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OBSERVATION OF THE RELEASE OF SIMVASTATIN FROM BIODEGRADABLE POLYMERIC IMPLANT

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ABSTRACT

Subcutaneous implantation is currently the most utilized routes of the potential of sustained drug delivery system. Present investigation explores the scope of sustaining the release of Simvastatin by using Gelatin-Sodium Alginate combination biodegradable implants. Simvastatin is an antihyperlipidemic drug that is used for chronic conditions like coronary heart disease. Implants were formulated in varied ratios of Gelatin and Sodium alginate, i.e. 70:30, 80:20 and 90:10 % w/w by heating and congealing method. They were then exposed to formaldehyde for different time periods like 3 Hrs, 6 Hrs, 12 Hrs and 24 Hrs for hardening. The implants were evaluated for thickness, weight variation, presence of free of formaldehyde and in vitro drug release studies. The implants formulated with 70:30 formulation hardened for 12 Hrs showed the maximum sustained action of 102 Hrs (4.25 days). The kinetic data was determined by finding the best fit of the release data to these models. Implants were found to follow the Korsmeyer-Peppas model of kinetics the best. Also good correlations were obtained with Higuchi model.

Keywords: Biodegradable Implant, Gelatin, Sodium Alginate, Formaldehyde, Simvastatin

INTRODUCTION

Hyperlipidemia or hyperlipoproteinemia involves abnormally elevated levels of any or all lipids and/or lipoproteins in the blood **[1, 2]**. It is the most common form of dyslipidemia (which also includes any decreased lipid levels). There are mainly five

types of hyperlipidemias such as familial hyperchylomicronemia (Type I), familial hypercholesterolemia (Type IIA), familial combined (mixed) hyperlipidemial (Type IIB), familial dysbetalipoproteinemia (Type III), familial hypertriglyceridemia (Type IV), familial mixed hypertriglyceridemia (Type V) **[3]**. Simvastatin works on all of these types of hyperlipidemias. So it is very much effective on chronic diseases such as coronary heart disease. Polymeric drug delivery systems are an attractive alternative to control the release of drug substances to obtain defined blood levels over a specified time. The patients suffering from some disease conditions such as heart disorders, osteoporosis, tumors, often benefit from such long-term drug delivery systems due to improved patient compliance **[4, 5]**. Sustained release drug delivery systems are those which are designed to release drug continuously at sufficiently slow or controlled rate over an extended period of time to provide prolonged therapeutic effect. In the recent years, focus on the development of controlled release drug delivery systems has increased. A Subcutaneous implant of drug pellets is known to be the first medical approach aiming to achieve prolonged and continuous administration of drugs. Subcutaneous implantation is currently one of the most utilized routes to investigate the potential of sustained drug delivery system. This is because ready accessibility of drugs to unusual absorption sites such as tumor, bone marrow, slow absorption of drugs at a fixed rate through subcutaneous tissue, low reactive nature of subcutaneous tissue to the foreign material, easy removal of the device at any time, if needed **[6, 7, 8]**. We tried to observe here how much better sustained action could be obtained by fabricating Simvastatin with two different biodegradable polymers like Gelatin & Sodium Alginate in different ratio 70:30, 80:20 & 90:10.

MATERIALS AND METHODS

Materials

Simvastatin was obtained as a gift sample from Renata Limited, Mirpur, Dhaka, Bangladesh. Purified Gelatin was purchased from Merck Specialities Private Limited, Mumbai. Sodium Alginate was purchased from Loba Chemie Pvt. Ltd., Mumbai. Other chemicals used were of analytical grade.

Preparation of Implant

Biodegradable implants of the drug Simvstatin were prepared by the use of two biodegradable polymers Gelatin and Sodium Alginate by heating and congealing method. The implants were prepared using 10% Drug Load and at 3 different polymer ratios (70:30, 80:20, 90:10).

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. 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. Simvastatin was dissolved separately in a beaker with a small quantity of 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 upto 3 mm height and allowed to gel by placing the petri-dish on ice for 30 minutes. Then they were dried at room temperature for 72 hours in aseptic cabinate. After that the implants were placed in formaldehyde for hardening **[7, 8, 9, 10, 11]**.

Hardening of Implants

A Petri-dish containing Formaldehyde solution (37% v/v) was placed in an empty glass dessicators. A wire mesh contained the implants was kept on the top of the petri-dish and the dessicator was closed immediately. The Implants were made to react with formaldehyde vapors for different time interval such as 3, 6, 12 and 24 hours. Then they were removed from the desiccator for air drying which takes approximately 72 hours, to make the reaction between formaldehyde and implant completed. Then the implants were kept in an open air in aseptic condition for a week to make sure that the residual formaldehyde gets evaporated.

This procedure is repeated for the preparation of all the implant containing the composition of 70:30, 80:20, 90:10 w/w gelatin and sodium alginate **[7, 8, 9, 10, 11]**.

Evaluation of Subdermal Implants

Weight Variation of Implants

Weight Variation was checked by weighing three implants individually **[13, 14, 15]**. **Table 1** shows the average weight of implants (70:30) hardened with formaldehyde.

Measurement of Implants 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 **[13, 14, 15]**. **Table 1** shows the average thickness of implants (70:30) hardened with formaldehyde.

Photographic Imaging

Photographs of drug loaded implants were taken using digital camera (SONY CYBERSHOT, DSC– S650, 7.2 Mega Pixels). Surface morphology greatly influences the release kinetics of implants **[12]**. The kinetics of drug release is greatly dependent on the morphological characters of implants. **Figure 1** displays randomly

selected digital images of Gelatin-Sodium Alginate polymeric implants.

Test for Free Formaldehyde

The Simvastatin implants were prepared by exposing them under formaldehyde exposure for hardening at different time interval. Since formaldehyde is toxic in nature, free formaldehyde testing became necessary to ensure that the final sample of formulations were of free from any residual formaldehyde. To ascertain the absence of free formaldehyde, the implants were subjected to pharmacopoeial test for free formaldehyde **[16]**. The sample solution and the standard solution were compared with each other according to visual color change. The intense the yellow color of the solution of the samples, the greater the amount of free formaldehyde. This comparison shows that the standard solution gave a sharp yellow color when treated with the reagent indicating the presence of formaldehyde and the sample solution gave a colorless condition with the reagent, which is indicative of having no free formaldehyde. So, from this observation we may be sure that these implants did not retain any free formaldehyde. The visible color change of 70:30 **formulation is shown in Figure 2**.

In-vitro Dissolution Studies

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 Simvastatin implants. A minimum of 3 implants from each formulation and exposure time were taken, and their weight recorded. They were then transferred to rubber capped glass vessels containing 100 ml of Phosphate Buffer, pH 7.4. At predetermined time intervals, 10 ml of sample is withdrawn from the dissolution vessels using 10 ml conventional disposable syringe, after mild stirring of the dissolution vessel for a few seconds to ensure uniform distribution of drug throughout the dissolution medium. 10 ml of fresh medium (phosphate buffer, pH 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 238.2 nm (λmax of Simvastatin 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 **[10, 17, 18]**.

Kinetic Modelling of Drug Release

To analyze the mechanism of drug release from the polymeric implant, the *in vitro*

dissolution data of the formulations were fitted to the Zero order, First order, Higuchi model and Korsmeyer- Peppas model **[19, 20, 21, 22]**. The goodness of fit was evaluated using the correlation coefficient values (r^2) **[20]**.

Statistical Analysis

Results were expressed as mean ± S.D. Statistical analysis was performed by linear regression analysis. Coefficients of determination (R2) 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.

RESULTS AND DISCUSSION

In-vitro Drug Release Studies

Sustained release of drugs from biodegradable matrices is accepted to occur by three mechanisms: diffusion through the polymer continuum, liberation from the matrix via polymer degradation, or a combination of drug diffusion and polymer degradation **[23]**. The profile and kinetics of drug release are important because they correlate the in-vitro in-vivo drug responses by comparing results of pharmacokinetics and dissolution profile patterns **[20, 21, 22]**. To analyze the in-vitro release data, various kinetic models were used to describe the release kinetics **[24, 25, 26]**. The drug release studies of Simvastatin 70:30 formulation in phosphate buffer pH 7.4 indicated 100% of drug release in 102 hours **(Figure 3)**.

The methods of approach to investigate the kinetics of drug release from controlled release formulation can be classified into three categories such as Statistical methods, Model dependent methods and Model independent methods **[27]**. The kinetics of Simvastatin from 70:30 Gelatin-Sodium Alginate polymer ratio with different hardening times were fitted to Higuchi, Korsmeyer-Peppas, Zero Order and First Order 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 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. The Korsmeyer-Peppas equation describes the mode of release of drugs from swellable matrices **[28]**. As observed, the Korsmeyer-Peppas fits for

70:30 Gelatin-Sodium Alginate implants showed the highest R^2 values among all models (R^2 values in **Table 2)**. Good correlations were also obtained with Higuchi model. According to these models, Simvastatin release from the 70:30 Gelatin-Sodium Alginate Implants is diffusion controlled with the drug leaving the matrix through pores and channels formed by the entry of dissolution medium. On the consideration of release exponent (n) values, as the most of the hardening times follow the Non-Fickian Diffusion, so we can say the release of drug is controlled by both diffusion & erosion mechanism.

From **Figure 3**, the following interpretations can be drawn:

- The formulation containing Gelatin-Sodium Alginate in the ratio 70:30 showed optimum sustained effect
- Hardening the implants with formaldehyde sustained drug release, with the optimum hardening time being 12 hours
- The formulation containing 70:30 Gelatin-Sodium Alginate hardened for 12 Hrs with formaldehyde showed maximum sustained action of drug release.

Figure 1: Digital Images of Gelatin-Sodium Alginate Polymeric Implants

Figure 2: Visual Analysis of Free Formaldehyde Testing (70:30)

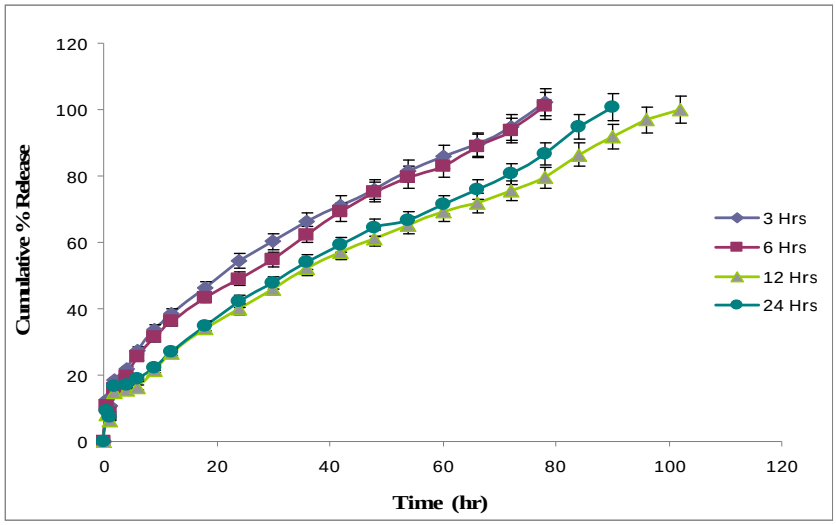

Figure 3: Drug Release Profile of Implants Formulated with 70:30 Gelatin-Sodium Alginate Polymer at Different Hardening Times

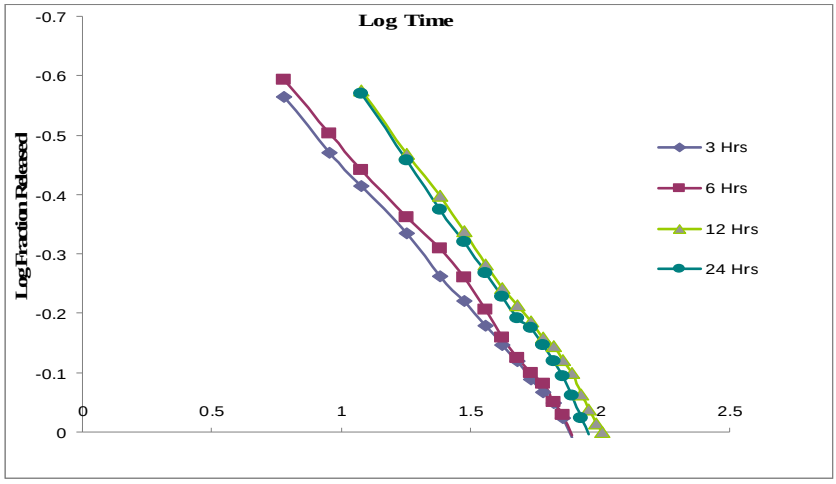

Figure 4: Korsmeyer-Peppas Plot of Implants Formulated with 70:30 Gelatin-Sodium Alginate Polymer at Different Hardening Times

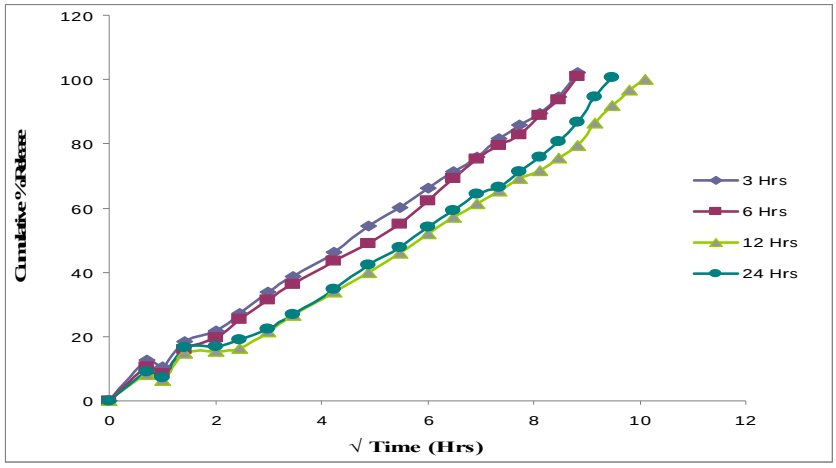

Figure 5: Higuchi Plot of Implants Formulated with 70:30 Gelatin-Sodium Alginate Polymer at Different Hardening Times

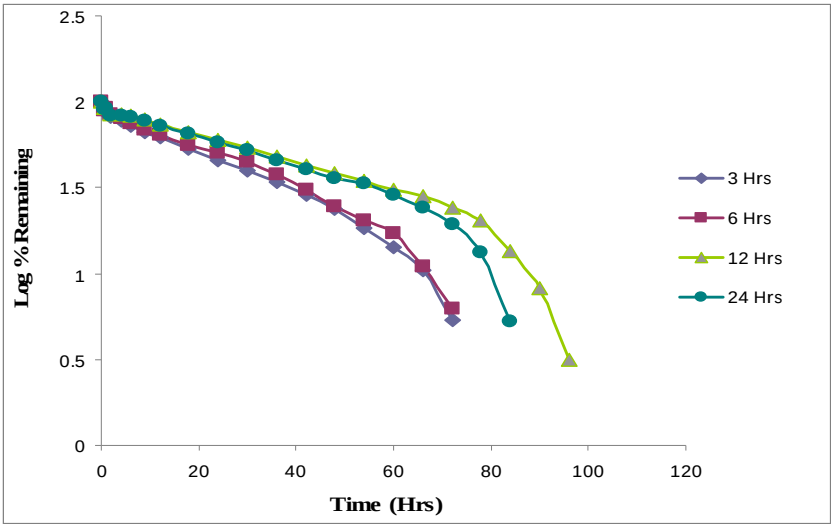

Figure 6: First Order Plot of Implants Formulated with 70:30 Gelatin-Sodium Alginate Polymer at Different Hardening Times

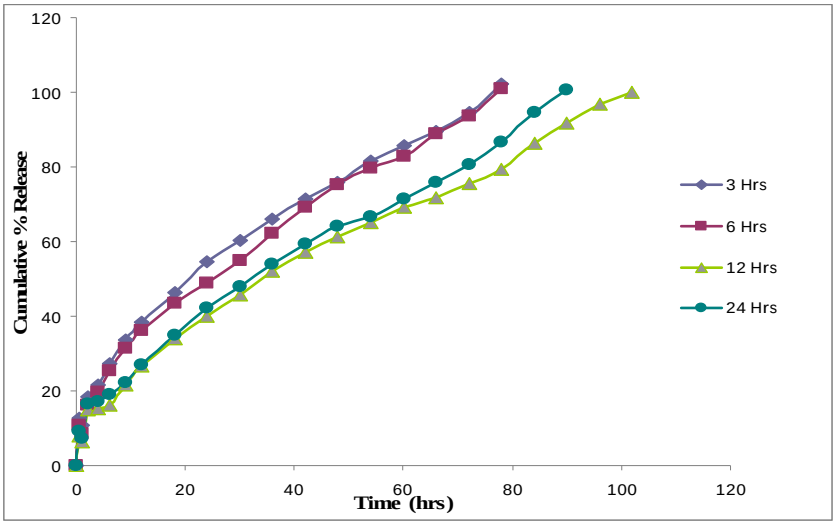

Figure 7: Zero Order Plot of Implants Formulated with 70:30 Gelatin-Sodium Alginate Polymer at Different Hardening Times

Table 1: Formulae of Implants Prepared

Ingredients	Formulation		
	70:30	80:20	90:10
Drug	0.5 gm	0.5 gm	0.5 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 qs to	15 ml	15 ml	15 ml

Table 2: Various Experimental Parameters of Prepared Implants (70:30) Hardened with Formaldehyde

S. No.	Hardening Time (Hrs)	Weight of Implants (mg) ± SD	Thickness of Implants (mm) ± SD
1	3	205.13 ± 0.12	1.51 ± 0.012
2	6	205.15 ± 0.13	1.51 ± 0.01
3	12	205.15 ± 0.13	1.51 ± 0.017
4	24	205.23 ± 0.07	1.51 ± 0.015

Table 3: Fitting Comparison of Equations of Higuchi, Korsmeyer-Peppas, First Order and Zero Order for Describing Release Profiles of Simvastatin from 70:30 Gelatin-Sodium Alginate Implants

Kinetic Model		Hardening Time (Hrs)			
		3	6	12	24
Higuchi	Rate constant (% release/√hr)	11.003	11.005	9.6882	9.9961
	R^2	0.9974	0.9947	0.9881	0.983
Korsmeyer	Rate constant (log fraction release/ log hr)	0.5008	0.5289	0.6086	0.6277
	R^2	0.9988	0.9954	0.9967	0.9952
First Order	Rate constant (log % remaining/ hr)	-0.0144	-0.0137	-0.011	-0.011
	R^2	0.9637	0.9599	0.8803	0.9057
Zero Order	Rate constant (% Release/hr)	1.1548	1.1639	0.9017	0.9963
	R^2	0.9513	0.9634	0.9754	0.9785

CONCLUSION

Rationale of the present study was to prevent first pass metabolism of the drug, to increase the bioavailability, to decrease the frequency of administration and to sustain the drug release at least

for 15 days **[4]**. Implants have been developed to avoid daily injections and improve patient compliance. However their administration and withdrawal require surgical intervention which is a compliance problem. To address this problem, use of biodegradable polymers has increased in recent studies. Biodegradable polymers are highly desirable in these situations because they degrade in the body to biologically inert and compatible molecules. No secondary surgical procedures are needed after completion of the dosing regimen **[29]**. Gelatin-Sodium Alginate based implants of Simvastatin having uniform character can be prepared with minimum batch to batch variation. Gelatin-Sodium Alginate combination biodegradable implants exhibited long term drug release under *in-vitro* conditions. The implants containing 70:30 % w/w Gelatin: Sodium Alginate and hardened for 12 hours were found to produce the most satisfactory drug release. Since the drug of choice has found its use in many long term conditions, this system shows sufficient promise as a candidate for further future development.

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