*IOSR Journal of Pharmacy and Biological Sciences (IOSR-JPBS)*
*e-ISSN:2278-3008, p-ISSN:2319-7676. Volume 11, Issue 3 Ver. IV (May - Jun.2016), PP 123-132*
*www.iosrjournals.org*

# Effect of Excipients on the Release of Simvastatin from Biodegradable Polymeric Implant

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***Abstract****: The objective of the present study was to develop and evaluate a sustained release Gelatin-sodium alginate biodegradable polymeric implant containing Simvastatin, an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, which reduces low-density-lipoprotein (LDL) cholesterol. Implants were prepared by heating and congealing method with different polymer ratios and excipients. Implants were hardened using crosslinking agent formaldehyde with varying exposure time. The implants were evaluated for thickness, weight variation, loading efficiency and in-vitro drug release studies. The in-vitro release of Simvastatin from implants containing Gelatin-Sodium Alginate at 80:20 ratios and crosslinked with formaldehyde for 24 hrs was found to produce drug release for longest time (22 days). The results obtained from the in-vitro dissolution study were fitted to different kinetic models in order to determine the possible drug release mechanisms. Most of the implants were found to follow the Korsmeyer-Peppas model, which describes the drug Simvastatin was released through diffusion and erosion mechanism from swellable matrices of Gelatin-sodium alginate. Drug loading efficiency and drug release was found to be influenced significantly by the addition of different excipients and variation in hardening times. Further research on this is expected to contribute greatly in antihyperlipidemic therapy with biodegradable implants.*

***Keywords -*** *biodegradable, gelatin, implant, simvastatin, sodium alginate*

## I. Introduction

Biodegradable polymers are material with the ability to function for a temporary period and subsequently degrade, under a controlled mechanism, into products easily eliminated in the body's metabolic pathways [1]. Biodegradable systems have gained much popularity over nondegradable delivery system, as they are eventually absorbed or metabolized and excreted by the body. This alleviates the need for surgical removal of the implant after the conclusion of therapy increasing patient compliance. The major advantage of this systems include, controlled administration of a therapeutic dose at a desirable rate of delivery, maintenance of drug concentration within an optimal therapeutic range for prolonged duration of treatment, reduction of adverse side effects, minimization of the needs for frequent dose.

Control of hypercholesterolemia is important for the prevention of coronary heart disease (CHD). Currently, 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, also known as statins, are the most effective class of drugs for lowering serum low-density lipoprotein (LDL) cholesterol concentrations [2]. They are first-line therapeutic agents for patients with hypercholesterolemia. The HMG-CoA reductase inhibitor Simvastatin is widely used and has been shown to reduce morbidity and mortality from CHD. Simvastatin is an inactive lactone pro-drug that is hydrolyzed by esterases to simvastatin acid, the active competitive inhibitor of HMG-CoA reductase. Simvastatin and simvastatin acid are mainly metabolized by the cytochrome P450 (CYP) 3A4 to 3′, 5′-dihydrodiol, 3′-hydroxy and 6′-exomethylene. Simvastatin reduce low-density lipoprotein cholesterol, total cholesterol, and triglycerides and slightly increase high-density lipoprotein cholesterol.In this research Simvastatin, have been entrapped into Gelatin-sodium alginate biodegradable polymeric implants crosslinked with formaldehyde vapor for sustained drug delivery. 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 [3]. This reaction is of great practical importance, in particular, for preparation and development of controlled drug delivery systems [4]. Slow release of Simvastatin can inhibit LDL cholesterol biosynthesis for a prolonged period of time.

## II. Materials And Methods

### *2.1 Materials*

All the chemicals and reagents used in this study were of analytical grade. Simvastatin was obtained as a gift from Renata Limited, Bangladesh. Purified Gelatin, Sodium Alginate, Glyceryl Mono Stearate (GMS), Palmitic Acid and Cetostearyl Alcohol were purchased from Loba Chemie Pvt. Ltd, Mumbai. Guar Gum was purchased from BASF, Germany. Acetonitrile was purchased from Fischer Chemical, New Jersey. Suitable storage conditions were maintained to store the working chemicals and reagents.

### *2.2 Preparation of Implants*

Biodegradable implants of Simvstatin were prepared by the use of two biodegradable polymers Gelatin and Sodium Alginate by heating and congealing method. The implants were prepared using 5% drug load and with 3 different polymer ratios (70:30, 80:20, 90:10) and different excepients to obtain a gelatin-Na alginate matrix to be used as the active substance carrier and getting prolonged drug release action from its implantable form. Table 1 and 2 shows different formulations that have been prepared.

**Table 1:** Formulation chart of implant with drug and polymer

| Name of Formulation | Drug loading | Polymer ratio | Formaldehyde Exposure |
|---|---|---|---|
| F1A | 5% | 70:30 | 12 hour |
| F1B | 5% | 70:30 | 24 hour |
| F2A | 5% | 80:20 | 12 hour |
| F2B | 5% | 80:20 | 24 hour |
| F3A | 5% | 90:10 | 12 hour |
| F3B | 5% | 90:10 | 24 hour |

The excipients used in different formulations are shown Table 2.

**Table 2:** Formulation chart of implant with different excipients

| Name of Formulation | Drug loading | Polymer ratio | Formaldehyde Exposure | Excipients |
|---|---|---|---|---|
| F4A | 5% | 80:20 | 12 hour | Palmitic acid |
| F4B | 5% | 80:20 | 24 hour | Palmitic Acid |
| F5A | 5% | 80:20 | 12 hour | Glyceryl Mono Stearate |
| F5B | 5% | 80:20 | 24 hour | Glyceryl Mono Stearate |
| F6A | 5% | 80:20 | 12 hour | Cetostearyl Alcohol |
| F6B | 5% | 80:20 | 24 hour | Cetostearyl Alcohol |
| F7A | 5% | 80:20 | 12 hour | Guar Gum |
| F7B | 5% | 80:20 | 24 hour | Guar Gum |

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 up to 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 cabinet. After that the implants were placed in a formaldehyde desiccator for hardening. Formulations varied with respect to Gelatin-Sodium Alginate polymer ratios [5,6,7].

### *2.3 Hardening of implants*

A petri-dish containing Formaldehyde solution (37% v/v) was placed in empty glass desiccators. Implants were kept in separate petridishes and placed in the desiccators for exposure to formaldehyde vapors.for different time periods such as 12 and 24 hours. Then they were removed from the desiccator for air drying which takes approximately 72 hours, to make the crosslink reaction between gelatin and sodium alginate. Then the implants were kept in an open air in aseptic condition for a week to make sure that the residual formaldehyde gets evaporated [5].

### *2.4 Characterization of Implants*

#### *2.4.1 Measurement of implant thickness and weight variation*

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. Weight Variation of Implants was checked by weighing three implants of a particular formulation and exposure time individually [5].

#### *2.4.2 Scanning electron microscope (SEM)*

Prepared implants were analyzed for their surface morphology by scanning electron microscope. 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. Scanning electron microscope (SEM) was used to observe interior morphology at cross section of hot-melt extrudates. Firstly, hot-melt extrudates were cut into approximately 3-5 mm pieces.

#### *2.4.3 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 5 mg of prepared implant sample were placed in a

sealed aluminium pan, before heating under nitrogen flow (300 ml/min) at a scanning rate 10ºC min 1 from 50°C to 200°C. An empty aluminum pan was used as reference (Dhaka, Bangladesh).

***2.4.4 Determination of drug content***

The amount of drug that was actually loaded in implants during fabrication process was determined by spectrophotometric analysis. For determining the drug content of Simvastatin loaded implants, first the implants was weighed and then crushed in a mortar and pestle. Then it was dissolved in 1 ml hot phosphate buffer, pH 7.4 by vigorous ultrasonication. Then 3ml acetonitrile and 7 ml buffer was added for precipitating the polymer and extracting the drug in solvent. Then it was centrifuged at 3000 RPM for 10-12 minutes to separate the solid material. 1 ml of supernatant was withdrawn into 100 ml volumetric flask and made the volume upto mark with acetonitrile and phosphate buffer, pH 7.4 with the ratio of 30:70. Then it was analyzed at 238.2 nm (λmax of Simvastatin) in UV spectrophotometer. Simvastatin concentration was calculated from the standard curve. The percentage of loading efficiency (%LE) of implants was determined with the formula:

%Loading Efficiency (LE) = (LD/AD) x 100
LD is the amount of loaded drug in the implant and
AD is the amount of added drug in the formulation [8].

***2.5 Test of free formaldehyde***

To ascertain the absence of free formaldehyde, implants were subjected pharniacopoeial test for free formaldehyde.

***2.5.1 Qualitative test of free formaldehyde***

The sample of implants were crushed and dissolved in 3 m1 methanol and 7m1 phosphate buffer pH 7.4. They were then sonicated and centrifuged, until getting supernatant. The 1 ml of this supernatant was then transferred in test tube and made up to 10 ml by Phosphate buffer. Standard solution was prepared by transferring 1 ml of formaldehyde solution in test tube and making its volume up to 10 ml with Phosphate buffer, pH 7.4. For the preparation of reagent (needed to carry out the free formaldehyde) at first 15.4 mg ammonium acetate salt was weighed and dissolve in small amount of distill water. Then 0.2 ml of glacial acetic acid was added to the solution. After mixing the both solution it was diluted up to 100 ml. 0.2 ml acetyl acetone was added to the final solution. 1 ml of standard solution and 1 ml of sample solution were taken in separate test tubes. To each test tube 4 ml of distilled water and 5 ml of acetyl acetone reagent were added. They were then placed in water bath at 40°C for 40 minutes to observe any visible color change.

***2.5.2 Quantitative test of free 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 80ºC. 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. 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. The absorbance of the filtered solution was then observed in Double Beam UV-VIS spectrometer (UV-1700, 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 [9].

***2.6 In-vitro drug release 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. Three 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, 5 ml of sample is withdrawn from the dissolution vessels using 5 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. 5 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 (UV- 1700 SHIMADZU) at 238.2 nm (λ max 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.

### *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.

## III. Results And Discussion

### *3.1 Measurement of implant thickness and weight*

The thickness of implants was checked by taking 3 implants from each batch of formulations and measured their thickness individually by using digital slide calipers. Table 3 shows variations in thickness of the implants with different polymer ratio including 70:30, 80:20 and 90:10 which were hardened for 12 and 24 hours with standard deviation.

Weight of implants was checked by weighing three implants of a particular formulation and exposure time individually. The Table 3 shows the weight of implants of 70:30, 80:20 and 90:10 polymer ratios hardened by formaldehyde for 12 hours and 24 hours with standard deviation.

**Table 3:** Thickness and weight variation of different implants

| Formulations | Thickness of implants (mg) ± SD | Weight of implants (mg) ± SD |
|---|---|---|
| F1A | 1.73±0.015 | 209±0.95 |
| F1B | 1.74±0.012 | 208±0.88 |
| F2A | 1.76±0.010 | 210±0.98 |
| F2B | 1.81±0.013 | 213±1.07 |
| F3A | 1.77±0.011 | 203±1.13 |
| F3B | 1.75±0.017 | 205±0.65 |

### *3.1 Observation through Scanning Electron Microscope (SEM)*

Fig. 1 displays a 100 times magnified polymeric implant micrograph before and after drug release. Figure at the left side shows that, the SEM micrograph of Cetostearyl alcohol incorporated Simvastatin loaded polymeric implant surface before drug release is rough. The rough implant surface as observed in the SEM micrograph is indicative of the hydrophilic nature of the polymer matrix [10]. The entrapment of drug is relatively lower compared to 100% entrapping capability and it also correlate with loading efficiency found from drug content analysis. The loading efficiency was found 69.58 % when Cetostearyl alcohol was incorporated in the implant. Figure at the right side being more porous and rough we can say that very low amount of drug was remaining after drug release which also comply with the figure.

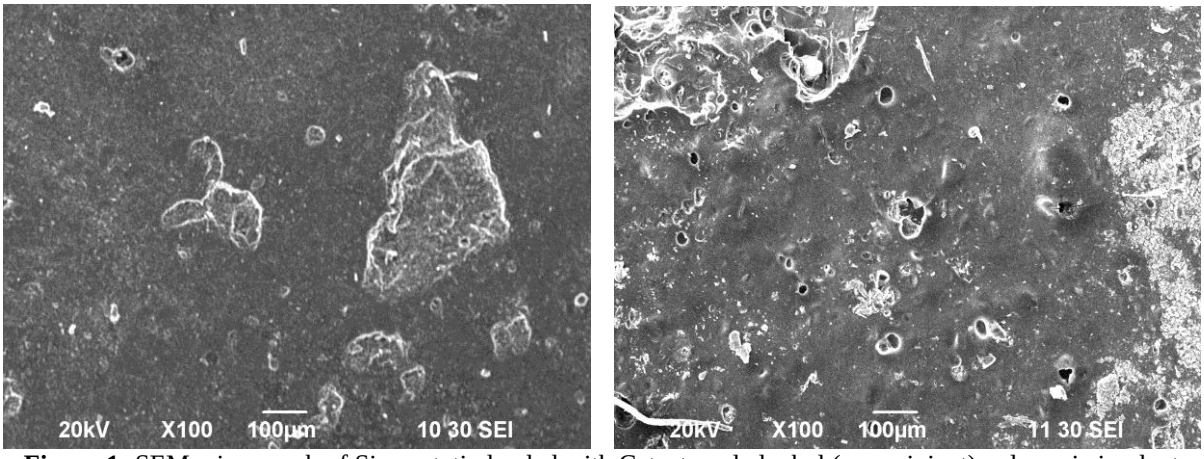


**Figure 1:** SEM micrograph of Simvastatin loaded with Cetostearyl alcohol (as excipient) polymeric implant surface before and after drug release

### *3.2 Differential scanning calorimetry (DSC) of drug and polymer*

The DSC provides qualitative and quantitative information on endothermic / heat absorption (e.g., melting) and exothermic / heat releasing (e.g., solidification or fusion) processes of materials. These processes display sharp deviation from the steady state thermal profile, and exhibit peaks and valleys in a DSC thermogram (Heat flow vs. Temperature profile). The latent heat of melting or fusion can then is obtained from the area enclosed within the peak or valley.

DSC of pure crystalline Simvastatin as obtained from the source was performed. Fig. 2 displays the DSC thermogram of pure Simvastatin. The DSC scan of crystalline Simvastatin in Fig. 2 exhibits the endothermic peak at 141.87°C (onset about 139.41°C and endset about 144.57°C).

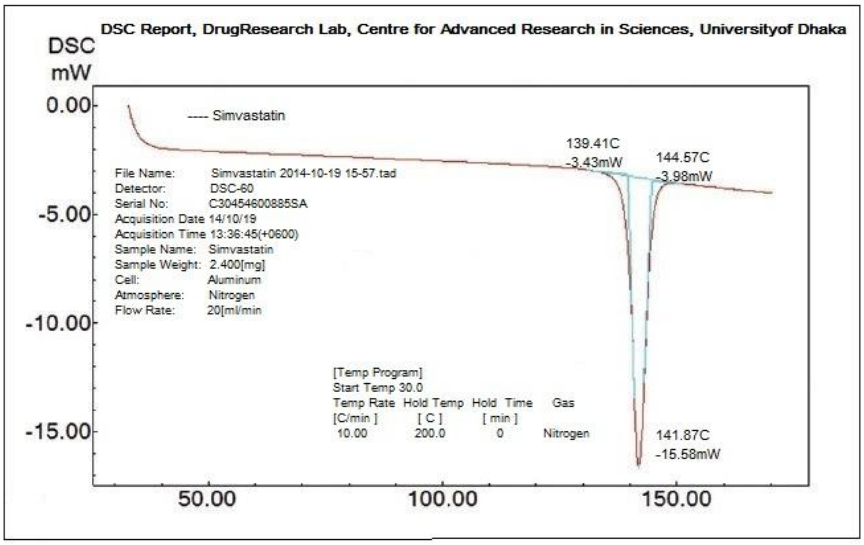


**Figure 2:** DSC thermogram of pure crystalline Simvastatin

The DSC scans of Simvastatin incorporated in Gelatin-Sodium alginate mixture was also performed and shown in Fig. 3. The figure exhibits two endothermic peaks. Gelatin and sodium alginate having the first broad endothermic peak (corresponding onset and offset temperatures are 55°C and 120°C, respectively) appearing at 82.15°C. The other small and broad endothermic peak also found at onset temperature 133.74°C and offset temperature is at 144.83°C with the peak at 137.6°C is for the drug Simvastatin.

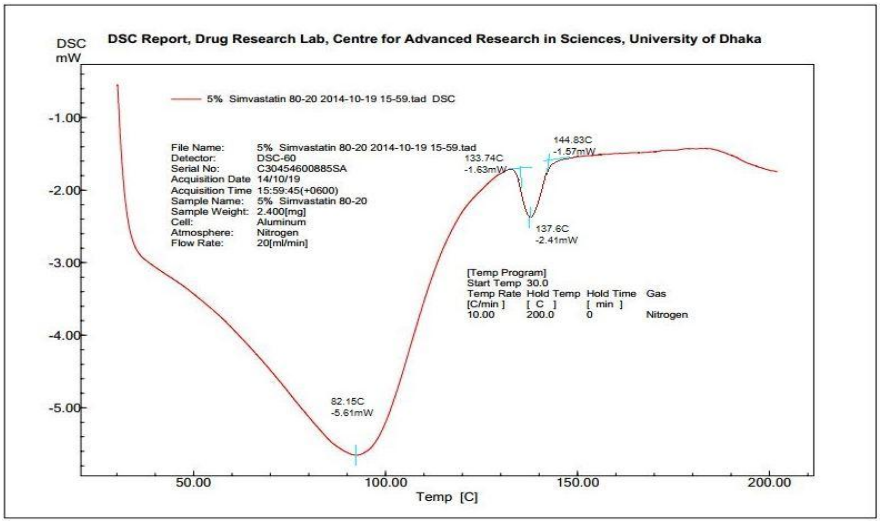


**Figure 3:** DSC thermogram of Simvastatin incorporated in Gelatin-Sodium Alginate polymeric implant

This indicates there was no drug polymer interaction and drug exists in crystalline form in the formulation, even though there has been a little bit shifting (from 141.87°C to 137.6°C for the endothermic peak) which is probably due to the presence of Gelatin-Sodium alginate in the formulation.

### *3.4 Test for free formaldehyde*

#### 3.4.1 Qualitative test for free formaldehyde

In the qualitative test for free formaldehyde, the standard formaldehyde solution shows bright yellow color. The implants, after being subjected to the pharmacopoeial test for free formaldehyde, were observed for visible color changes against the standard solution. The intense the yellow color of the solution of the samples, the greater the amount of free formaldehyde. All the sample solutions were found to be colorless, which indicates that these implants did not retain any formaldehyde.

#### 3.4.2 Quantitative test for free formaldehyde

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 [12]. The concentration of crosslinked formaldehyde with gelatin was found to be 0.1323 µg/ml equivalent to 0.1323 ppm which is within formaldehyde tolerable range in human body.

### *3.5 Effect of excipients on drug loading efficiency*

The effect of incorporation of different excipients on drug loading efficiency of Simvastatin was studied for 5% 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 5% load of Simvastatin are represented in the Table 4. Loading efficiency was found to be in the range between 48.92% to 81.93% in different formulations. The highest loading efficiency was found with Palmitic Acid (81.93%) and the lowest with GMS (48.92%). The loading efficiency was found to decrease in the following sequence:

Palmitic Acid > Guar Gum > Drug Only > Cetostearyl Alcohol > GMS

**Table 4:** Effect of excipients on Simvastatin loading efficiency

| Excipients | Actual Drug Content Mean± SD | Loading Efficiency (%) |
|---|---|---|
| Drug Only | 10.89±0.86 | 72.44 |
| Cetostearyl Alcohol | 5.13±0.76 | 50.71 |
| Palmitic Acid | 11.97±0.98 | 81.93 (maximum) |
| Glyceryl Monostearate | 5.49±0.24 | 48.92 (minimum) |
| Guar Gum | 10.64±0.96 | 69.35 |

Palmitic Acid is practically insoluble in water and it can be used as a sustained-release drug carrier. It decreases the passage for drug which may result in high drug loading efficiency [11]. 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 [13]. Cetostearyl Alcohol is insoluble in aqueous buffer and is widely used in modified release dosage form. Cetostearyl alcohol is used because of its emollient, water-absorptive, and emulsifying properties. It enhances stability, improves texture, and increases consistency. The percentage of Cetostearyl Alcohol that is used in this formulation may act as a water absorptive agent for which it may reduce drug loading efficiency. Guar Gum decreased the Simvastatin loading efficiency. Guar gum has been used as a suspending agent [15].

### 3.5 *In-vitro Drug Release Studies*

The drug release rate from a polymeric matrix depends on interactions between the active ingredients and polymer [14]. The implants were formulated with three polymer ratios, namely 70:30, 80:20 and 90:10 of gelatin-Sodium Alginate composition and were subjected to different formaldehyde exposure time (12 hours and 24 hours) for hardening.

**Table 5:** Overview of calculated time describing the in vitro Simvastatin release from Gelatin-Sodium Alginate biodegradable polymeric implant

| Formulations | Polymer ratio of implants | Hardening time | Time (days) taken for drug release to be completed from implants |
|---|---|---|---|
| F1A | 70:30 | 12 hours | 16 |
| F1B | 70:30 | 24 hours | 18 |
| F2A | 80:20 | 12 hours | 18 |
| F2B | 80:20 | 24 hours | 22 (Maximum) |
| F3A | 90:10 | 12 hours | 12 |
| F3B | 90:10 | 24 hours | 16 |

The Fig. 4 represent drug release profile of implants of polymer ratio 70:30, 80:20 and 90:10 formulations at their different hardening times (12 hours and 24 hours).

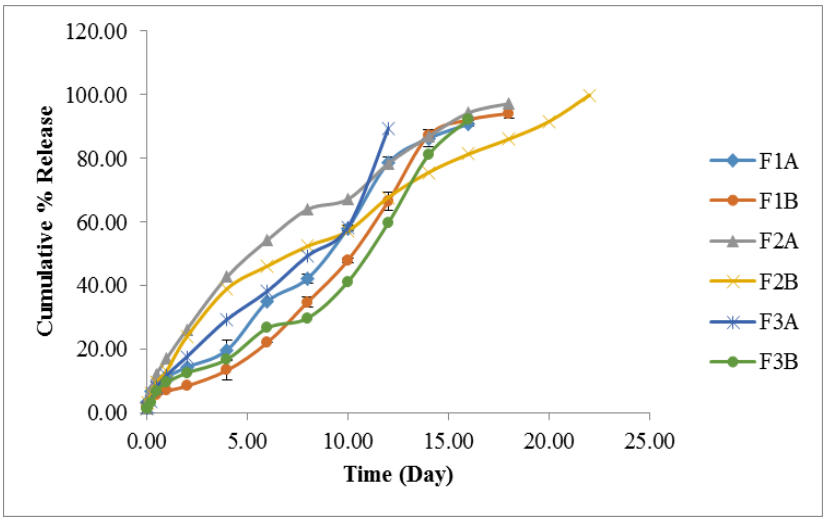


**Figure 4:** Drug release profile of implants of different formulations at their different hardening times (12 hrs and 24 hours).

The formulation containing Gelatin-Sodium Alginate in the ratio 80:20 showed optimum sustained effect. Hardening the implants with formaldehyde sustained drug release. The formulation containing 80:20 Gelatin-Sodium Alginate hardened for 24 hrs with formaldehyde showed maximum sustained action of drug release (22 Days).

In the literature, plenty of theoretical or empirical release models are described [16, 17]. Zero order, First order kinetics, Higuchi and Korsmeyer-Peppas models have been chosen to describe the Simvastatin 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. The Korsmeyer-Peppas equation describes the mode of release of drugs from swellable matrices [16, 18]. Korsmeyer-Peppas kinetic model is applied when the release mechanism deviates from Ficks law [19], assuming perfect sink conditions, rapid surface equilibrium between the polymer and water, symmetric devices, and uniformly dispersed drug in the dry sample.

The most suited mathematical model applied for describing the kinetics of drug release process is the one which best fits the experimental results.

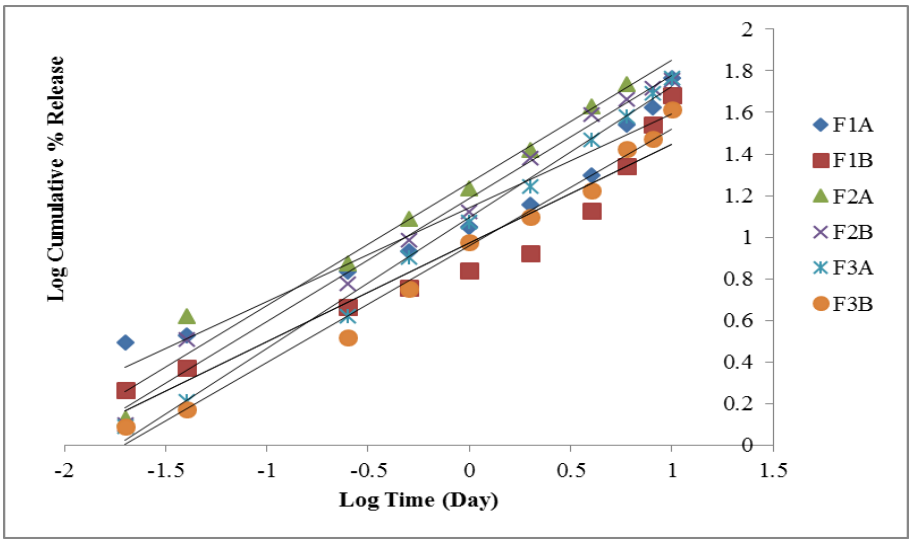


**Figure 5:** Korsmeyer-Peppas plot of Simvastatin release from implants at 12 and 24 hours hardening time

**Table 6:** Fitting comparison of equation of Higuchi, korsmeyer-peppas, First order and Zero order for describing Simvastatin release from implants at 12 and 24 hours exposure time

| Formulations | Kinetic model | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Zero order | | First order | | Higuchi | | Korsmeyer-Peppas | |
| | m value | $R^2$ | m value | $R^2$ | m value | $R^2$ | n value | $R^2$ |
| F1A | 5.70 | 0.986 | -0.057 | 0.916 | 21.89 | 0.916 | 0.45 | 0.946 |
| F1B | 5.47 | 0.972 | -0.062 | 0.873 | 21.90 | 0.871 | 0.48 | 0.918 |
| F2A | 5.47 | 0.958 | -0.072 | 0.937 | 23.61 | 0.985 | 0.58 | 0.973 |
| F2B | 4.43 | 0.964 | -0.047 | 0.975 | 21.07 | 0.971 | 0.59 | 0.987 |
| F3A | 6.44 | 0.974 | -0.052 | 0.920 | 21.59 | 0.916 | 0.63 | 0.995 |
| F3B | 5.20 | 0.958 | -0.052 | 0.820 | 19.54 | 0.853 | 0.56 | 0.987 |

From Table 6, the Korsmeyer-Peppas release rate constant for all implants were found to be within 0.50-1.00 ($0.50<n<1.00$) which indicates the release pattern follows anomalous transport mechanism which appears to indicate a coupling of the diffusion and swelling controlled mechanism [20].

### *3.6 Effect of excipients on drug release*

Excipients have various effects on drug release profile. The rate and extent of drug release from implants can be controlled by the use of excipients in the formulation. These agents can act as rate modifier by increasing or retarding the rate of release depending upon the nature of the agent. They probably extent their effects by influencing the way of formulation formed and therefore on the release characteristics of the sustained release implants [15].

Palmitic acid, which is insoluble in water, may create a porous matrix characterised by a series of interconnecting channels developed inside it and holding the dissolved drug and soluble compound molecules that diffuse outward due to the concentration gradient in formulation F4A and F4B [11]. As GMS is also insoluble in water, drug release from GMS incorporated implant F5A and F5B is generally achieved by penetration of the release medium into the polymeric system and dissolution of the drug, followed by the diffusion of the drug solution through the swellable matrices ($R^2$ values in Table 8). Drug solubility plays a significant role in its release duration and kinetics from GMS incorporated implant [13]. The release period differed from one formula to another due to the influence of respective excipients. The time ranged from 12-20 days depending on the excipient characteristics (Table 7).

Simvastatin release was studied for up to 25 days for all excipients. Result of in vitro release are summarized in Table 8 and also graphically represented in the Fig. 6.

**Table 7:** Overview of calculated time describing the in vitro Simvastatin release from Gelatin-Sodium Alginate biodegradable polymeric implant with different excipients

| Formulations | Excipients | Hardening time | Calculated time (days) for drug release |
|---|---|---|---|
| F4A | Palmitic Acid | 12 hours | 16 |
| F5A | Glyceryl Monostearate | 12 hours | 20 |
| F6A | Cetostearyl Alcohol | 12 hours | 18 |
| F7A | Guar Gum | 12 hours | 12 |
| F4B | Palmitic Acid | 24 hours | 16 |
| F5B | Glyceryl Monostearate | 24 hours | 16 |
| F6B | Cetostearyl Alcohol | 24 hours | 18 |
| F7B | Guar Gum | 24 hours | 14 |

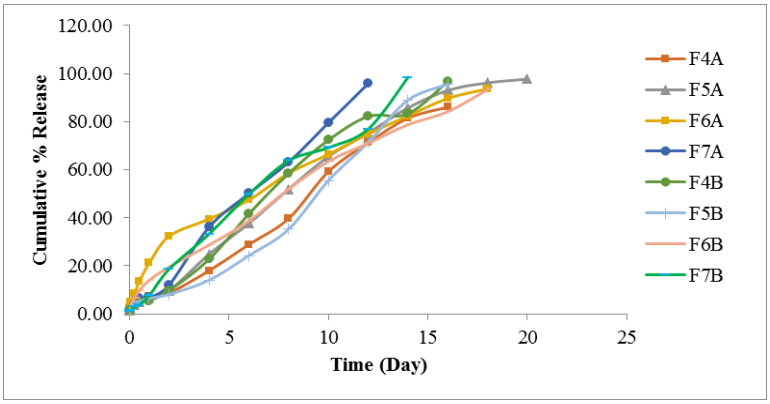


**Figure 6:** Release of Simvastatin from implants with four different excipients at different hardening time

The kinetics of Simvastatin from 80:20 Gelatin-Sodium Alginate polymer implant hardened for 12 hours with different excipients were fitted to Higuchi, Korsmeyer-Peppas, Zero Order and First Order plots. Here Korsmeyer-Peppas plot is shown in the graph (Fig.7) and analyzed to identify drug release characteristics for implants with different excipients. The respective data are presented in the Table 8.

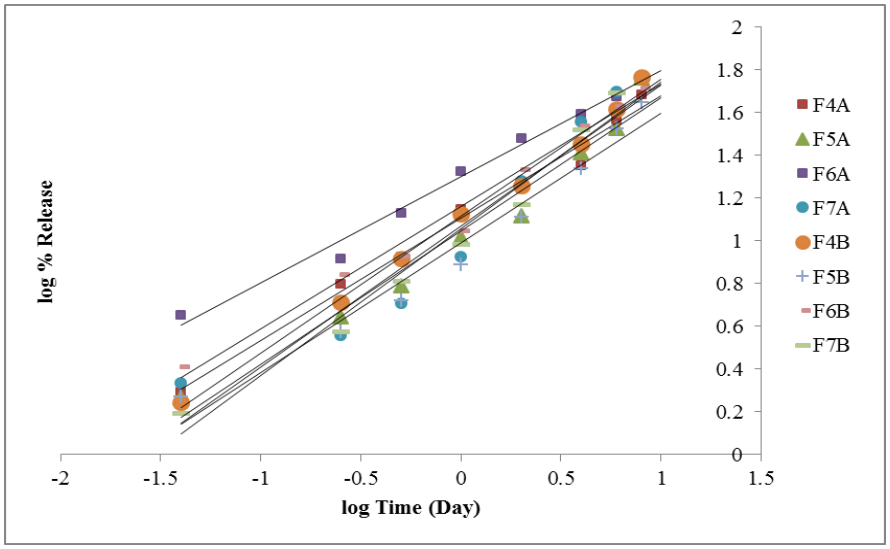


**Figure 7:** Korsmeyer-Peppas plot of Simvastatin release from implants with different excipients at 12 and 24 hours hardening time

**Table 8:** Fitting comparison of equation of Higuchi, korsmeyer-peppas, First order and Zero order for describing Simvastatin release from implants at 12 and 24 hours exposure time with different excipients

| Formulations | Kinetic Model | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Zero Order | | First Order | | Higuchi | | Korsmeyer-Peppas | |
| | n | $R^2$ | n | $R^2$ | n | $R^2$ | m | $R^2$ |
| F4A | 5.55 | 0.979 | -0.05 | 0.95 | 21.22 | 0.943 | 0.57 | 0.987 |
| F5A | 5.41 | 0.969 | -0.07 | 0.917 | 23.92 | 0.959 | 0.62 | 0.969 |
| F6A | 5.09 | 0.957 | -0.06 | 0.937 | 21.97 | 0.985 | 0.49 | 0.989 |
| F7A | 7.92 | 0.976 | -0.05 | 0.982 | 26.42 | 0.95 | 0.66 | 0.927 |
| F4B | 6.31 | 0.985 | -0.06 | 0.958 | 24.96 | 0.941 | 0.64 | 0.994 |
| F5B | 5.89 | 0.933 | -0.06 | 0.849 | 21.67 | 0.866 | 0.60 | 0.965 |
| F6B | 5.14 | 0.986 | -0.05 | 0.954 | 21.63 | 0.977 | 0.57 | 0.984 |
| F7B | 6.85 | 0.957 | -0.07 | 0.894 | 25.17 | 0.943 | 0.68 | 0.974 |

As can be seen from Table 8, the release phase of most of the implants with excipients best fitted to korsmeyer-peppas kinetic model. The Korsmeyer-Peppas release rate constant for the implants was found to be within 0.50-1.00 ($0.50<n<1.00$) which indicates the major mechanism of drug release being nonfickiann diffusion, that means drug is released through the diffusion and erosion mechanism from swellable matrix [21].

## IV. Conclusion

For the treatment of hypercholesterolemia as well as prevention of coronary heart disease (CHD), Simvastatin is the choice of drug and it is used daily for 1 to 5 years in the form of oral tablet. So, a prolonged drug delivery system for Simvastatin will be more patient compliant. It is evident from this studies that the Gelatin-sodium alginate implants could be suitable drug carrier systems for long-term delivery of Simvastatin. Extensive efforts are being made for sustaining its release for prolonged use and research works have already been reported on capturing the drug, utilizing nonbiodegradable implant technology. The present study discovered that Simvastatin could be entrapped into Gelatin-sodium alginate implants with high drug loading efficiency (48.92 -81.93%) and also provide sustained drug release for a period of 12-22 days. Therefore, it can be an attractive candidate for further future development.

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