“PREPARATION AND EVALUATION OF SUSTAINED RELEASE MATRIX TABLETS USING SPHERICALLY CRYSTALLINE FLUVASTATIN SODIUM”

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ABSTRACT
To prepare and evaluate sustained release matrix tablets of spherically crystalline fluvastatin sodium to enhance micromeritics of fluvastatin sodium by CRYSTALLO-CO-AGGLOMERATION (CCA) technique along with using HYD ROXYPROPYL METHYL CELLULOSE (HPMC) and xanthan gum as rate retarding polymer. To prepare directly compressible matrix tablets of fluvastatin sodium spherical agglomerates. The prepared spherical agglomerates were evaluated in terms of %yeild, drug content, dissolution studies, Differential scanning calorimetry (DSC), Fourier transform infrared spectroscopy (FTIR), X-ray diffraction (XRD) studies, Scanning electron microscopy (SEM). The prepared Optimized fluvastatin sodium spherical agglomerates tablets were evaluated for weight variation, Hardness, thickness, Friability, Drug content, dissolution study, swelling index, kinetic modeling and stability etc.
The FTIR and DSC indicate drug poymr compactibility. The XRD revealed a characteristic decrease in crystallinity. SEM study showed that the crystal possess a good spherical shape with regular surface. The evaluation of spherical agglomerates prepared tablets even after stability showed no significant change in tablet properties and sustain release tablets prepared
by spherical agglomerates showed effective sustain release over period of time. On the basis of these evaluation parameters it was concluded that optimized Sustain release matrix tablets made by spherically crystalline fluvastatin sodium in which F7 sustained drug release for 12 hrs and release 99.26% of drug.

**KEYWORD:** Spherical crystallization, % yeild, DSC, XRD, SEM, bulk density, tapered density, bulkiness, angle of repose, Hausner's ratio, etc.

**INTRODUCTION**

As these are the types of controlled drug delivery system, which release the drug in uninterrupted manner by mainly two different ways both dissolution controlled as well as diffusion controlled mechanisms. To control the release profile of the drugs, which are having different solubility properties, the drug is dispersed in swellable hydrophilic substances, an insoluble matrix of rigid non swellable hydrophobic materials or plastic materials.1-2 One of the least complicated approaches to the manufacture of sustained release dosage forms involves the direct compression of blend of drug, retardant material and additives to formulate a tablet in which the drug is embedded in a matrix of the retardant. Alternatively drug and retardant blend may be granulated prior to compression. The materials most widely used in preparing matrix systems include both hydrophilic and hydrophobic polymers. Commonly available hydrophilic polymers include Hydroxypropyl methylcellulose (HPMC), Hydroxypropyl cellulose (HPC), Hydroxyethyl cellulose (HEC), Xanthan gum, Sodium alginate, Poly (ethylene oxide) and cross-linked homopolymers and copolymers of Acrylic acid. It is usually supplied in micronized forms because small particle size is critical to the rapid formation of gelatinous layer on the tablet surface. 3-5 Introduction of matrix tablet as sustained release (SR) has given a new breakthrough for novel drug delivery system (NDDS) in the field of Pharmaceutical technology. It excludes complex production procedures such as coating and pelletization during manufacturing and drug release rate from the dosage form is controlled mainly by the type and proportion of polymer used in the preparations. Hydrophilic polymer matrix is widely used for formulating an SR dosage form.6-10 In terms of sustained release matrix systems are widely used for the purpose. A system which prolongs and controls the release of the drug that is dissolved or dispersed. In fact, a matrix is defined as a well-mixed composite of one or more drugs with gelling agent i.e. hydrophilic polymers. By the sustained release method therapeutically effective
concentration can be achieved in the systemic circulation over an extended period of time, thus achieving better compliance of patients.

**Figure 0.1: Materials used for matrix tablets.**

**Figure 0.2: Release from matrix tablets.**

**Spherical Crystallization**

Spherical crystallization is one of such particle design technique in which crystallization and agglomeration process are carried out at one fell swoop. Kawashima et al, in 1990, developed spherical crystallization technique.
“Spherical Crystallization process transforms the fine crystal obtain during crystallization into a spherical agglomerates by which crystallization and agglomeration can be carried out simultaneously in one step and which has been successfully utilized for improvement of flowability, compactability and bio-availability of crystalline drugs”.

Developing novel methods to increase the bioavailability of drugs that inherently have poor aqueous solubility is a great challenge to formulate solid dosage form. Mechanical micronization of crystalline drugs and incorporation of surfactants during the crystallization process are the techniques which are now-a-days commonly used to improve the bioavailability of poorly soluble drugs. “Addition of surfactant generally leads to less significant increase in aqueous solubility”. To overcome this problem Kawashima developed a spherical crystallization technique that led to improving the flow and direct compressibility of number of microcrystalline drugs.

**Factors controlling the process of agglomeration.**
1. Solubility profile.
2. Mode and intensity of agitation .
3. Temperature of the system .
4. Residence time.

**Spherical crystallization techniques.**
1. Wet spherical agglomeration method (WSA).
2. Quasi-Emulsion Solvent Diffusion method (QESD, Transient emulsion).
3. Ammonia diffusion system (ADS).
5. Neutralization technique (NT).

**METHOD**
Fluvastatin sodium agglomerates were prepared using a two solvent system comprising acetone: acetonitrile (good solvent, bridging liquid and bad solvent, respectively). In a vessel, hpmc k15m was dissolved in adequate amount of acetonitrile.Fluvastatin sodium was dissolved in acetone maintained at 50°C. The latter dispersal was added immediately to the dispersion containing dissolved polymer under constant stirring conditions (500,600,700rpm) respectively kept at 50°C temperature. The stirring was continued for 20 min, which were then filtered and dried overnight. Three batches were prepared by changing the concentration.
of hpmck15m (0.5, 1.0 and 1.5 % w/v). The formulation, 1.5% hpmck15m yields a maximum of 83±0.33 % and hence it was selected as basic polymer with same concentration for further formulations.

Preparation and evaluation of sustained release matrix tablets using spherically crystalline fluvastatin sodium by Crystallo-Co-Agglomerates method is a process, in which it transforms crystals directly in to a compact spherical form during the crystallization process and then prepared sustained release matrix tablet of fluvastatin sodium respectively.

**Evaluation of spherical agglomerates**
The prepared spherical agglomerates were evaluated in terms of %yield, drug content, dissolution studies, Differential scanning calorimetry (DSC), Fourier transform infrared spectroscopy (FTIR), X-ray diffraction (XRD) studies, Scanning electron microscopy (SEM). The prepared Optimized fluvastatin sodium spherical agglomerates tablets were evaluated for weight variation, hardness, thickness, Friability, Drug content, dissolution study, swelling index, kinetic modeling and stability etc.

**Differential Scanning Calorimetry (DSC)**
A differential scanning calorimeter DSC was used to monitor the thermal events during heating. Samples weighing 2-3 mg were placed in open aluminum pans and heated from 55 to 2500C at a rate of 100C per min. Nitrogen was used as a purge gas at a flux rate of 50 ml/min. The onsets of the melting points and enthalpies of fusion were recorded by the software.

**X-Ray Diffractometry**
X-ray diffraction (XRD) patterns of fluvastatin sodium agglomerates and pure drug fluvastatin sodium powder were collected in transmission using an X-ray diffractometer with a rotating anode (Philips, X-pert-MPD) with Cu Kα1 radiation (monochromator graphite) generated at 40 mA and 45 kV. Powder was packed into the rotating sample holder between two films (PETP).To check crystallinity at 2Ө.

**Scanning Electron Microscopy (Sem)**
Scanning electron micrographs of fluvastatin sodium agglomerates was taken using a scanning electron microscope (JEOL, JSM-5610LV). Samples was fixed on an aluminum
stub with conductive double-sided adhesive tape and coated with gold in an argon atmosphere (50 Pa) at 50mA for 50 sec.

**Swelling behavior study**

The extent of swelling was measured in terms of % weight gain by the tablet. One tablet from each formulation was kept in a petridish containing deareated water. At the end of 1h, the tablet was withdrawn, soaked with tissue paper, and weighed. Then for every 2 h, weights of the tablet were noted, and the process was continued till the end of 12h. Percentage weight gain by the tablet was calculated by formula:

\[ \% \text{ Swelling} = \left( \frac{M_t - M_o}{M_o} \right) \times 100 \]

Where, \(M_t\) = Weight of tablet at time ‘t’ and \(M_o\) = Weight of tablet at time 0.

**Particle Size Determination**

Particle size was determined using the optical microscopy. Optical microscopy was used to observe the crystal habit (size and shape) in this study. Optical microscopy was the simplest instrument to capture images of crystal habits, especially for wet samples or samples in solution. Optical microscopy (OM) can be divided into eyepiece, objective lens, object holder and stage.

**Determination of % Practical**

- The practical yield is calculated by using following equation 27:

\[ \% \text{ Practical yield} = \left( \frac{\text{Weight of prepared spherical agglomerates}}{\text{Theoretical weight}} \right) \times \frac{100}{100} \]

**Drug Content Analysis**

- For determination of drug content the spherical agglomerates of Fluvastatin sodium equivalent to 100 milligram of fluvastatin sodium were triturated and dissolved and dilute with water. Appropriately diluted samples were filtered through Whatman filter paper 41(pore size 25 μm) and drug content was determined spectrophotometrically at 304.2 nm using UV-Visible spectrophotometer.

**Weight variation**

Weight variation test was performed for twenty tablets from each batch and average values were calculated and then sum of individual weight was calculated. Then the difference is calculated to determine.
(W20- Wavg)/W20*100
Where W20 = Total weight of 20 tablet
Wavg = Avg weight of 20 tablet

**Friability test**
Friability test was performed using Roche friabilator. Ten tablets were weighed and placed in the friabilator, which was then operated for 25 revolutions per minute. After 100 revolutions the tablets were dusted and reweighed. The percentage friability was determined using formula:

\[
\% \text{ Friability} = \frac{W_0 - W_t}{W_0} \times 100
\]
Where \( W_0 \) and \( W_t \) are initial and final weight respectively, before and after hundred revolutions

**Drug content**
Ten tablets of each formulation were weighed and powdered. The quantity of powder equivalent to 100 mg of fluvastatin sodium was taken in a 100 ml volumetric flask and made up to the volume with deaerated water. The contents were agitated in a magnetic stirrer at 37oC for 24 hours. At the end of 24 hours content were analyzed spectrophotometrically at 304.2 nm after suitable dilutions.

**Thickness test**
Tablet thickness should be controlled within a ±5% variation of a standard value. Varnier calliper was used to determine the thickness of tablet.

**Hardness test**
The tablet's hardness was measured by Monsanto hardness tester. For measuring the hardness tablet to be tested was held between a fixed and a moving jaw of hardness test apparatus (Monsanto) and reading of the indicator is adjusted to zero. The screw knob was moved forward until the tablet broke and the force required for breaking the tablet was noted.

**Swelling behaviour of Tablets**
The extent of swelling was measured in terms of % weight gain by the tablet. The swelling behaviours of all controlled release formulations were studied. Initially one tablet from each formulation was kept in a petridish containing deaerated water. The tablet was removed, lightly blotted with tissue paper to remove excess buffer, and reweighed for every 1 h; the
weights of the tablet were noted. Percentage weight gain by the tablet was calculated by the following formula:

\[ S. \ I. = \left( \frac{W_t - W_0}{W_0} \right) \times 100, \]

Where S.I. is the swelling index, \( W_t \) the weight of tablet at time \( t \) (h), and \( W_0 \) the weight of tablet at zero time.

**In Vitro Drug Release Studies**

*In vitro* dissolution studies, prepared tablets were performed in triplicate in a USP XXIII six station dissolution test apparatus (Veego Model No.6 DR, India) at 100 rpm and at 37°C ± 1°C using 1000 ml of deaerated water as dissolution medium for 12 h. Aliquots of 5 ml were withdrawn at predetermined time intervals and replaced with an equivalent amount of fresh dissolution media maintained at the same temperature. The samples were filtered, diluted suitably and then analyzed by measuring the absorbance at 304.2 nm by UV spectrophotometer (Shimadzu UV-1800)

Table 1: Kinetic Studies

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Models</th>
<th>Equation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Zero Order</td>
<td>( Q_t = Q_0 + K_0 , t )</td>
</tr>
<tr>
<td>2</td>
<td>First Order</td>
<td>( \ln Q_t = \ln Q_0 + K_1 , t )</td>
</tr>
<tr>
<td>3</td>
<td>Higuchi</td>
<td>( Q_t = K_h , t^{1/2} )</td>
</tr>
<tr>
<td>4</td>
<td>Korsmeyer-Peppas</td>
<td>( \frac{M}{M_0} = K_t )</td>
</tr>
</tbody>
</table>

Table and graph

**Table 2: Preliminary Trials For Selection Of Stirring Speed.**

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>SS1</th>
<th>SS2</th>
<th>SS3</th>
<th>SS4</th>
<th>SS5</th>
<th>SS6</th>
<th>SS7</th>
<th>SS8</th>
<th>SS9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluvastatin sodium(gram)</td>
<td>1.8</td>
<td>1.8</td>
<td>1.8</td>
<td>1.8</td>
<td>1.8</td>
<td>1.8</td>
<td>1.8</td>
<td>1.8</td>
<td>1.8</td>
</tr>
<tr>
<td>HPMC K15M (%)</td>
<td>0.5%</td>
<td>1.0%</td>
<td>1.5%</td>
<td>0.5%</td>
<td>1.0%</td>
<td>1.5%</td>
<td>0.5%</td>
<td>1.0%</td>
<td>1.5%</td>
</tr>
<tr>
<td>Acetone(ml)</td>
<td>3</td>
<td>3</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>Acetonitrile(ml)</td>
<td>9</td>
<td>9</td>
<td>9</td>
<td>9</td>
<td>9</td>
<td>9</td>
<td>9</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>Stirring speed(RPM)</td>
<td>500</td>
<td>600</td>
<td>700</td>
<td>500</td>
<td>600</td>
<td>700</td>
<td>500</td>
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<td>700</td>
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</tbody>
</table>

**Table 3: Optimization Of Stirring Rate.**

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>SS1</th>
<th>SS2</th>
<th>SS3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluvastatin sodium</td>
<td>1.8</td>
<td>1.8</td>
<td>1.8</td>
</tr>
<tr>
<td>HPMC K15M (%)</td>
<td>0.5</td>
<td>1.0</td>
<td>1.5</td>
</tr>
<tr>
<td>Acetone(ml)</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Acetonitrile(ml)</td>
<td>9</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>Stirring speed(RPM)</td>
<td>600</td>
<td>600</td>
<td>600</td>
</tr>
</tbody>
</table>
Table 4: Particle size, percentage partial yield and drug content.

<table>
<thead>
<tr>
<th>Formulation Code</th>
<th>Particle size (μm) n=100</th>
<th>% Practical Yield</th>
<th>Drug Content (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SS1</td>
<td>150.42</td>
<td>80.55±0.55</td>
<td>97.96±0.05</td>
</tr>
<tr>
<td>SS2</td>
<td>149.56</td>
<td>83.33±0.33</td>
<td>98.69±0.02</td>
</tr>
<tr>
<td>SS3</td>
<td>158.78</td>
<td>82.77±0.73</td>
<td>98.22±0.04</td>
</tr>
</tbody>
</table>

Table 5: Flow properties of spherical agglomerates.

<table>
<thead>
<tr>
<th>Formulation Code</th>
<th>Angle of repose (θ)</th>
<th>Bulk density (g/cm³)</th>
<th>Tapped density (gm/cm³)</th>
<th>Carr’s index (%)</th>
<th>Hausner’s ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug</td>
<td>58.25±1.51</td>
<td>0.187±0.09</td>
<td>0.257±0.06</td>
<td>27.29±0.54</td>
<td>1.374±0.08</td>
</tr>
<tr>
<td>SS1</td>
<td>38.04±0.89</td>
<td>0.300±0.02</td>
<td>0.361±0.07</td>
<td>16.26±0.62</td>
<td>1.24±0.09</td>
</tr>
<tr>
<td>SS2</td>
<td>31.04±1.00</td>
<td>0.375±0.08</td>
<td>0.420±0.08</td>
<td>11.90±0.56</td>
<td>1.130±0.06</td>
</tr>
<tr>
<td>SS3</td>
<td>38.05±1.12</td>
<td>0.292±0.06</td>
<td>0.352±0.04</td>
<td>17.40±0.28</td>
<td>1.202±0.02</td>
</tr>
</tbody>
</table>

Figure 1

Figure 2(1)
Table 6: Formulation of Tablets (Preliminary Trials).

<table>
<thead>
<tr>
<th>Formulation Ingredients</th>
<th>MT1</th>
<th>MT2</th>
<th>MT3</th>
<th>MT4</th>
<th>MT5</th>
<th>MT6</th>
<th>MT7</th>
<th>MT8</th>
<th>MT9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluvastatin sodium agglomerates</td>
<td>40</td>
<td>40</td>
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<td>40</td>
<td>40</td>
<td>40</td>
<td>40</td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>Hpmc K15M</td>
<td>20</td>
<td>40</td>
<td>60</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>20</td>
<td>40</td>
<td>60</td>
</tr>
<tr>
<td>Xanthan gum</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>20</td>
<td>40</td>
<td>60</td>
<td>60</td>
<td>40</td>
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<tr>
<td>MCC</td>
<td>132</td>
<td>112</td>
<td>92</td>
<td>132</td>
<td>112</td>
<td>92</td>
<td>112</td>
<td>112</td>
<td>112</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
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<tr>
<td>Talc</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
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</table>
Table 7: Independent and dependent variable.

<table>
<thead>
<tr>
<th>Independent variable</th>
<th>Dependent variable</th>
</tr>
</thead>
<tbody>
<tr>
<td>X1 HPMC (Polymer)</td>
<td>Y1 Swelling Index (At 6 Hrs)</td>
</tr>
<tr>
<td>X2 Xanthan GUM(Polymer)</td>
<td>Y2 %Drug release</td>
</tr>
<tr>
<td></td>
<td>Y3 Swelling Index (At 12 Hrs)</td>
</tr>
</tbody>
</table>

Table 8: Levels of independent variables.

<table>
<thead>
<tr>
<th>Coded value</th>
<th>Actual value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>X1 HPMC(Polymer)</td>
</tr>
<tr>
<td>-1</td>
<td>20</td>
</tr>
<tr>
<td>0</td>
<td>40</td>
</tr>
<tr>
<td>+1</td>
<td>60</td>
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</table>

Table 9: Composition of the factorial design batches.

<table>
<thead>
<tr>
<th>Formulation ingredients</th>
<th>Formulation batch code</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>F1</td>
</tr>
<tr>
<td>Fluvastatin sodium agglomerates</td>
<td>40</td>
</tr>
<tr>
<td>HPMC K15M</td>
<td>20</td>
</tr>
<tr>
<td>Xanthan gum</td>
<td>20</td>
</tr>
<tr>
<td>MCC</td>
<td>112</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>4</td>
</tr>
<tr>
<td>Talc</td>
<td>4</td>
</tr>
</tbody>
</table>

Table 10: Pre-Compression Parameters for Optimization of polymers Concentration.

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Angle of repose ($^\circ$)</th>
<th>Bulk density (g/cm$^3$)</th>
<th>Tapped density (g/cm$^3$)</th>
<th>Carr's Index (%)</th>
<th>Hausner’s ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>MT1</td>
<td>24.21±0.11</td>
<td>0.459±0.005</td>
<td>0.532±0.009</td>
<td>13.72±0.17</td>
<td>1.222±0.02</td>
</tr>
<tr>
<td>MT2</td>
<td>23.62±0.23</td>
<td>0.468±0.003</td>
<td>0.554±0.004</td>
<td>15.52±0.19</td>
<td>1.179±0.07</td>
</tr>
<tr>
<td>MT3</td>
<td>24.67±0.21</td>
<td>0.479±0.004</td>
<td>0.648±0.007</td>
<td>12.59±0.16</td>
<td>1.193±0.08</td>
</tr>
<tr>
<td>MT4</td>
<td>26.84±0.16</td>
<td>0.429±0.006</td>
<td>0.505±0.005</td>
<td>13.18±0.11</td>
<td>1.186±0.05</td>
</tr>
<tr>
<td>MT5</td>
<td>22.19±0.16</td>
<td>0.441±0.006</td>
<td>0.408±0.006</td>
<td>12.93±0.25</td>
<td>1.152±0.06</td>
</tr>
<tr>
<td>MT6</td>
<td>23.39±0.15</td>
<td>0.452±0.002</td>
<td>0.526±0.001</td>
<td>14.06±0.12</td>
<td>1.176±0.05</td>
</tr>
<tr>
<td>MT7</td>
<td>44.42±0.21</td>
<td>0.472±0.004</td>
<td>0.606±0.007</td>
<td>22.11±0.16</td>
<td>1.283±0.08</td>
</tr>
<tr>
<td>MT8</td>
<td>31.32±0.16</td>
<td>0.400±0.006</td>
<td>0.469±0.006</td>
<td>14.71±0.25</td>
<td>1.172±0.06</td>
</tr>
<tr>
<td>MT9</td>
<td>23.81±0.08</td>
<td>0.423±0.004</td>
<td>0.468±0.005</td>
<td>9.81±0.11</td>
<td>1.153±0.06</td>
</tr>
</tbody>
</table>
### Table 11: Post-Compression Parameters for Optimization of polymers Concentration.

<table>
<thead>
<tr>
<th>Evaluation parameter</th>
<th>MT1</th>
<th>MT2</th>
<th>MT3</th>
<th>MT4</th>
<th>MT5</th>
<th>MT6</th>
<th>MT7</th>
<th>MT8</th>
<th>MT9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thickness (mm)</td>
<td>3.11±0.58</td>
<td>3.11±0.22</td>
<td>3.11±0.99</td>
<td>3.11±0.27</td>
<td>3.11±0.26</td>
<td>3.11±0.24</td>
<td>3.11±0.44</td>
<td>3.11±0.36</td>
<td>3.11±0.25</td>
</tr>
<tr>
<td>Hardness (kg/cm²)</td>
<td>5.3±0.10</td>
<td>5.2±0.04</td>
<td>5.8±0.65</td>
<td>5.9±0.58</td>
<td>5.4±0.18</td>
<td>5.7±0.55</td>
<td>5.5±0.36</td>
<td>5.5±0.11</td>
<td>5.4±0.14</td>
</tr>
<tr>
<td>Friability</td>
<td>0.19±0.25</td>
<td>0.16±0.22</td>
<td>0.15±0.33</td>
<td>0.29±0.33</td>
<td>0.14±0.36</td>
<td>0.09±0.16</td>
<td>0.21±0.06</td>
<td>0.14±0.23</td>
<td>0.11±0.09</td>
</tr>
<tr>
<td>% Weight variation (mg)</td>
<td>202±1.54</td>
<td>200±1.36</td>
<td>201±1.10</td>
<td>199±1.10</td>
<td>200±1.55</td>
<td>201±1.98</td>
<td>202±1.22</td>
<td>195±1.23</td>
<td>200±1.01</td>
</tr>
<tr>
<td>% Drug content</td>
<td>96.5±0.26</td>
<td>98.51±0.11</td>
<td>98.02±0.03</td>
<td>98.10±0.66</td>
<td>98.23±0.55</td>
<td>99.88±0.94</td>
<td>98.01±0.83</td>
<td>96.56±0.71</td>
<td>99.24±0.37</td>
</tr>
</tbody>
</table>

### Table 12: Post-Compression Parameters for Optimization of polymers Concentration.

<table>
<thead>
<tr>
<th>Evaluation parameter</th>
<th>MT1</th>
<th>MT2</th>
<th>MT3</th>
<th>MT4</th>
<th>MT5</th>
<th>MT6</th>
<th>MT7</th>
<th>MT8</th>
<th>MT9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thickness (mm)</td>
<td>3.11±0.58</td>
<td>3.11±0.22</td>
<td>3.11±0.99</td>
<td>3.11±0.27</td>
<td>3.11±0.26</td>
<td>3.11±0.24</td>
<td>3.11±0.44</td>
<td>3.11±0.36</td>
<td>3.11±0.25</td>
</tr>
<tr>
<td>Hardness (kg/cm²)</td>
<td>5.3±0.10</td>
<td>5.2±0.04</td>
<td>5.8±0.65</td>
<td>5.9±0.58</td>
<td>5.4±0.18</td>
<td>5.7±0.55</td>
<td>5.5±0.36</td>
<td>5.5±0.11</td>
<td>5.4±0.14</td>
</tr>
<tr>
<td>Friability</td>
<td>0.19±0.25</td>
<td>0.16±0.22</td>
<td>0.15±0.33</td>
<td>0.29±0.33</td>
<td>0.14±0.36</td>
<td>0.09±0.16</td>
<td>0.21±0.06</td>
<td>0.14±0.23</td>
<td>0.11±0.09</td>
</tr>
<tr>
<td>% Weight variation (mg)</td>
<td>202±1.54</td>
<td>200±1.36</td>
<td>201±1.10</td>
<td>199±1.10</td>
<td>200±1.55</td>
<td>201±1.98</td>
<td>202±1.22</td>
<td>195±1.23</td>
<td>200±1.01</td>
</tr>
<tr>
<td>% Drug content</td>
<td>96.5±0.26</td>
<td>98.51±0.11</td>
<td>98.02±0.03</td>
<td>98.10±0.66</td>
<td>98.23±0.55</td>
<td>99.88±0.94</td>
<td>98.01±0.83</td>
<td>96.56±0.71</td>
<td>99.24±0.37</td>
</tr>
</tbody>
</table>

### Table 13: % Drug Release of Formulation MT1 to MT9.

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Time(hours)</th>
<th>% Drug release</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>30 min</td>
</tr>
<tr>
<td>MT1</td>
<td>0</td>
<td>16.50±0.12</td>
</tr>
<tr>
<td>MT2</td>
<td>0</td>
<td>14.75±0.11</td>
</tr>
<tr>
<td>MT3</td>
<td>0</td>
<td>13.87±0.06</td>
</tr>
<tr>
<td>MT4</td>
<td>0</td>
<td>16.37±0.15</td>
</tr>
<tr>
<td>MT5</td>
<td>0</td>
<td>16.25±0.25</td>
</tr>
<tr>
<td>MT6</td>
<td>0</td>
<td>11.87±0.12</td>
</tr>
<tr>
<td>MT7</td>
<td>0</td>
<td>09.37±0.06</td>
</tr>
<tr>
<td>MT8</td>
<td>0</td>
<td>11.75±0.25</td>
</tr>
<tr>
<td>MT9</td>
<td>0</td>
<td>12.12±0.36</td>
</tr>
</tbody>
</table>
Table 14: Results of Pre-Compression Parameters of Batch F1 to F9.

<table>
<thead>
<tr>
<th>Formulation Code</th>
<th>Angle of repose (°)</th>
<th>Bulk density (g/cm³)</th>
<th>Tapped density (g/cm³)</th>
<th>Carr’s Index (%)</th>
<th>Hausner’s ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>31.21±0.11</td>
<td>0.465±0.005</td>
<td>0.550±0.009</td>
<td>15.91±0.17</td>
<td>1.182±0.02</td>
</tr>
<tr>
<td>F2</td>
<td>31.62±0.23</td>
<td>0.434±0.03</td>
<td>0.512±0.004</td>
<td>15.23±0.19</td>
<td>1.179±0.07</td>
</tr>
<tr>
<td>F3</td>
<td>44.42±0.21</td>
<td>0.472±0.004</td>
<td>0.606±0.007</td>
<td>22.11±0.16</td>
<td>1.283±0.08</td>
</tr>
<tr>
<td>F4</td>
<td>38.81±0.16</td>
<td>0.425±0.006</td>
<td>0.526±0.005</td>
<td>19.20±0.11</td>
<td>1.236±0.05</td>
</tr>
<tr>
<td>F5</td>
<td>31.32±0.16</td>
<td>0.400±0.006</td>
<td>0.469±0.006</td>
<td>14.71±0.25</td>
<td>1.172±0.06</td>
</tr>
<tr>
<td>F6</td>
<td>39.12±0.15</td>
<td>0.444±0.002</td>
<td>0.540±0.001</td>
<td>17.77±0.12</td>
<td>1.216±0.05</td>
</tr>
<tr>
<td>F7</td>
<td>23.81±0.08</td>
<td>0.423±0.004</td>
<td>0.468±0.005</td>
<td>9.81±0.11</td>
<td>1.153±0.06</td>
</tr>
<tr>
<td>F8</td>
<td>19.85±0.18</td>
<td>0.489±0.008</td>
<td>0.546±0.002</td>
<td>10.98±0.14</td>
<td>1.162±0.02</td>
</tr>
<tr>
<td>F9</td>
<td>24.12±0.11</td>
<td>0.431±0.007</td>
<td>0.506±0.006</td>
<td>14.82±0.21</td>
<td>1.214±0.06</td>
</tr>
</tbody>
</table>

Table 15: Evaluation of post-Compression Parameters of Batch F1 to F9.

<table>
<thead>
<tr>
<th>Evaluation parameter</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>
</tr>
</thead>
<tbody>
<tr>
<td>Thickness (mm)</td>
<td>3.11±0.92</td>
<td>3.11±0.27</td>
<td>3.11±0.44</td>
<td>3.11±0.22</td>
<td>3.11±0.36</td>
<td>3.11±0.68</td>
<td>3.11±0.25</td>
<td>3.11±0.17</td>
<td>3.11±0.34</td>
</tr>
<tr>
<td>Hardness (kg/cm²)</td>
<td>5.7±0.16</td>
<td>5.2±0.20</td>
<td>5.5±0.11</td>
<td>5.5±0.21</td>
<td>5.4±0.14</td>
<td>5.1±0.36</td>
<td>5.7±0.25</td>
<td>5.4±0.14</td>
<td>5.5±0.21</td>
</tr>
<tr>
<td>Friability</td>
<td>0.21±0.25</td>
<td>0.14±0.40</td>
<td>0.21±0.06</td>
<td>0.20±0.33</td>
<td>0.14±0.23</td>
<td>0.23±0.16</td>
<td>0.11±0.09</td>
<td>0.16±0.23</td>
<td>0.21±0.03</td>
</tr>
<tr>
<td>%Weight variation (mg)</td>
<td>198±1.25</td>
<td>200±1.36</td>
<td>202±1.22</td>
<td>198±1.88</td>
<td>195±1.23</td>
<td>197±1.98</td>
<td>200±1.01</td>
<td>195±1.23</td>
<td>202±1.26</td>
</tr>
<tr>
<td>%Drug content</td>
<td>97.54±0.83</td>
<td>98.58±0.27</td>
<td>98.01±0.83</td>
<td>97.99±0.19</td>
<td>96.56±0.71</td>
<td>97.88±0.29</td>
<td>99.24±0.37</td>
<td>96.56±0.64</td>
<td>98.01±0.56</td>
</tr>
</tbody>
</table>
Table 16: Swelling behaviour study.

<table>
<thead>
<tr>
<th>Time(hr)</th>
<th>% Release</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>F1</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>15.45</td>
</tr>
<tr>
<td>2</td>
<td>22.34</td>
</tr>
<tr>
<td>3</td>
<td>27.14</td>
</tr>
<tr>
<td>4</td>
<td>31.98</td>
</tr>
<tr>
<td>6</td>
<td>38.67</td>
</tr>
<tr>
<td>8</td>
<td>28.02</td>
</tr>
<tr>
<td>10</td>
<td>19.34</td>
</tr>
<tr>
<td>12</td>
<td>20.12</td>
</tr>
</tbody>
</table>

Figure: 6
Table 17: % Drug Release of Formulation F1 to F9.

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Time(hours)</th>
<th>0</th>
<th>30min</th>
<th>1</th>
<th>2</th>
<th>4</th>
<th>6</th>
<th>8</th>
<th>10</th>
<th>12</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%Drug release</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F1</td>
<td>0</td>
<td>17.25±0.12</td>
<td>23.75±0.13</td>
<td>38.50±0.18</td>
<td>54.87±0.13</td>
<td>70.12±0.15</td>
<td>84.50±0.05</td>
<td>98.12±0.17</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>F2</td>
<td>0</td>
<td>12.87±0.11</td>
<td>22.06±0.04</td>
<td>33.47±0.16</td>
<td>50.08±0.17</td>
<td>66.44±0.13</td>
<td>70.62±0.04</td>
<td>79.88±0.13</td>
<td>91.29±0.21</td>
<td></td>
</tr>
<tr>
<td>F3</td>
<td>0</td>
<td>09.37±0.06</td>
<td>22.50±0.09</td>
<td>29.62±0.14</td>
<td>47.12±0.11</td>
<td>61.37±0.19</td>
<td>68.62±0.14</td>
<td>77.87±0.16</td>
<td>88.50±0.16</td>
<td></td>
</tr>
<tr>
<td>F4</td>
<td>0</td>
<td>12.87±0.15</td>
<td>20.25±0.08</td>
<td>33.87±0.06</td>
<td>50.87±0.03</td>
<td>69.50±0.16</td>
<td>80.75±0.17</td>
<td>89.50±0.13</td>
<td>95.37±0.16</td>
<td></td>
</tr>
<tr>
<td>F5</td>
<td>0</td>
<td>11.75±0.25</td>
<td>19.50±0.02</td>
<td>31.25±0.01</td>
<td>48.50±0.08</td>
<td>62.25±0.21</td>
<td>74.37±0.18</td>
<td>83.25±0.05</td>
<td>92.62±0.17</td>
<td></td>
</tr>
<tr>
<td>F6</td>
<td>0</td>
<td>11.50±0.12</td>
<td>16.25±0.07</td>
<td>28.25±0.06</td>
<td>43.12±0.16</td>
<td>59.50±0.14</td>
<td>70.25±0.13</td>
<td>80.12±0.10</td>
<td>89.37±0.12</td>
<td></td>
</tr>
<tr>
<td>F7</td>
<td>0</td>
<td>12.12±0.36</td>
<td>20.12±0.45</td>
<td>34.12±0.88</td>
<td>53.87±0.11</td>
<td>69.25±0.06</td>
<td>80.87±0.91</td>
<td>88.62±0.73</td>
<td>96.25±0.25</td>
<td></td>
</tr>
<tr>
<td>F8</td>
<td>0</td>
<td>11.37±0.62</td>
<td>17.25±0.46</td>
<td>34.37±0.03</td>
<td>45.50±0.16</td>
<td>59.37±0.37</td>
<td>71.62±0.73</td>
<td>82.75±0.81</td>
<td>90.25±0.57</td>
<td></td>
</tr>
<tr>
<td>F9</td>
<td>0</td>
<td>10.12±0.27</td>
<td>15.12±0.28</td>
<td>26.12±0.68</td>
<td>39.50±0.76</td>
<td>53.25±0.49</td>
<td>65.12±0.91</td>
<td>75.12±0.27</td>
<td>84.62±0.53</td>
<td></td>
</tr>
</tbody>
</table>

Figure: 7
Figure 8: Contour plot and response surface plot showing effect of Swelling index at (6hrs) of variables X1 and X2.

Table 18: Anova for % Swelling index (6hrs).

<table>
<thead>
<tr>
<th>Source</th>
<th>Sum of Squares</th>
<th>Df</th>
<th>Mean square</th>
<th>F value</th>
<th>p– value Prob &gt; F</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model</td>
<td>3051.93</td>
<td>5</td>
<td>610.39</td>
<td>14.98</td>
<td>0.0248</td>
</tr>
<tr>
<td>X1</td>
<td>1039.11</td>
<td>1</td>
<td>1039.11</td>
<td>25.50</td>
<td>0.0150</td>
</tr>
<tr>
<td>X2</td>
<td>628.12</td>
<td>1</td>
<td>628.12</td>
<td>15.41</td>
<td>0.0294</td>
</tr>
<tr>
<td>X1X2</td>
<td>338.19</td>
<td>1</td>
<td>338.19</td>
<td>8.30</td>
<td>0.0635</td>
</tr>
<tr>
<td>X1²</td>
<td>1031.79</td>
<td>1</td>
<td>1031.79</td>
<td>25.32</td>
<td>0.0151</td>
</tr>
<tr>
<td>X2²</td>
<td>14.71</td>
<td>1</td>
<td>14.71</td>
<td>0.36</td>
<td>0.5904</td>
</tr>
<tr>
<td>Residual</td>
<td>122.26</td>
<td>3</td>
<td>40.75</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Significant
The Model F-value of 14.98 implies the model is significant. There is only a 2.48% chance that an F-value this large could occur due to noise. Values of "Prob > F" less than 0.0500 indicate model terms are significant.

Table 19: Summary output of regression analysis for effect of X1 & X2 on Y1.

<table>
<thead>
<tr>
<th>Regression statistics</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Prediction R Square</td>
<td>0.6815</td>
</tr>
<tr>
<td>R Square</td>
<td>0.9615</td>
</tr>
<tr>
<td>Adjusted R square</td>
<td>0.8973</td>
</tr>
<tr>
<td>Observations</td>
<td>9</td>
</tr>
<tr>
<td>F Value</td>
<td>14.98</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Coefficient value</th>
<th>Coefficient value</th>
</tr>
</thead>
<tbody>
<tr>
<td>b0</td>
<td>+89.42</td>
</tr>
<tr>
<td>b1</td>
<td>+13.16</td>
</tr>
<tr>
<td>b2</td>
<td>+10.23</td>
</tr>
<tr>
<td>b1b2</td>
<td>-9.19</td>
</tr>
<tr>
<td>b1^2</td>
<td>-22.71</td>
</tr>
<tr>
<td>b2^2</td>
<td>+2.71</td>
</tr>
</tbody>
</table>

**Equation:**

\[ Y1 = +89.42 + 13.16X1 + 10.23X2 - 9.19X1X2 - 22.71X1^2 + 2.71X2^2 \]

Decreased from -1 level to +1 level.
Figure 9: Contour plot and response surface plot showing effect of swelling index at (12 hrs) of variables X1 and X2.

Table 20: ANOVA for % Swelling time(12hrs).

<table>
<thead>
<tr>
<th>Source</th>
<th>Sum of Squares</th>
<th>Df</th>
<th>Mean square</th>
<th>F value</th>
<th>p– value</th>
<th>Prob &gt; F</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model</td>
<td>670.56</td>
<td>5</td>
<td>134.11</td>
<td>31.21</td>
<td>0.0086</td>
<td>Significant</td>
</tr>
<tr>
<td>X1</td>
<td>89.86</td>
<td>1</td>
<td>89.86</td>
<td>20.91</td>
<td>0.0196</td>
<td></td>
</tr>
<tr>
<td>X2</td>
<td>198.26</td>
<td>1</td>
<td>198.26</td>
<td>46.14</td>
<td>0.0065</td>
<td></td>
</tr>
<tr>
<td>X1X2</td>
<td>50.41</td>
<td>1</td>
<td>50.41</td>
<td>11.73</td>
<td>0.0417</td>
<td></td>
</tr>
<tr>
<td>X1²</td>
<td>283.60</td>
<td>1</td>
<td>283.06</td>
<td>65.88</td>
<td>0.0039</td>
<td></td>
</tr>
<tr>
<td>X2²</td>
<td>48.97</td>
<td>1</td>
<td>48.97</td>
<td>11.40</td>
<td>0.0432</td>
<td></td>
</tr>
<tr>
<td>Residual</td>
<td>12.89</td>
<td>3</td>
<td>4.30</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

The Model F–value of 31.21 implies the model is significant. There is only a 0.86% chance that an F–value this large could occur due to noise. Values of "Prob > F" less than 0.0500 indicate model terms are significant.

Table 21: Summary output of regression analysis for effect of X1 & X2 on Y2.

<table>
<thead>
<tr>
<th>Regression statistics</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Prediction R Square</td>
<td>0.8232</td>
</tr>
<tr>
<td>R Square</td>
<td>0.9811</td>
</tr>
<tr>
<td>Adjusted R square</td>
<td>0.9497</td>
</tr>
<tr>
<td>Observations</td>
<td>9</td>
</tr>
<tr>
<td>F Value</td>
<td>31.21</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Coefficient value</th>
<th>Coefficient value</th>
</tr>
</thead>
<tbody>
<tr>
<td>b0</td>
<td>+39.28</td>
</tr>
<tr>
<td>b1</td>
<td>+3.87</td>
</tr>
<tr>
<td>b2</td>
<td>+5.75</td>
</tr>
<tr>
<td>b1b2</td>
<td>-3.55</td>
</tr>
<tr>
<td>b12</td>
<td>-11.90</td>
</tr>
<tr>
<td>b22</td>
<td>+4.95</td>
</tr>
</tbody>
</table>

Equation:

\[ Y2=+39.28+3.87X1+5.75X2-3.55X1X2+11.90(X1)^2+4.95(X2)^2 \]
Figure 10: Contour plot and response surface plot showing effect of % drug release of variables X1 and X2.

Table 22: ANOVA for % drug release.

<table>
<thead>
<tr>
<th>Source</th>
<th>Sum of Squares</th>
<th>Df</th>
<th>Mean square</th>
<th>F value</th>
<th>p– value Prob &gt; F</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model</td>
<td>98.21</td>
<td>5</td>
<td>19.64</td>
<td>29.68</td>
<td>0.0329</td>
</tr>
<tr>
<td>X1</td>
<td>0.021</td>
<td>1</td>
<td>0.021</td>
<td>0.031</td>
<td>0.8760</td>
</tr>
<tr>
<td>X2</td>
<td>39.35</td>
<td>1</td>
<td>39.35</td>
<td>59.64</td>
<td>0.0164</td>
</tr>
<tr>
<td>X1X2</td>
<td>7.57</td>
<td>1</td>
<td>7.57</td>
<td>11.44</td>
<td>0.0774</td>
</tr>
<tr>
<td>X1²</td>
<td>6.22</td>
<td>1</td>
<td>6.22</td>
<td>9.40</td>
<td>0.0919</td>
</tr>
<tr>
<td>X2²</td>
<td>0.25</td>
<td>1</td>
<td>0.25</td>
<td>0.38</td>
<td>0.6022</td>
</tr>
<tr>
<td>Residual</td>
<td>1.32</td>
<td>2</td>
<td>0.68</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The Model F-value of 29.68 implies the model is significant. There is only a 3.29% chance that an F-value this large could occur due to noise. Values of "Prob > F" less than 0.0500 indicate model terms are significant.
Table 23: Summary output of regression analysis for effect of X1 & X2 on Y3.

<table>
<thead>
<tr>
<th>Regression statistics</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Prediction R Square</td>
<td>0.7256</td>
</tr>
<tr>
<td>R Square</td>
<td>0.9867</td>
</tr>
<tr>
<td>Adjusted R square</td>
<td>0.9535</td>
</tr>
<tr>
<td>Observations</td>
<td>9</td>
</tr>
<tr>
<td>F Value</td>
<td>29.68</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Coefficient value</th>
<th>Coefficient value</th>
</tr>
</thead>
<tbody>
<tr>
<td>b0</td>
<td>+92.72</td>
</tr>
<tr>
<td>b1</td>
<td>-0.080</td>
</tr>
<tr>
<td>b2</td>
<td>-3.49</td>
</tr>
<tr>
<td>b1b2</td>
<td>-2.80</td>
</tr>
<tr>
<td>b12</td>
<td>+2.00</td>
</tr>
<tr>
<td>b22</td>
<td>-0.40</td>
</tr>
</tbody>
</table>

Equation:
\[ Y3 = +92.72 - 0.080X1 - 3.49X2 - 2.80X1X2 + 2.00(X1)^2 - 0.40(X2)^2 \]

Kinetic Modeling of Dissolution Data

Table 24: Kinetic Modeling data of F7 batch.

<table>
<thead>
<tr>
<th>F7</th>
<th>Zero order</th>
<th>First order</th>
<th>Higuchi Model</th>
<th>Korsmeyer and Peppas</th>
</tr>
</thead>
<tbody>
<tr>
<td>R²</td>
<td>0.945</td>
<td>0.964</td>
<td>0.992</td>
<td>0.586</td>
</tr>
<tr>
<td>Slope</td>
<td>7.827</td>
<td>0.106</td>
<td>29.71</td>
<td>0.975</td>
</tr>
</tbody>
</table>

Figure 11: Cumulative % Drug Release vs Time (hr).
Figure 12: Log cumulative % drug Retained vs Time (hrs).

Figure 13: Cumulative % drug Release vs SQRT.

Figure 14: Log %cumulative release vs Log time.

Comparison of Optimized Batch with Marketed Product by in Vitro Drug Release

Brand name: Lescol (Fluvastatin sodium extended release tablet)

Manufactured by: Novartis
Table 25: Comparison of optimized batch with marketed product.

<table>
<thead>
<tr>
<th>Time(hrs)</th>
<th>Optimized batch(F7)</th>
<th>Marketed product</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20.12</td>
<td>16.28</td>
</tr>
<tr>
<td>2</td>
<td>34.12</td>
<td>27.89</td>
</tr>
<tr>
<td>4</td>
<td>53.87</td>
<td>51.39</td>
</tr>
<tr>
<td>6</td>
<td>69.25</td>
<td>71.29</td>
</tr>
<tr>
<td>8</td>
<td>80.87</td>
<td>99.21</td>
</tr>
<tr>
<td>10</td>
<td>88.62</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>96.25</td>
<td></td>
</tr>
</tbody>
</table>

By the comparison with extended release fluvastatin sodium tablet, it is observed that sustain release matrix tablet of fluvatsatin sodium have an better drug release profile in terms of long term drug release as a sustain release formulation.

**Stability Study**

To determine the change in physical properties and in vitro release profile on Storage, optimized batch were stored at 40°C ± 0.5 °C and 75% ± 5% relative Humidity in stability chamber. Samples were evaluated at 1 month time for drug Content, In vitro drug release study, hardness, thickness. Accelerated stability study data of Optimized batch F7.

Table 26: Stability study of optimized batch (F7).

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Initial</th>
<th>After 1 month at 40°C and 75% RH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thickness(mm)</td>
<td>3.11±0.25</td>
<td>3.11±0.99</td>
</tr>
<tr>
<td>Hardness(Kg/cm²)</td>
<td>5.7±0.25</td>
<td>5.7±0.23</td>
</tr>
<tr>
<td>Drug content (%)</td>
<td>99.24±0.37</td>
<td>98.22±0.29</td>
</tr>
<tr>
<td>Cumulative Drug release (%) (At the end of 12 hr)</td>
<td>96.25±0.25</td>
<td>95.99±0.22</td>
</tr>
</tbody>
</table>

RESULTS AND DISCUSSION

In this study, the attempt was made to develop sustain release matrix tablet from spherical crystals of drug fluvastatin sodium (BCS class II) by using crystallo-co-agglomeration (cca) technique of Spherical crystallization. Hydrophillic polymer hydroxypropyl methylcellulose (hpmc) were tried in order to prepare spherical agglomerates. The stirring speed for spherical crystallization was optimized (600rpm) in order to obtain desired sphericity and particle size. The stirring rates have significant effect on morphology of the prepared agglomerates and it was seen that spherical agglomerates with uniform particle size were produced at optimum stirring speed. The mean particle size of agglomerates was found to be higher for HPMC as compared to untreated fluvastatin sodium. This method of spherical crystallization changes
the crystal habit to spherical crystals which were clearly seen in SEM images. The FTIR, DSC results showed no chemical interaction between the drug and the polymers, and. The XRD revealed that crystallinity was reduced significantly in agglomerates with HPMC polymer which were mainly attributed to partial amorphization. Then, optimized spherical agglomerate was used to prepare sustained release matrix tablets of optimized spherical agglomerates.

Fluvastatin sodium SR matrix tablets using Hydroxy propyl methyl cellulose and xanthan gum as release retarding polymers.

Fluvastatin sodium is oral antihyperlipidimic drug which lowers lipid level and has been selected to prepare sustained release dosage forms:

1. Fluvastatin sodium sustained release matrix tablet were prepared using Hydroxy Propyl Methyl Cellulose and xanthan gum combination as base polymer by direct compression method.
2. FT-IR spectral analysis showed that characteristic peak of pure drug fluvastatin sodium was retained in the spectra of all the formulations indicating the inactness of the drug in all the formulations.
3. The prepared factorial tablets were evaluated for number of parameters like thickness, diameter, weight variation, swelling index and in vitro release studies, from these evaluation it is concluded that F7 batch was optimized batch.
4. All the prepared tablets were of smooth surface and elegant texture.
5. The tablets prepared were checked visually for its appearance & surface texture.
6. The weights of the tablets were in the range of 200 ± 5 mg. The thickness of the tablet was in the range of 3.11 ± 0.17 to 3.11 ± 0.92mm. Drug content uniformity study showed uniform dispersion of the drug throughout the formulation in the range of 96.56±0.71 to 99.24±0.37.
7. The maximum drug release was found to be 96.25 % over a period of 12 hour in combination of HPMC K15M and xanthan gum based tablets (F7) and it was Optimized batch as it sustain drug release for 12 hrs and gave maximum drug Release.
8. The formulations were also subjected to model fitting analysis to know the order and mechanism of drug release from the formulations by treating the data according to zero – order, first – order, Higuchi and peppas equations. The optimized batch follows Higuchi release.
9. Stability studies revealed that there were no significant changes in physical Properties, % CDR and drug content of formulation F7.

10. It can be concluded that Hydroxy Propyl Methyl Cellulose and xanthan gum combination polymer respectively can be used as an effective matrix former to sustain the release of fluvastatin sodium for an sustain period of 12 hr.

The prepared tablets were evaluated for number of parameters like thickness, Diameter, weight variation, swelling index and in vitro release studies, from these Evaluation it is concluded that F7 batch was optimized batch.

CONCLUSION
Fluvastatin sodium is hyperlipidmic, drug which lowers lipid level and has been selected to prepare sustained release.

Dosage forms. It is BCS class II drug. Fluvastatin sodium is poor micromeratic properties drug, their micromeritics is increased by crystallo-co-agglomeration (CCA) method. The highest improvement in micromeritics of drug were observed in Fluvastatin sodium agglomerates (F2) and its tablets with HPMCK15M prepared by crystallo-co-agglomeration (CCA) with maximum yield of 83.33±0.33 and particle size of 149.56 Than prepared Fluvastatin sodium sustain release matrix tablets of spherical agglomerates by using direct compression method using hydroxy propyl methyl cellulose and xanthan gum as release retarding polymers.Optimized batch F7 showed no remarkable changes in physical-chemical properties as well in drug release before and after performing stability studies. So it can be concluded that matrix tablet prepared by spherical agglomerats of fluvastatin sodium tablets is a good dosage form than conventional dosage form and extended release dosage form.

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