ABSTRACT

Chronopharmaceutical delivery system of simvastatin was prepared by dip coating method using different concentration of pH sensitive polymers along with hydrophilic diluents (microcrystalline cellulose). The optimized formulation containing 30mg of drug, 100mg of microcrystalline cellulose and different ratio of coating polymer Eudrajit S 100, L 100 and ethylcellulose. The optimized formulation were found to release the drug after a predetermined lag time of 6 hr, at the end of 10 hr it shows 96.2% of drug release. The physicochemical property and post compressed studies were satisfactory. The in-vitro release of core tablet were evaluated by visual method, The in-vitro comparative study with marketed products shows satisfactory result at the end of 10th hr. Acid uptake, Rupture test, Swelling test were performed in pH 1.2 and pH 7.4 and there was only negligible percentage of drug release in pH 1.2. SEM and stability were performed and its shows satisfactory result. Compared to conventional dosage form pulsatile drug delivery shows negligible side effects and may release drug according to pathological condition of the disease.

KEYWORD: MCC, SSG, Dip coated method.

1. INTRODUCTION

Oral controlled drug delivery systems represent the most popular form of controlled drug delivery systems for the obvious advantages of oral route of drug administration. Such systems release the drug with constant or variable release rates. The oral controlled release system shows a typical pattern of drug release in which the drug concentration is maintained in the therapeutic window for a prolonged period of time (sustained release), thereby ensuring sustained therapeutic action.[1] However, there are certain conditions for which such a release pattern is not suitable. These conditions demand release of drug after a lag time. In other
words, it is required that the drug should not be released at all during the initial phase of dosage form administration. Such a release pattern is known as pulsatile release.[2] There are many conditions that demand pulsatile release like, 1) Body functions that follow circadian rhythm. e.g. Secretion of hormones, acid secretion in stomach and gastric emptying. 2) The lag time is essential for the drugs that undergo degradation in gastric acidic medium (e.g: peptide drugs) and irritate the gastric mucosa or induce nausea and vomiting. 3) The drugs that undergo first-pass metabolism resulting in reduced bioavailability, altered steady state levels of drug and metabolite and potential food drug interactions require delayed release of the drug to the extent possible.[3] Pulsatile systems are basically time-controlled drug delivery systems in which the system controls the lag time independently of environmental factors like pH, enzymes, gastro-intestinal motility etc. The multiple unit systems like pellets or Mini tablets are preferred for drug dosage forms because the coating of the medicated units can be formulated to trigger the release in order to comply with the release profile of a pulsatile design.[4,5] Simvastatin, a hydroxymethylglutaryl-CoA (HMG-CoA) reductase inhibitor (statin) is an antihyperlipidemic agent. Simvastatin lowers the lipid level in blood and thereby prevent cardiovascular disease.[6] It is used in treatment of hypercholesterolemia, as it reduces levels of low-density lipoproteins and triglycerides, and raises high-density lipoprotein levels. Simvastatin is a BCS class-II drug. It is very sensitive to oxidization and having very short half-life of about 2 to 3 hrs.

MATERIALS
Simvastatin and ethyl cellulose was procured as gift sample from Fourrtsindia pvt limited, Chennai. Eudragit L 100 and RS 100 was procured as a gift sample from Madras pharmaceuticals, Chennai. Isopropyl alcohol and Di butyl phthalate purchased from chandan and co chemical.

2. METHODS
2.1 Formulation of core tablets by direct compression[7]
Tablets of simvastatin were made by direct compression method. All ingredients were weighed accurately and blended homogeneously for 15 minutes by trituration using glass mortar and pestle. Microcrystalline cellulose was used as direct compressing agent. Sodium starch glycylate were used as disintegrating agents. Magnesium stearate and Talc were used as lubricants. Tablets were compressed in Minipress Tablet Compression Machine using 6 mm round concave punches.

Table 1: Composition of core tablet.
2.2 Coating of the core tablet by Dip coating method

In this method selected polymers dissolve in organic solvent iso propyl alcohol, at a concentration of 10% w/v. Core tablet were coated by dipping the core tablet in the coating solution.\textsuperscript{[8]} Coating procedure repeated until total weight of 300mg is attained.

Table 2: Polymer ratio (coating).

<table>
<thead>
<tr>
<th>Polymer</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
<th>F6</th>
<th>F7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethyl cellulose</td>
<td>3%</td>
<td>3%</td>
<td>3%</td>
<td>3%</td>
<td>3%</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>Eudragit L 100</td>
<td>3%</td>
<td>4.5%</td>
<td>3%</td>
<td>1.5%</td>
<td>1.5%</td>
<td>-</td>
<td>1.5%</td>
</tr>
<tr>
<td>Eudragit S 100</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>3%</td>
<td>4.5%</td>
</tr>
<tr>
<td>Di butyl phthalate</td>
<td>1%</td>
<td>1%</td>
<td>1%</td>
<td>1%</td>
<td>1%</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>Iso propyl alcohol</td>
<td>200ml</td>
<td>200ml</td>
<td>200ml</td>
<td>200ml</td>
<td>200ml</td>
<td>200ml</td>
<td>200ml</td>
</tr>
</tbody>
</table>

3. EVALUATION

3.1 Saturation Solubility Studies

Plain simvastatin in excess quantity were placed in glass-stoppered flasks containing 10 ml of suitable buffer respectively. The samples were placed in a mechanical shaker at 37°C and 100 rpm until equilibrium was achieved (24 h).\textsuperscript{[9]} The aliquots were filtered through filter paper. The filtrates were diluted appropriately in distilled water and assayed spectrophotometrically at 238 nm. The result was shown in Figure no. 1.

![Fig 1: solubility studies of simvastatin](image)

3.2 Drug-excipient compatibility studies
The compatibility between drug and polymers was evaluated using Infrared spectroscopy (IR). The samples of physical mixture were heated at 55°C for three weeks to obtain more reliable conclusions. The result was shown in Figure no. 2, 3 and 4.

Fig 2: FTIR for pure drug.

Fig 3: FTIR For drug, EC, Eudragit S 100.

Fig 4: FTIR for drug, EC, Eudragit L-10

3.3 Pre-compression parameters
Pre-compression parameters like Bulk Density, tapped density, Compressibility Index, Hausner’s Ratio and Angle of Repose were performed for all the formulations (blend) and the values was found to be within the limits.[11]

3.4 Post compression studies
The post compression parameters like friability, weight variation, hardness and thickness were performed For all formulations and the values was shows in table no.3.

Table 3: Post compression parameters.

<table>
<thead>
<tr>
<th>Formulation Code</th>
<th>Thickness (mm)</th>
<th>Hardness (Kg/cm²)</th>
<th>Weight Variation (mg)</th>
<th>Friability (%)</th>
<th>Drug content (%)</th>
<th>Disintegration Time (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DF1</td>
<td>4.32±0.2</td>
<td>5.06±0.2</td>
<td>0.301±0.1</td>
<td>0.58±0.2</td>
<td>98.2</td>
<td>11.8±0.02</td>
</tr>
<tr>
<td>DF2</td>
<td>4.36±0.11</td>
<td>5.72±0.02</td>
<td>0.298±0.1</td>
<td>0.61±0.3</td>
<td>100.2</td>
<td>20.1±0.01</td>
</tr>
<tr>
<td>DF3</td>
<td>4.33±0.2</td>
<td>5.82±0.6</td>
<td>0.299±0.4</td>
<td>0.84±0.01</td>
<td>99.6</td>
<td>21.4±0.16</td>
</tr>
<tr>
<td>DF4</td>
<td>4.30±0.4</td>
<td>5.61±0.03</td>
<td>0.298±0.2</td>
<td>0.68±0.3</td>
<td>99.9</td>
<td>19.06±0.08</td>
</tr>
<tr>
<td>DF5</td>
<td>4.29±0.1</td>
<td>5.70±0.1</td>
<td>0.300±0.1</td>
<td>0.62±0.1</td>
<td>100.2</td>
<td>12.09±0.10</td>
</tr>
<tr>
<td>DF6</td>
<td>4.28±0.02</td>
<td>5.48±0.05</td>
<td>0.302±0.09</td>
<td>0.66±0.2</td>
<td>99.6</td>
<td>21.28±0.19</td>
</tr>
<tr>
<td>DF7</td>
<td>4.31±0.1</td>
<td>5.85±0.08</td>
<td>0.299±0.05</td>
<td>0.81±0.2</td>
<td>100.4</td>
<td>26.09±0.02</td>
</tr>
</tbody>
</table>

3.5 Disintegration test for simvastatin coated tablet
Disintegration test on coated tablet of simvastatin was performed by using phosphate buffer pH.7.4. The result were shown in table no 3.

3.6 Drug content
Randomly 10 tablets were weighed and powered. The power equivalent to 100mg was weighed accurately and transferred to 100ml of volumetric flask then dissolved with 5ml of methanol then the flask is sonicated for 5 min. The Volume then made up to 100ml with phosphate buffer pH 7.4. Above solution were filtered through wahtman paper and absorbance were measured at 238nm.[12] The results were shown in table no 3.

3.7 In-vitro dissolution studies of core tablet
The in vitro release pattern of core tablets was studied as visually by taking images of the core tablets in a petri dish containing dissolution medium (Phosphate buffer pH7.4) at the specific time intervals of 10 min up to 1hr.[13] The result was shown in Figure no.6.
3.8 In-vitro dissolution studies of coated tablet

Dissolution testing of coated tablet of simvastatin was performed by using pH 1.2, 6.8 and 7.4 phosphate buffers for 10 hrs, 2hrs in pH 1.2 (HCL) followed by 3hrs in 6.8 pH and 5 hrs in 7.4 pH. The Dissolution study was carried out at 37°C and 50 rpm by using USP type II apparatus.\(^{14}\) 1ml sample of were removed from dissolution medium at every 1 hr and diluted to 10ml with respective pH buffer. and its absorbance was checked by using UV spectroscopy at 238nm. The results were shown in figure no7. The kinetic studies were performed and the result was shown in table no.4.
3.9 IN-VITRO COMPARATIVE STUDY

Dissolution studies for innovator-1 (SIMCOR), innovator-2 (ZOCOR IM) and F7 formulation

The dissolution study (F-7, SIMCOR, ZOCOR) was carried out for 10 hours using USP paddle type 2 dissolution apparatus in 0.1N HCL (pH 1.2) was placed in dissolution flask and allowed to obtain temperature at 37±0.5°C and 50 rpm for first 2 hr followed by 3 hr in 6.8 pH and 7.4 pH phosphate buffer. A 1ml samples were collected from each vessel at every 1hr up to 10 hr for ZOCOR sample were collected at 15mins interval and diluted to 10ml with respective pH medium. The absorbance was measured by using UV spectroscopy at 238nm. The results were shown in Figure no.8.
3.10 Acid uptake studies
Tablet was weighed and placed in the disintegration tubes. The disintegration basket was filled with 0.1N HCl and the test was performed up to 2 hrs. The tablets were removed from the disintegration basket then dehydrated with tissue paper and take weight again. The percentage of weight gain was reported as percentage acid uptake\(^{[17]}\) the result were shown in figure no.9.

\[
FA= \frac{(TF-TI)}{TI} \times 100
\]

Where; \(FA\) = percentage of acid uptake, \(TF\) = final weight of the coated tablet, \(TI\) = initial weight of the coated tablet.

![Fig 9: acid uptake studies.](image)

3.11 Rupture test
The Rupture test on coated tablets was carried out using USP paddle 2 apparatus. Here all other Parameters were same as In-Vitro Dissolution Method. The rupture time was carried out in pH- 1.2, 6.8 and 7.4. This was determined by Rupture test. The result was shown in figure no.10.

![Fig 10: rupture test for optimized formulation DF7 in different pH](image)

a) Initial (0 hr)  b) 3.55 hr  c) 6.40 hr

a) pH 1.2 b) pH 6.8  c) pH 7.4.
3.12 Swelling studies

The percentage swelling capacity of tablets was determined in the containers with 10 ml of pH 1.2 and pH 7.4 phosphate buffers. Tablets were removed from containers at predetermined regular intervals, blotted with tissue paper, weighed and again placed in medium till the outer coating of tablet started to rupture.\textsuperscript{[18]} The % swelling was calculated using the formula. The result was shown in Figure no.11.

\[ \text{% swelling} = \frac{(W_t - W_o)}{W_o} \times 100 \]

Where, \( W_t \) is weight of wet tablet at time, \( W_o \) is weight of dry tablet.

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Initial</th>
<th>After 5hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>DF7 pH (1.2)</td>
<td><img src="image1.png" alt="Image" /></td>
<td><img src="image2.png" alt="Image" /></td>
</tr>
<tr>
<td>DF7 Ph(7.4)</td>
<td><img src="image3.png" alt="Image" /></td>
<td><img src="image4.png" alt="Image" /></td>
</tr>
</tbody>
</table>

Fig 11: swelling study of F7 formulation.

3.13 Surface morphology study

The external surface morphology was evaluated by using the SEM (Sem-jeol Jsm-840, nanotechnology lab, SRM University, katankulathur). The tablet were mounted directly on the SEM sample stub using the double sided sticking tape and coated with gold film (thickness 200 nm) under the pressure low vacuum. The voltage was used is 20KV and the width was 3.5mm. The result was shown in Figure no. 12.

Fig 12: Surface morphology of F7 formulation.
3.14 Accelerated stability studies
Accelerated stability studies were performed as per the ICH guidelines for a period of 3 months and evaluated for physical appearance, hardness and drug content. [18]

RESULT AND DISCUSSION
Physico-chemical parameters
Solubility studies and compatibility study were studied. The pure drug simvastatin show partial solubility in distilled water and shows highest amount of solubility in pH 7.4. There is no significant difference in the FTIR spectra of pure drug and physical mixture of drug and polymer, All major peaks of Simvastatin were observed at wavenumbers 3550.31 cm\(^{-1}\) (free O–H stretching vibrations); 2960 and 2877 cm\(^{-1}\) (C–H stretching vibrations); and 17047 cm\(^{-1}\) (stretching vibration of ester and lactone carbonyl functional groups); 1267, 1166 and 1064 cm\(^{-1}\)(C-O stretching of esters and anhydrides) were retained in physical mixtures with simvastatin, which clearly indicate that no interaction exists between pure drug and polymer.

The results were shown in Figure no. 1, 2, 3 and 4.

Pre-compression studies like bulk density, Hauser ratio, carrs index, tapped density, and angle of Repose was evaluated. The value of bulk density and tapped density was within a limit from 0.2-0.3gm/ml. The value of hausner ratio was found to be in the range of 1.034-1.094. The value of carrs index was found to be 5.62 to 10.2% and the angle of repose for all the formulations was found to be in the range of 24.23°-28.31° which ensure good flow property.

All the formulation F1-F7 was evaluated for post compression parameters such as weight variation, thickness, hardness, friability, drug content, disintegration, in-vitro dissolution, swelling studies, rupture studies, acid uptake studies etc. The weights of all the tablets were found to be uniform with low standard deviation values. The measured hardness of tablets for all the formulations was ranged between 5.06 to 5.85 kg/cm\(^2\). The % friability for all the formulations was found to be 0.48-0.71%. The values of drug content were found to be 98.22-100.4%. The values of disintegration were found to be 11.48-26.09 min. The results were shown in Table no.3.
IN VITRO RELEASE

CORE TABLET
All the seven formulation of prepared core tablet of simvastatin were subjected to in–vitro studies. These studies were carried out using a petri dish containing dissolution medium up to 1 hr. The result was shown Figure no. 6.

COATED TABLET
All the formulations (F1- F7) of prepared coated tablets of simvastatin were subjected to in-vitro release studies. The Formulations F1, F2 and F3 were formulated with different ratios of pH sensitive polymers (Ethyl cellulose, Eudragit L 100). Formulation DF4, F5 and F6 were formulated with different ratios of pH sensitive polymers (Ethyl cellulose, Eudragit S100). F7 were formulated with combination of Ethyl cellulose, Eudragit L 100, Eudragit S100.

Formulation F1to F7 was remaining intact in pH 1.2 for 2 hrs. Release of drug was negligible. Formulations F1, F2, F3 were found to be 91.6, 84.5 and 68.2% of drug release at the end of 6 to 8 hrs. For all three formulations lag time was found to be between 3to 4 hrs, it is in range of pH 6.8. This may be based on the solubility nature of the polymer and concentration of the polymer used in the formulation.

The drug release for the formulations F4, F5 was found to be 80.2, 77.4% at the end of 10 hrs. The lag time of these formulations was found to be between 5.5 – 6.5 hrs, as the concentration of polymer increasing the lag time also increases there by decrease in the drug release. Though the required lag time of 6 hr was obtained in F5 formulation but the drug release was low. So, to in order to increase the release of drug the formulation F6 was formulated with same ratio for formulation DF5 with increase in concentration of Micro crystalline cellulose. The drug release was found to be 89.7% at the end of 10 hrs.

For further increase of drug release formulation F7 was formulated with different ratio of (ethyl cellulose, eudragit L 100, eudragit S100) the combination of these polymer shows good sustaining efficacy compared to other formulation, the % of drug release was based on the chronopharmacological behavior of the disease, shows 96.2% of release at the end of 10 hr compared to other formulation. Which indicate the concentration of drug was more for the site of action compared to other formulation the result was shown in Figure no. 7.
Drug release data of formulation F7 was best explained by Higuchi equation, as the plot showed highest linearity ($r^2 = 0.9694$), followed by zero order equation ($r^2 = 0.9111$). As the drug release was best fitted in Higuchi kinetics, indicating that the rate of drug release is diffusion. The result was shown in Table no. 4.

Further the mechanism of drug release was found by Korsmeyer-Peppas equation, the diffusion exponent “n” was between 0.5-1.0, which appears to indicating the mechanism is non-Fickian diffusion. And indicates that the drug release was controlled by more than one process both diffusion and dissolution.

The comparative study was done for best formulation (F7) and marketed product SIMCOR, and ZOCOR. At the end of 10 hr study the formulation F7 shows 96.2% of drug release and The marketed product SIMCOR shows 78.9% of drug release at the end of 10hr and the marketed product ZOCOR shows 91.9% of drug release at the end of 60 min. the result was shown in figure no. 8.

**ACID UPTAKE STUDIES**

The optimized formulation of Simvastatin coated tablets (F7,) was studied for acid uptake studies. The formulation F7 shows acid uptake values in the range of 0.013% which are less than 5% indicating significant protection of drug from acidic environment, The results were shown in Figure no. 9.

**RUPTURE STUDIES**

The optimized formulation F7 are subjected to rupture test. The rupture time of optimized formulation F7 was found to be in a range between 5.5 to 6.40 hr. it ensures there was no rupture in 1.2 pH. The result was shown in a Figure no 10.

**SWELLING STUDIES**

formulations F7 of prepared coated tablets of simvastatin were subjected to swelling studies. The swelling studies of pulsatile tablet during 5 hrs studies were found to have very good sustaining efficacy. The percentage swelling at the end of 5th hour of formulation F7 was found to be less in pH 1.2 compared to pH 7.4. The results were shown in Figure no.11.

**SURFACE MORPHOLOGY**

The surface morphology of an optimized formulation F7 shows uniform swelling of the polymer in pH 7.4. The results were shown in Figure no. 12.
STABILITY
Stability studies were carried out of the most satisfactory formulation F-7 at 40 ± 2°C / 75 ± 5% RH for three months as per ICH guidelines. There was no major changes in the various evaluation parameters at the end of 3 months.

CONCLUSION
HMG-CoA reductase inhibitors, statins, reduce cholesterol levels, increased expression of LDL receptors and decrease triacylglycerol (TAG) rich lipoproteins. Chronotherapy with HMG-CoA reductase inhibitors have suggested that evening dosing could be more effective than morning dosing. Chronotherapeutic treatment with immediate-release dosage forms may be unfeasible if the symptoms of the disease are pronounced during the night or early morning. Therefore, therapy with modified-release dosage forms with controlled higher drug plasma levels during the time of diseases attack or incidence could be more effective treatment than with immediate release dosage forms. Pulsatile drug delivery systems are designed to release drug as a pulse manner after a pre-determined lag time. To increase the drug release at the site of action of a disease according to circadian rhyme, at right time, right amount. Two novel coating techniques are used. This novel techniques increase the lag time and shows burst release according to the need of the pathophysiology of the disease compared to conventional tablets, thereby increase the bioavailability.

REFERENCE