration. The first order rate equation describes the release from the system where release rate dependent process is concentration dependent. Higuchi describes the release of drugs from insoluble matrix as a square root of a time-dependent process based on the fickian diffusion ($n < 0.43$) for the formulated implants in the polymer ratio of 70:30 and 90:10, whereas the prepared implants using a polymer ratio 80:20 have an exponential 'n' value between 0.43 to 0.85, which is described as anomalous, implying that a combination of diffusion and erosion contributes to the control of drug release.

Polymer ratio	Rate Constant and R^2 Value								
	Time (Hr)	Zero		First		Higuchi		Korsmeyer-Peppas	
		K_0	R^2	K_1	R^2	K_H	R^2	n	R^2
70:30	6	3.041	0.93	-0.016	0.90	8.413	0.86	0.375	0.935
	12	2.259	0.95	-0.011	0.93	10.25	0.90	0.375	0.90
	24	2.250	0.99	-0.013	0.95	7.23	0.94	0.342	0.97
80:20	6	2.03	0.97	-0.091	0.934	9.27	0.95	0.441	0.91
	12	1.69	0.98	-0.0112	0.98	8.41	0.96	0.478	0.90
	24	1.38	0.98	-0.0089	0.95	7.28	0.96	0.473	0.90
90:10	6	2.764	0.968	-0.015	0.901	9.275	0.95	0.355	0.934
	12	2.561	0.988	-0.013	0.942	8.407	0.96	0.35	0.90
	24	2.250	0.99	-0.011	0.95	7.277	0.95	0.34	0.97

Table 4: Rate constant and R^2 values of different kinetic release models formulate implants for different polymer ratios.

Figure 8: Photographic images of gelatin-sodium alginate polymeric implants.

Figure 9: Drug release profile of implants formulated with 80:20 gelatin-sodium alginate polymer at different hardening times.

Figure 10: Zero-order plot of implants formulated with 80:20 gelatin-sodium alginate polymer at different hardening times.

Figure 11: First-order plot of implants formulated with 80:20 gelatin-sodium alginate polymer at different hardening times.

Figure 12: Higuchi plot of implants formulated with 80:20 gelatin-sodium alginate polymer at different hardening times.

Figure 13: Levothyroxine sodium release from implants with four different excipients (GMS, stearic acid, PEG and cetyl alcohol) with drug only.

Conclusion

Polymeric drug delivery systems are an attractive alternative to control release of drug. For the treatment of hypothyroidism, Levothyroxine Sodium is the choice of drug and can be given through implants in comorbidities condition in patients with CHF, malabsorption syndrome, or diarrhea (these comorbidities will reduce the absorption of a drug). Therefore, a prolonged drug delivery system (as implants) for Levothyroxine Sodium will be more patient compliant. It is evident from this study that the Gelatin-Sodium Alginate implants could be a suitable drug carrier systems for long-term delivery of Levothyroxine Sodium. The present study found that Levothyroxine Sodium could be entrapped into Gelatin-Sodium Alginate implants with high drug-loading efficiency (65 - 78)% and also provide sustained drug release for a period of 10 - 45 days. Therefore, it can be an attractive candidate for future development.

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