Formulation and Evaluation of Simvastatin Injectable in situ Implants

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ABSTRACT

Simvastatin is anti-hyperlipidemic drug which is used to control elevated cholesterol or hypercholesterolemia. The drug undergoes extensive first pass metabolism and has a t1/2 of 3 h. It has poor bioavailability (about 5%) and high protein binding (>95%). The dosage form currently available is conventional uncoated tablet administered once daily. The objective of the present study was to improve the bioavailability of the drug by formulating an intraperitoneal implant and to sustain the drug release for atleast 15 days. The formulation was prepared by polymer precipitation method. In this method, the polymer drug solution is injected into the aqueous buffer from which the solvent dissipates into buffer and forms a solid implant. The optimized formulations were evaluated for drug content, cumulative percentage drug release, solvent ratio, surface morphology and drug interactions. From our studies, it was observed that the drug entrapment efficiency increased and the burst release decreased with increase in the polymer concentration. We could achieve sustained release of the drug with optimized formulation. The formulation with 20% polymer concentration exhibited moderate burst release and sustained release for 15 days. The in situ implants showed no drug polymer interactions. The SEM configurations showed polymer precipitation and the crosslinking of the polymer. Pharmacokinetic studies performed on rats confirmed sustained drug release up to 15 days. The bioavailability of the drug was also found to be improved and showed a 3 fold increase when compared to control tablets (ZOCOR 10 mg). Hence in addition to our studies, further research and clinical investigations can certainly help in proposing Simvastatin in situ implants as a treatment alternative in hyperlipidemic patients.

Key words: In situ drug delivery, in situ implants, simvastatin, polycaprolactone, PLGA, implants, hyperlipidemia, statins, sustained release, parenteral depot

INTRODUCTION

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 (Schoenhammer et al., 2009). Injectable in situ forming implants are classified into five categories, according to their mechanism of depot formation: (1) thermoplastic pastes, (2) in situ cross linked systems, (3) in situ polymer precipitation, (4) thermally induced gelling system and (5) in situ solidifying organogels. Of these, in situ polymer precipitation systems have become commercial available so far.
The in situ Forming Implant (ISFI) systems have several advantages compared to traditional pre-formed implant systems. Due to their injectable nature, implant placement is less invasive and painful for the patient thereby improving comfort and compliance. Additionally, the manufacturing process required for fabrication is relatively mild. Currently, only two FDA approved products are on the market utilizing this type of system, Elgard® and Atridox®, Elgard®, using the Atrigel® delivery system and marketed by Sanofi-Aventis in the US (Medigene in Europe), is a subcutaneously injected implant that releases Leuprolide acetate over a period of 3 months to suppress testosterone levels for prostate cancer treatment (Sartor, 2003). Atridox® (Tolmarc Inc.) is another ISFI system that also uses the Atrigel® delivery system to deliver the antibiotic agent, Doxycycline to the sub-gingival space to treat periodontal disease (Buchter et al., 2004). Some disadvantages of in situ implants are high burst release, potential solvent toxicity and high viscosity of the polymeric solution which may lead to problems during administration (Kranz et al., 2001).

Dunn et al. (1999) developed an implant using biodegradable polymer dissolved in water miscible organic solvent which undergoes a process called liquid de-mixing when injected into aqueous phase. This technology has been utilized for the delivery of model proteins, LHRH-antagonists, narcotic antagonists, growth factors, anti-inflammatory agents and antibiotics (Tipton and Fujita, 1991; Radomsky et al., 1993). Statins like Simvastatin, Lovastatin, Fluvastatin, Rosuvastatin, Atorvastatin are class of drugs generally used to lower blood levels by reducing the production of cholesterol by the liver. Simvastatin is a water insoluble drug with very poor oral absorption and a short half-life of 3 h. The bioavailability of the drug is 5% and exhibits rapid first pass metabolism. Simvastatin is generally administered as once daily tablet in the treatment of patients with heart disorders. Several approaches have been investigated in order to control the levels of cholesterol in the body. Zhang et al. (2011) developed spherical mesocellular foam (MCF) loaded with a poorly water soluble drug, intended to be orally administered, able to improve the dissolution rate and enhance the drug loading capacity. They found that spherical MCF has a high drug loading efficiency up to 37.5%. Kang et al. (2004) prepared Self-Micro Emulsifying Drug Delivery System (SMEDDS) for enhancing bioavailability of Simvastatin. SMEDDS form resulted in about 1.5 fold increase in bioavailability of Simvastatin compared to conventional tablet. Bae et al. (2011) have studied the positive influences on in vitro and in vivo osteogenesis of photo-cured Hyaluronic Acid (HA) hydrogels loaded with Simvastatin (SVS). The results showed sustained release of Simvastatin from these Hydrogels and had significant influence on osteogenesis. Zhang et al. (2010) prepared Simvastatin loaded lipid nanoparticles (SLNs) with different components to enhance its oral bioavailability. The oral bioavailability of drug after its incorporation into the lipid nanoparticles was improved by 3.37-fold for SLNs compared to free drug in rats. Preparation and characterization of Polyactic acid and Polycaprolactone nanocomposites by melt blending technique was also studied and the results showed increase in mechanical properties and thermal stability (Hoidy et al., 2010). White, free-flowing and spherical PLGA microspheres were prepared using emulsion technique which showed sustained drug release (Gupta et al., 2010; Rudra et al., 2011). The above approaches could increase the bioavailability of the drug and prolonged the release of the drug for a period of 12-48 h. In situ depot systems can thus be used for long term therapy and extended release of the drug for a period of months up to years. Implantable technology is also preferred in the treatment of osteoporosis, mainly in the hip joint failure (Ridzwan et al., 2005, 2007; Zuki et al., 2006). Some of the advancements in the implantable technology include the implantable stimulation using an inductive power system.
that combines power transfer with data transmission for implantable biomicrosystem (Hmida et al., 2007). Ion stimulation using some rare earth ions for laser or amplifier action was also studied (Benaissa et al., 2007). Cochlear implants and microsensor systems are currently one of the most preferred choices for measuring and recording neural signals from auditory nerve (Ghorbel et al., 2006). In the present study, Simvastatin injectable in situ implants were formulated in order to achieve drug release up to at least 15 days. These formulations could further be investigated to improve the bioavailability of the drug and avoid first pass metabolism thereby improving patient compliance in hyperlipidemic patients.

MATERIALS AND METHODS

Materials: Simvastatin (SVS) was a kind gift from Marksan’s Pharma Ltd, Verna, Goa, Polycaprolactone (PCL) was purchased from Hi-media, Hyderabad. Poly (D, L-Lactide-co-glycolide) (PLGA) was a gift sample from NATCO Research Centre, Hyderabad. All the solvents were of HPLC grade and were purchased from SD fine chemicals, Hyderabad.

Method of preparation

PCL implants: In situ implants were prepared by polymer precipitation method. In this method PCL is dissolved in the organic phase containing acetonitrile (ACN) and dichloromethane (DCM). Different formulations were prepared using 5-40% of polymer. To this polymer solution, 75 mg of drug was added. The polymer–drug solution was stirred vigorously until clear solution was formed. 1 ml of this solution was gradually injected into 50 ml of aqueous phase containing 7.4 phosphate buffer for the formation of implant (Kranz et al., 2008; Liu et al., 2010).

PLGA implants: In this method, PLGA was dissolved in the organic phase containing Dimethyl Sulfoxide (DMSO) and dichloromethane (DCM). Polymer concentrations of 30 and 40% were prepared. The further steps in the preparation of the implant were similar to that of PCL implant.

Characterization and evaluation of SVS in situ implants: The prepared in situ implants were evaluated for various parameters such as drug entrapment efficiency, evaluation of in vitro release, SEM, FTIR, evaluation of in vivo release (Kranz et al., 2008; Liu et al., 2010).

Drug entrapment efficiency (DEE): The amount of drug entrapped was estimated by dissolving the implant in the highly basic phase using 0.1 N NaOH under vigorous shaking for 12 h. The resultant solution was filtered using No. 1 Whatmann filter paper. The drug content in the solution was analysed spectrophotometrically using UV-VIS single beam spectrophotometer at 238 nm with further dilutions against appropriate blank. The amount of the drug entrapped in the implant was calculated using the formula:

\[
\text{DEE} = \frac{\text{Amount of drug actually present}}{\text{Theoretical drug load expected}} \times 100
\]

Scanning electron microscopy (SEM): The dried in situ implants were coated for 70 sec under an argon atmosphere with gold-palladium and then observed under a Scanning Electron Microscope (JSM-5200 SEM, Tokyo, Japan).
FTIR: The drug-polymer containing in situ implant and the pure drug were subjected to the Fourier-transform infrared spectroscopy (Shimadzu 8400 S FTIR) in order to check the possible drug-polymer interactions.

**In vitro drug release studies:** In vitro release studies were performed using modified diffusion apparatus using dialysis membrane (Himedia with Mwt cut off 12,000-14,000 kDa). In situ implants were placed into conical vials open on one side and closed with dialysis membrane on other side. The formulations were placed into 50 ml 7.4 pH phosphate buffer at 37°C. At 1, 3, 5, 7, 9, 12, 15, 20, 24, 28, 32, 40, 48 and 72 h time intervals, 5 mL samples were withdrawn and assayed. Each time the vials were replaced with aliquots of fresh medium. After 48 h the complete medium was withdrawn and replaced by fresh medium to avoid saturation of the medium. The drug content was measured using UV-VIS single beam spectrophotometer at 238nm. The obtained data were fitted into mathematical equations (zero order, first order and Highuchi models) in order to describe the kinetics and mechanism of drug release from the implant formulations.

**Stability studies:** To assess the physical and chemical stability of the in situ implants, stability studies were conducted for 1 month under different storage conditions mentioned in ICH guidelines. The samples containing optimized formulation (F4) were packed wrapped in aluminium foil inside screw capped glass vials and stored at 5±3°C, 25±2°C/60±5% RH and 40±2°C/75±5% RH. After 30 days the formulation was checked for physical appearance and drug content.

**In vivo drug release studies:** In vivo animal studies were done in accordance with CPCSEA Guidelines after due approval by Sri Venkateshwara Institutional ethical committee (Protocol no. SVCP/IAEC/2011/14). Drug release from in situ forming implants was examined in 12 week old male rats. The animals were divided into two groups. One group of rats was administered with 50 μL of the injectable implant containing 20%PCL solution. Other group of rats was administered with 1 mL of oral suspension of marketed tablet (ZOCOR 10mg). Blood samples were collected at predetermined time intervals at the end of 1, 7 and 15 days. The blood samples were centrifuged immediately after collection and the resultant plasma was stored at -20°C for analysis. The drug content was analysed using High Performance Liquid Chromatography (HPLC).

**Chromatographic system and conditions:** HPLC (Shimadzu Co. Kyoto, Japan) equipped with LC-10 AT solvent delivery unit, SPD-10 AVP UV-Spectrophotometric detector, Spinechrom software, Rheodyne injector of 25 μL capacity was used. The separation was performed on C18 analytical column (250×4.6 mm, i.d.,). The mobile phase consisted of a degassed mixture of acetonitrile and pH 4.6 phosphate buffer (65:35). The mobile phase was freshly prepared, sonicated and filtered before use and delivered at a flow rate of 1.5 mL min⁻¹. The column was maintained at ambient temperature (20°C) and the compounds eluted were recorded by the detector at 238 nm.

**Sample extraction procedure:** Heparinized blood samples from the animals were centrifuged and plasma was collected into eppendorf tubes. The samples were frozen at -20°C for storage and analysed within 7 days. At the time of analysis Plasma (1.0 mL) was mixed with 50 μL of a mixture of acetonitrile-water (60:40 v/v) in a 3 mL centrifuge tube. Separation of the phase from precipitate was achieved by centrifugation at 1500 g for 3 min. The supernatant was transferred to another centrifuge tube. Fresh acetonitrile (400 μL) was then added to the first tube and the same
extraction procedure was repeated twice. The supernatants thus collected from the extractions of
the same sample were pooled. This fraction was finally centrifuged and evaporated to dryness
under vacuum. The samples were filtered through a Millipore filter (0.45 μm) and then
reconstituted with (200 μL) acetonitrile-water (25:75, v/v). Aliquots of each sample (20 μL) were
analyzed using HPLC (Carlucci et al., 1992).

RESULTS AND DISCUSSIONS

Formulation and optimization: Formulations were prepared using different concentrations of
degree PCL and two different ratios (2:1 ACN:DCM and 1:2 ACN:DCM) of solvent. Formulations
before injection into buffer are clear and transparent as shown in Fig. 1a. Upon injection of the
polymer solutions into the phosphate buffer medium, the polymer solidified as the solvent dissipated
into the aqueous medium and formed implants (Kranz et al., 2008). The scanning electron
microscopy (Fig. 7) revealed hard rod shaped structures. Based on the results, Acetonitrile and
dichloromethane in the ratio of 2:1 was selected as a solvent system as it showed faster implant
formation within 20 sec when injected into the aqueous buffer.

In situ implants containing polymer PLGA were prepared in two different concentrations of 30
and 40% in the solvent ratio 2:1 DMSC:DCM. The in situ implants using PLGA polymer formed
within 20 sec when the solution was injected into the aqueous phase. The formed solid implants
were soft and slightly porous in nature as shown in Fig. 1d. This ratio was found to be best suitable
for quick implant formation.

Fig. 1(a-d): Formation of implant using different polymers and solvent ratios. (a) PCL and PLGA
formulations before injection into aqueous buffer; (b) PCL-SVS implant with solvent
ratio ACN:DCM in ratio 2:1 after injection into buffer; (c) PCL implant containing
solvent ratio DCM:ACN in ratio 2:1 after injection into buffer and (d) PLGA implant
formed after injected into buffer
Table 1: Formulations of SVS in situ implants using two different polymers

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
<th>F6</th>
<th>F7</th>
<th>F8</th>
<th>F9</th>
<th>F10</th>
<th>F11</th>
<th>F12</th>
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<tbody>
<tr>
<td>Simvastatin (g)</td>
<td>0.075</td>
<td>0.075</td>
<td>0.075</td>
<td>0.075</td>
<td>0.075</td>
<td>0.075</td>
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<td>0.075</td>
<td>0.075</td>
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<td>0.075</td>
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<tr>
<td>PCL (%)</td>
<td>5</td>
<td>10</td>
<td>15</td>
<td>20</td>
<td>30</td>
<td>35</td>
<td>40</td>
<td>30</td>
<td>35</td>
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<td>-</td>
<td>-</td>
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<tr>
<td>PLGA (%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>30</td>
<td>40</td>
</tr>
<tr>
<td>ACN (mL)</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0.5</td>
<td>0.5</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>DMSO (mL)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>DCM (mL)</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>1</td>
<td>1</td>
<td>0.5</td>
<td>0.5</td>
<td>-</td>
</tr>
</tbody>
</table>

Fig. 2: Drug entrapment efficiency of different formulations

**Effect of solvents:** When water miscible solvent acetonitrile is used in higher concentration, soft rod-shaped solid implant formed within seconds as the solvent dissipated into the aqueous phase as shown in Fig. 1b. Formulations F1 to F7 were prepared by using the same solvent system.

When the water immiscible dichloromethane was used in higher amounts, solid implant was formed after 2-3 h depending on the concentration of the polymer. The implant formed was porous and patch-like solid as shown in Fig. 1c. Formulations F8 to F10 were prepared using this solvent system. Different formulations using different polymers and solvents are shown in Table 1.

**Evaluation of in situ implants:** The prepared in situ implants were evaluated for various parameters such as drug entrapment, in vitro drug release and in vivo drug release.

**Drug entrapment efficiency:** The entrapment efficiency of various formulations was studied. Drug loading percentage in the range of 70-80% was observed for F4, F5, F6 and F7. With increase in the drug to polymer ratio, the percentage drug encapsulated was also found to increase as seen in the Fig. 2. In case of F1, F2, F3 formulations, as the polymer concentration is less, only 50-60% of drug was found to be entrapped.

In F7 as the polymer concentration is higher, 83% drug entrapment was observed. In the case of F8, F9, F10 which were prepared using more proportion of DCM (ACN:DCM 1:2) the drug entrapment was found to be lower i.e; 55-65% owing to the leakage of drug into the organic phase.

The entrapment efficiency of PLGA formulations was studied. From the results it can be seen that drug loading percentage of F11 and F12 formulations was in the range of 75-79%. By increasing the drug to polymer ratio percentage of drug encapsulated also increased.

**In vitro drug release studies of in situ implants:** In vitro diffusion studies were performed using dialysis membrane with 7.4 pH phosphate buffer. Comparison of in vitro release studies of various formulations are shown in Fig. 3 and 4. As the polymer concentration is decreased, more
Fig. 3: Comparative dissolution profile of F1-F7 prepared with PCL and solvent (2:1 ACN:DCM)

Fig. 4: Comparative dissolution profiles of F8-F10 prepared with PCL and solvent (1:2 ACN:DCM)

burst release is seen. Formulation with 20% polymer concentration (F4) showed a sustained release of drug for 15 days and it has shown 25% of drug release at 72 h equals the therapeutic dose for 3 days. On the 15th day, 71% of drug release was achieved indicating that more sustained drug levels are possible in a period of one month. The graph representing the sustained release of F4 is shown in Fig. 5.

More prominent burst release was observed in case of F1, F2, F3 formulations. Although, F5, F6 and F7 formulations showed sustained action with less burst release, they could not reach therapeutic drug levels as shown in Fig. 3. This could be due to the fact that increased polymer concentration retarded the drug release. The formulations prepared using DCM in more amounts (F8, F9 and F10) showed clear burst effect and lesser drug release as shown in the Fig. 4. From the above results, F4 was found to be the most suitable formulation and hence was optimized for the conduct of further studies.
Fig. 5: Drug release of the optimized F4 in situ implant

Fig. 6: Comparison of dissolution profiles of PLGA formulations F1 and FII

In the case of formulations prepared using PLGA (F11 and F12), as the polymer concentration is decreased more burst release was observed. F12 showed more sustained release (11% at 72 h) when compared to the F11 (15% at 72 h) and could not reach therapeutic levels of drug as shown in Fig. 6.

**Prediction of drug release mechanism:** The optimized formulation was fitted into different drug release plots. The formulation showed first order drug release pattern and Pickian diffusion.

**Stability studies:** The stability studies of PCL - SVS in situ implant (F4) at different temperatures as per ICH guidelines like 5±3°C, 25±2°C/60±5%RH, 40±2°C/75±5%RH was studied for 30 days. The physical appearance of the formulation was clear and transparent and it was observed that there was no colour change indicating physical stability. The drug content was analyzed and the data is presented in Table 2. From the data, it is observed that there was negligible change in the drug content indicating chemical stability.

**Characterization of in situ implants**
**Surface morphology by scanning electron microscopy (SEM):** SEM analysis was performed to understand the surface Morphology of the implant. The cross linking and the rod shaped structures are clearly seen as shown in Fig. 7.
### Table 2: Interpretation of stability studies

<table>
<thead>
<tr>
<th>Temperature</th>
<th>Interval</th>
<th>Physical appearance</th>
<th>Drug content after 30 days (%)</th>
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<tbody>
<tr>
<td>5±3°C</td>
<td>0 days</td>
<td>Clear</td>
<td>75</td>
</tr>
<tr>
<td></td>
<td>7 days</td>
<td>Clear</td>
<td></td>
</tr>
<tr>
<td></td>
<td>15 days</td>
<td>Clear</td>
<td></td>
</tr>
<tr>
<td></td>
<td>30 days</td>
<td>Clear</td>
<td></td>
</tr>
<tr>
<td>25±2°C/60±5% RH</td>
<td>0 days</td>
<td>Clear</td>
<td>70</td>
</tr>
<tr>
<td></td>
<td>7 days</td>
<td>Clear</td>
<td></td>
</tr>
<tr>
<td></td>
<td>15 days</td>
<td>Clear</td>
<td></td>
</tr>
<tr>
<td></td>
<td>30 days</td>
<td>Clear</td>
<td></td>
</tr>
<tr>
<td>40±2°C/75±5% RH</td>
<td>0 days</td>
<td>Clear</td>
<td>79</td>
</tr>
<tr>
<td></td>
<td>7 days</td>
<td>Clear</td>
<td></td>
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<tr>
<td></td>
<td>15 days</td>
<td>Clear</td>
<td></td>
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<tr>
<td></td>
<td>30 days</td>
<td>Clear</td>
<td></td>
</tr>
</tbody>
</table>

Fig. 7: SEM photograph of PCL in situ implant

**Drug interaction studies by FTIR:** FTIR spectra of pure drug and drug loaded PCL in situ implants F4 were studied to understand any possible interactions. It was observed that the main functional group peaks are in the range of reported values in both the pure drug and the formulation indicating no drug-polymer interactions. The main functional groups in the drug are OH group and C = O group. The reported frequencies are 3200-3650 cm⁻¹ and 1700-1725 cm⁻¹. The observed values for OH group are 3550 cm⁻¹ (drug) and 3518 cm⁻¹ (implant). The observed values for C = O group are 1724 cm⁻¹ (drug) and 1712 cm⁻¹ (implant) as shown in Fig. 8 and 9.

**In vivo pharmacokinetic studies:** The drug release kinetics in rats was investigated for a period of 15 days and the drug content data of the test and the control are shown in the Table 3 and 4. Sustained release of drug for 15 days was observed and Cₘₐₓ was achieved on the 15th day. When compared to control, test formulation has shown 3 fold increase in the bioavailability. On the 15th day, the drug concentration of test and control were found to be 37.30±25.13 µg mL⁻¹ and 1.02±0.58 µg mL⁻¹, respectively indicating there is clear sustained release of the drug from the implant. The chromatograms indicating the peaks of test and control with retention time 15 min are shown in Fig. 10 and 11.
Fig. 8: FTIR spectrum showing drug functional groups-Simvastatin

Fig. 9: FTIR spectra of Simvastatin in situ implant

Fig. 10: Chromatogram showing the test peaks of simvastatin
Table 3: Data for in vivo drug release of test containing injectable implant

<table>
<thead>
<tr>
<th>Time (days)</th>
<th>Concentration (µg mL⁻¹)</th>
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<tr>
<td>1</td>
<td>3.04±1.18</td>
</tr>
<tr>
<td>7</td>
<td>5.73±2.81</td>
</tr>
<tr>
<td>15</td>
<td>37.30±25.13</td>
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</table>

Table 4: Data for in vivo drug release of control containing marketed formulation

<table>
<thead>
<tr>
<th>Time (days)</th>
<th>Concentration (µg mL⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>11.95±1.93</td>
</tr>
<tr>
<td>7</td>
<td>2.35±0.590</td>
</tr>
<tr>
<td>15</td>
<td>1.02±0.580</td>
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Fig. 11: Chromatogram showing control peaks of Simvastatin

**DISCUSSION**

Simvastatin is a lipid lowering drug known for anti-hyperlipidemic activity. It is commercially available as tablet dosage form. The objective of the work was to formulate injectable in situ implant of the drug with two different polymers to sustain drug release for at least 16 days.

The injectable in situ implants of Simvastatin were prepared using polymers PCL and PLGA using different solvent ratios like ACN:DCM in the ratio 2:1 and DCM:ACN in the ratio 2:1 for PCL formulation and DMSO:DCM in the ratio of 2:1 for PLGA formulation. All the formulations were tested for drug content, SEM, in vitro drug release, stability, effect of solvents, in vivo drug release. Injectable in situ implants with 15 days release of drug (through dialysis membrane) could be successfully formulated in PCL 20% with ACN:DCM in the ratio 2:1. So, it is selected as optimized formulation of injectable in situ implants.

The drug content of the implants was checked and it was observed that with increase in the drug to polymer ratio, the percentage drug encapsulated was also found to increase and less burst effect was seen. With decrease in the polymer ratio, the percentage of drug encapsulated was found to decrease and more burst effect was observed.
In situ implants were prepared using two different ratios of solvents. It was observed that the implants prepared with polymer PCL and the solvent ratio ACN:DCM in the ratio of 2:1 formed in 20 sec when the polymer solution was injected into the buffer solution and the implants formed were soft. The implants with polymer PCL and the solvent ratio DCM:ACN in the ratio of 2:1 has taken 4 h to form the implant and the texture of the implant is brittle and porous.

The prepared injectable in situ implant possessed satisfactory physicochemical characteristics. In vitro release studies were conducted and the optimized formulations followed first order kinetics and Fickian transport mechanism. The surface morphology of the implant carried out by SEM showed crosslinking and rod shaped structures as against porous implants resulted in previous studies (Kranz and Bodmeier, 2008). The drug excipient interactions analysis proved that there is no chemical interaction between the drug and the polymers.

The drug release from all the implants was found to follow diffusion-controlled mechanism. Dialysis membrane was used as the diffusion barrier for the drug-release studies. From the results it was observed that Simvastatin in situ implant using 20% PCL concentration showed higher drug release than the formulations using other polymers. The drug release was found to have sustained up to 15 days as compared to PLGA-Secnidazole implants prepared in previous studies with 97% drug release within 24 h and 92% drug release in case of PLGA-doxycycline implants with in 24 h (Gad et al., 2008). Some extended release studies showed a 9% drug release after 8 days from Poly (sebacic-co-ricinoleic-ester-anhydride)-gentamicin implants (Krasko et al., 2007).

Stability studies were performed and the results showed that the formulation is stable at different temperatures. It was observed that there is no physical change in the formulation. In vivo studies were performed on Wistar rats using 2 groups (n = 6) as a test and control. Studies showed that injectable in situ implant containing PCL 20% was able to provide sustained release of drug for 15 days. When compared to marketed formulation (Zocor® 10mg) which showed a release up to 3 h, the drug release of the test formulation was found to have sustained up to 15 days. Bioavailability of Simvastatin was found to improve by 3-fold when compared to control. Maximum amount of drug (37.3 μg mL⁻¹) was released from the implant on 15th day. This indicated sustained action of drug when formulated as an implant. The in vivo studies performed in the previous studies showed Cmax of 5.57 mg mL⁻¹ for the Bupivacaine Hydrochloride in situ implant containing PLGA and reached after 1 h (Kranz et al., 2008). In another study there was continuous release seen up to 28 days with initial release up to 29% in case of thymosin alphas1 in situ implants (Liu et al., 2010).

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 atleast for 15 days. The in vitro release studies suggest that release rate was related to drug:polymer ratio. There are no Drug-Excipient interactions and formulation is stable for 30 days. Pharmacokinetic studies suggest that formulation has sustained the release for 15 days and there is 3 fold increase in bioavailability. From all the optimized parameters, we can conclude that injectable in situ implants can be successfully administered for the chronic disease conditions which need a long term therapy with less therapeutic dose.
REFERENCES


