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# FORMULATION, EVALUATION AND DEVELOPMENT OF FAST RELEASE TABLETS OF ROSUVASTATIN CALCIUM USING SUBLIMATION METHOD

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## ABSTRACT

**Aim:** The aim of the present work was to prepare Drug-β Cyclodextrin complex to increase solubility and prepared complex was used to formulate Fast Release Tablets (FRT). Increase in drug solubility by β-Cyclodextrin was evaluated by Higuchi connor's phase solubility studies. **Methods:** FRTs were prepared by direct compression, wet granulation and sublimation methods using Sodium starch glycolate, Croscarmellose sodium and Crospovidone as a superdisintegrants. Method giving satisfactory result was further studied and a $3^2$ full factorial design was applied to optimize the formulation. The concentrations of two Superdisintegrants showing best results were selected as independent variables. Disintegration time (Y1) and % Drug release at 5minute (Y2) were selected as dependent variables. The prepared tablets were evaluated for hardness, friability, disintegration time and in vitro drug release. **Results:** Rosuvastatin calcium FRTs prepared were found to be fulfilled all the requirements for tablets. The tablets prepared by sublimation method showed better results compared to direct compression and wet granulation and among all superdisintegrants, Sodium starch gycolate (X1) and Croscarmellose sodium (X2) significantly affected the disintegration time

(Y1) and % drug release at 5 minutes (Y2). Regression analysis and numerical optimization were performed to identify the best formulation. Formulation F10 prepared with Sodium starch glycolate (6.88mg) and Croscarmellose sodium (7.35 mg) was found to be the best formulation with disintegration time 11 sec and % drug release at 5minute of 93.68%. **Conclusion:** Fast release tablets of Rosuvastatin calcium were successfully formulated by sublimation technique with improved patient compliance and immediate onset of action.

**KEYWORDS:** Rosuvastatin calcium, Fast Release Tablets, Complexation, Sublimation Technique.

## INTRODUCTION

There are numerous systems reported in literature for drug delivery. Approximately 40% of the formulations on the market and an estimated 70% of the developed drugs by pharmaceutical companies are poorly soluble.[1] In addition, the discovery of new drug is a multi-stage complex process and takes average 7–10 years.[2,3] In some studies in 2016, an estimated average out- of - pocket cost per approved new drug was $1,395 million (2013 dollars) and the increase in the cost of drug discovery was estimated at an annual rate of 8.5% above general price inflation.[4,5] Studies have also indicated that 2644 people died during clinical test for 475 new drugs between 2005 and 2012.[6] In order to overcome these challenges, scholars have been motivated and prompted to formulate existing drugs in an innovative way for better bioavailability. Several studies have attempted to formulate, develop and evaluate fast release tablets using different techniques because of exhibiting low dissolution profiles, absorption and poor bioavailability.[7,8] It has been reported that approximately 50% of the population suffers from problem of difficulty in swallowing which resulting in patient noncompliance resulting in failure in therapy thereby. Advances in formulation of existing tablets is turning out to be the best solution in this competitive business for pharmaceutical industry which is currently facing deficit in innovative compositions and manufacturing techniques of medicines for new molecules. Oral drug delivery method and in particular fast release tablets remains the preferred administration route due to its high degree of patience acceptance such as children less than 5years of age, elderly people, pediatrics, geriatric and psychiatrics.[9] With regard to oral route of drug administration, fast release tablets or rather immediate release tablets that disintegrate and dissolve rapidly in saliva have emerged to be the commonly used pediatric and geriatric products.[9,10] Rosuvastatin Calcium fast release formulations and combinations prove a

promising solution to the above challenges as they can be administered without any external support and when swallowed disintegrate and dissolve rapidly in the saliva without the help of drinking water.[11,12] Rosuvastatin, is a drug class of statins chemically described as bis [(E)-7 [4-(4- fluorophenyl)-6 isopropyl-2[methyl (methyl-sulphonyl) amino] pyrimidin-5-yl] (3R, 5S) -3, 5-dihydroxyhept-6-enoic acid]. It is hydrophilic which makes it hepatoselective. For this reason, this drug is considered a substitute for atorvastatin and can be prepared fast release tablet formulation to treat patients with hypertension and dyslipidemia.[11,13] Rosuvastatin (Crestor, 5 mg, manufactured by Asstrazenecz,Banglore ) is a new and highly effective inhibitor of HMG-CoA reductase that has completed Phase-III clinical development for the treatment of patients with cardiovascular diseases, dyslipidaemia, hypertriglyceridemia as well as lowering of cholesterol.[11,14,15] It exhibits a high degree of specificity for uptake into the liver and is a potent in vitro and in vivo competitive inhibitor of HMG-CoA reductase.[13] It is a poorly water soluble drug in solutions of pH 4.0 and below.[12,13] Solubility of the drug is the major determining factor in its formulation and associated therapeutic efficacy.[16] Compared with other HMG-CoA inhibitors, RSV Ca does not appear to be metabolized significantly by cytochrome P4503A42 and therefore, may not possess the same potential for drug interaction as seen for some other statins, e.g. atorvastatin, lovastatin and simvastatin.[13] Clinical studies have proven that fast disintegrating tablets can enhance patient compliance, provide an immediate onset time of action, and increase bioavailability.[17] Present work is aimed at developing fast release tablets of Rosuvastatin calcium employing different methods such as direct compression, wet granulation and sublimation utilising characteristic of a complexing agent to improve the solubility and taste of the drug, a supardisintegrant for rapid ‘disintegration ‘and making up the drug formulation with auxiliary agent such as diluents, sweetners, flavours. The tablet when placed in mouth will disintegrate immediately and dissolve in a rapid onset with pleasant mouthful. A $3^2$factorial design is selected for the preparation of formulation tablets possessing optimal characteristic.

A number of researchers have worked on improvement of solubility of Rosuvastatin Calcium either by preparing SNEDDS,[18,19] direct compression,[20] using superdisintegrants, using solid dispersion technique,[21] or by addition of alkalizers[22] and have shown that their efforts resulted in enhancement of solubility of the drug. From the study of literature it has been found that floating drug delivery,[23] inclusion of mucoadhesive superdisintegrants (Croscarmellose sodium, sodium starch glycolate) has been popular in order to enhance

dissolution.[20] Melt granulation process have shown considerable increase in dissolution of drugs.[22,24,25] Present work on formulation of fast release tablet Rosuvastatin calcium has been carried out with a view to increase in solubility. Since it is a BCS class II drugs its solubility increase has been studied here with the use of complexing agent and superdisintegrants.

## MATERIALS AND METHODS

### Materials used in present work

API (Rosuvastatin Calcium) was procured as a gift sample from Mepro pharm Ltd, Ahmedabad. MCC. (Flocel, diluent) was gifted by Gujarat paraffin PVT Ltd, Ahmedabad. SPARC, Vadodara helped by giving superdisintegrants (sodium starch glycolate, Crospovidone, Croscarmelose sodium). Magnesium stearate (lubricant) and talc (glidant) was sponsored by LOBA chemic PVT Ltd, Mumbai. β-Clycodextrin (solubilizer) was acquired from Gangwal chem Ltd, Mumbai. Dibasic calcium phosphate (stabilizer) from Rankem. Subliming agent (Camphor) from Natraj PVT Ltd. Sucralose (sweetner) from SPARC, Vadodara. Menthol (flavour) was from RFCL Ltd, New Delhi.

### Apparatus used in present work

1. Digital Weighting balance (Shimadzu, model AX2000, Japan)
2. UV-visible Spectrophotometer (Shimadzu, model -1700, Japan)
3. Tray Dryer (Sapphire Machines)
4. Tap Density tester, USP (Electrolab)
5. Tablet Punching Machine (Karnavati)
6. Hardness Tester (Dr.Schleunigr Pharmatron tablet)
7. Roche Friabilator (Electrolab)
8. Disintegrator (Electrolab)
9. Dissolution Appratus (Electrolab)
10. Differential Scanning Calorimetry (Perkin elmer, Baconsfield, UK)
11. Fourier transform infra-red Spectroscopy ((Shimadzu, model -8400S, Japan)

### Experimental Methods

### Organoleptic characteristics of Rosuvastatin calcium

The organoleptic characteristics of Rosuvastatin calcium were first established. Its appearance was white crystalline powder and the taste was lightly bitter. The melting point of Rosuvastatin calcium was found using open capillary method. In addition the drug was

spotted on HPTLC plate and run in mobile phase Ethyl acetate: Glacial acetic acid 10:0.1 to investigate the purity of the sample.

**Spectroscopic Estimation of Rosuvastatin Calcium (Preparation of standard curve)**

Rosuvastatin calcium (100mg) was accurately weighed and dissolved in 100 ml. phosphate buffer pH 6.8 to form a stock solution (100µg/mL). The stock solution was further diluted suitably with phosphate buffer pH 6.8 to get a working standard solution of concentration 100 µg/mL. This working standard solution was suitably diluted to give a concentration 30µg/mL and this was then scanned in UV range. This showed absorption maximum 242nm(figure 2). Alquots (0.2, 0.4, 0.6, 0.8, 1.0, 1.2) mL of working standard solution corresponding to 2 - 12µg/mL were taken in a series of 10 mL volumetric flask and volume made up with phosphate buffer pH 6.8. The absorbance measurements of these solutions were carried out against phosphate buffer pH 6.8 as blank at 242 nm. A calibration curve of Rosuvastatin calcium was plotted (Figure2). The concentration of the unknown was read from the calibration graph or computed from the regression equation.

**FT-IR of Rosuvastatin Calcium**

Infrared spectra of Rosuvastatin calcium was obtained using Fourier transform infrared spectroscopy. The pallets were prepared on KBR press, and the spectra were recorded over the wave number 4000 to 400 cm-1. The spectra were obtained and comparatively analyzed (figure 5).

**Differential Scanning Calorimetry**

Calorimetric analysis was performed at Sree S.K. Patel College of Pharmaceutical Education and Research, Kherva, Gujarat, India. The instrument was calibrated with a reference standard and scanned over melting range.

**pH Dependent Solubility**

Solubility evaluation of Rosuvastatin calcium was performed in buffer of different pH concentration.

**Phase Solubility Study**[26]

Phase solubility study was conducted based on the analysis already established by Higuchi and Connors. An excess amount of Rosuvastatin calcium was added to 10ml of double distilled water, pH6.8 containing different concentration of β-CD (0.002 – 0.012mM) taken in

a series of 25 ml stoppered conical flasks and the mixtures were shaken in shaker for 72hours. Upon reaching equilibrium, a membrane filter of (pore size 0.45µm) was used to filter the solutions. Thereafter, carefully dilution of the filtered samples was done and assayed for content of drug by UV spectrophotometer at 242 nm against blank. The whole solubility experiments were done in triplicate. The quantity of dissolved drug was plotted against moles of carrier (β-CD). In addition, the stability constant (Ks) and complexation efficiency (CE) was found using the following equations:

$$Ks\ (1:1) = slope/So\ (1\text{-}Slope) \quad \text{Eq. (1)}$$

$$C.E. = slope/\ (1 - slope) \quad \text{Eq. (2)}$$

$$D: CD = 1: (1 + 1/CE) \quad \text{Eq. (3)}$$

Where is the solubility of Rosuvastatin calcium in the absence of carrier. (figure 4).

**Preparation of Rosuvastatin calcium β–cyclodextrin (β–CD) inclusion complex**

Rosuvastatin calcium (β–CD) Complexes were prepared in 1:1 drug to β–cyclodextrin molar ratio by kneading method. Since the Molecular weight of Rosuvastatin calcium is 1001.137 and that of β–cyclodextrin is 1135, therefore, 5mg of drug was added with 5.66mg of β–CD in 1:1 molar ratio for each tablet. Thereafter, a 1:1 ratio of drug and β–CD were homogeneously blended in glass motor thoroughly and wetted ethanol and kneaded thoroughly for 45min, the formed paste was dried. The dry mass was pulverized and sieved through number 100.

**Selection of Super-Disintegrant concentration**

The superdisintegrants – Sodium Starch Glycolate (SSG), Croscarmellose Sodium (CCS) and Crospovidone (CP) at concentration 8%, 8% and 6% respectively showed better result and were selected for preparing further of direct compression.

**Methods for preparation of Tablets**

**Direct compression**

The materials were individually weighed, passed through sieve # 44 and blended for 15min by using mortar and pestle. The powder mixture was then lubricated with talc and magnesium stearate and directly compressed by using single punch tablet press with the 6mm diameter of punch.

**Sublimation method**

The drug complex, subliming agent and other ingredients were accurately weighed, mixed and passed though sieve # 44. Finally, magnesium stearate and talc were added. The powder blend was subjected to compression. After compression the tablets were placed in hot air oven at 40 $^0$C till constant weight was obtained to ensure complete removal of volatile component. The subliming agent – Camphor at 10% concentration showed better result and was selected for preparing further batches by sublimation method.

**Wet granulation method**

Drug complex and other ingredients were accurately weighed and mixed. The binder polyvinyl pyrolidone in IPA is added to form wet mass. Granules were formed by passing through sieve # 40. Granules were dried at 40 $^0$C for about 15 minutes. After drying, super-disintegrant was added externally. Talc and magnesium stearate were added as glidant and lubricant respectively. The granules were then subjected to compression by single punch machine.

**Method adopting for compatibility studies**

**FTIR**

Infrared spectra of Rosuvastatin Calcium, drug complex and drug with other excipients were obtained using Fourier transform infrared (FTIR) spectroscopy. The pellets were prepared on KBR press, and the spectra were recorded over the wave number 4000 to 400 $cm^{-1}$. The spectra were obtained and comparatively analyzed.

The FTIR spectra of drug, drug complex and drug with excipients were recorded. (figure 7)

**Methods of comparison with different superdisintegrants**

Comparison of evaluation parameters such as wetting time, disintegration time and % drug release at 5min for sublimation methods, direct compression and wet granulation were done and presented as shown in (Figure 8, 9 and 10).

**Optimization of formulation**

In order to investigate the effect of formulation variables on the response variables and to predict an optimized formulation, a $3^2$ factorial design was adopted. Nine batches were prepared as per the design layout shown in Table 6, 7, and 8.

**Evaluation of optimized formulation**

The optimization was performed using design expert 9.0.4 by superimposing the contour plots of the response Y1 and Y2 and locating the region of optimal surface common to both the plots as shown in figure 12.5. In order to assist with evaluation process, the following parameters below were tested during the experimental study.

**Evaluation of Pre Compression Parameters of Powder**

Following parameters were evaluated during pre-compression studies:

Bulky Density ($D_b$)

Tapped Density ($D_t$)

Carr's Index (CI) or % Compressibility

Angle of Repose(Ɵ)

Hausner Ratio ($D_b/D_t$)

**Evaluation of Post Compression Parameters of Rosuvastatin Calcium**

It was carried out by investigating following parameters:

Weight Variation

Tablet Hardness (Crushing strength)

Thickness

Disintegration time

Friability (Mechanical strength)

Water Absorption Ratio

**Short Term Stability Study**

It is vital for formulation development person to develop a stable product from formulation as well as regulatory point of view. The regulatory agencies around the globe have rhetoric guidelines of product stability studies. The stability study is performed to check physical and chemical integrity of the formulation.[27] Selected batch F10 was subjected for stability study. All the tablets suitably packed in aluminium foil. The tablets to be tasted at room conditions were kept outside in petridish. At the end of every week the sealed tablets were opened and evaluated for different parameters.

For tablets to be studied at room temperature with 75% RH, clean and dry desiccators were taken and saturated sodium chloride was poured inside the desiccators. The holding plate was placed inside and the desiccators were closed properly. They were allowed to get saturated

for 1to 2 hrs. This gave the humidity chamber of 75% RH. Then the desiccators were reopened and the aluminium foil sealed orodispersible tablets were placed inside and the desiccators were closed. At the end of every week the sealed tablets were opened and evaluated for changing physical defects.

- Storage condition: (1) Room temperature (40˚c) and (2) Room temperature 75%RH.
- Time period: 4weeks (nearly one month).

At intervals of every one week, the tablets were examined for changes in various parameters.

**In Vivo Studies and Ethical Considerations**[28,29,30]

The bioavailability studies for optimized formulation of Rosuvastatin calcium (F10), and Marketed Formulation (Crestor) were carried out using male Wistar rats (200-250g). The animals were maintained in a clean room at temperature between $20^0$C ± $25^0$C with 12h light and dark cycles and controlled RH. The animals were fasted for 12h prior to commencement of the study as well as during the study and had access to water and libitum. The institutional animal ethical clearance (protocol letter no. CPCSEA/ LMCP/ CEUTICS/15/11) was obtained before conducting the studies. They were divided into three groups (six in each group); Group 1 served as a control group, whereas other three groups were treated with tablet formulation containing Complexation of Rosuvastatin calcium (F10) and Marketed Formulation respectively. Tablets with dose of 1.58 mg/kg body weight of rats were administered by dispersing in distilled water through oral feeding pipe. Blood samples were collected through the lateral tail vein of rats at 10, 20, 30 min followed by 1,2,3,4, and 6 hour after dosing. The blood samples were centrifuged at 3000 rpm for 10min and 100 µl of plasma samples were stored at - $20^0$C until analysis. The plasma concentration of the drug was determined by UV spectrophotometry at 240mm wavelength by taking plasma taken at 0 minute as blank. The results obtained were analysed for various non con-compartmental pharmacokinetic (PK) parameters.

**RESULTS**

The results are organized in accordance with the experimental plan. Firstly, the results for the preliminary studies are presented. Thereafter, compatibility and comparative study results are presented. Finally, formulation and evaluation studies are presented and winded up with stability plots. (tables and figures).

**Table 1: Selection of Binder Concentration.**

| Ingredients (mg) | B1 | B2 | B3 |
|---|---|---|---|
| Drug Complex | 10.65 | 10.65 | 10.65 |
| PVP (% in IPA) | 5 | 10 | 15 |
| Dibasic Calcium Phosphate | 10 | 10 | 10 |
| Talc | 3 | 3 | 3 |
| Magnesium stearate | 2 | 2 | 2 |
| Sucralose | 0.5 | 0.5 | 0.5 |
| MCC | 173.85 | 165.85 | 165.85 |

**Table 2: Comparison of direct compression, wet granulation and sublimation method.**

| Batch | Disint time (sec) | % Drug release at 5 min | Batch | Disint time (sec) | % Drug release at 5 min | Batch | Disint time (sec) | % Drug release at 5 min |
|---|---|---|---|---|---|---|---|---|
| D1 | 360 | 14.22 | W1 | 211 | 15.32 | S1 | 13 | 81.32 |
| D2 | 26 | 41.8 | W2 | 23 | 66.86 | S2 | 11 | 87.68 |
| D3 | 25 | 50.53 | W3 | 21 | 74.05 | S3 | 10 | 92.04 |
| D4 | 26 | 31.29 | W4 | 26 | 69.40 | S4 | 11 | 84.50 |
| D5 | 17 | 67.25 | W5 | 17 | 77.38 | S5 | 8 | 92.83 |
| D6 | 19 | 48.77 | W6 | 19 | 75.82 | S6 | 10 | 85.28 |
| D7 | 18 | 52.69 | W7 | 21 | 73.83 | S7 | 9 | 89.68 |
| D8 | 18 | 43.78 | W8 | 16 | 79.17 | S8 | 10 | 82.70 |

**Table 3: Design layout and evaluation of factorial design batches.**

| Ingredients | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 |
|---|---|---|---|---|---|---|---|---|---|
| Drug complex | 10.65 | 10.65 | 10.65 | 10.65 | 10.65 | 10.65 | 10.65 | 10.65 | 10.65 |
| SSG | - | - | - | 4 | 4 | 4 | 8 | 8 | 8 |
| CCS | - | 4 | 8 | - | 4 | 8 | - | 4 | 8 |
| Camphor | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 |
| Dibasic calcium phosphate | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Talc | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| Magnesium stearate | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| Sucralose | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 |
| MCC (Flocel ) | 153.85 | 149.85 | 145.85 | 149.85 | 145.85 | 141.85 | 145.85 | 141.85 | 137.85 |

**Table 4: Evaluation of Pre and Post – Compression parameters of tablets prepared by $3^2$ Factorial Design.**

| **Pre - compression parameters** | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Batch** | **F1** | **F2** | **F3** | **F4** | **F5** | **F6** | **F7** | **F8** | **F9** |
| **Bulk Density** | 0.52 | 0.55 | 0.57 | 0.53 | 0.52 | 0.55 | 0.57 | 0.53 | 0.51 |
| **Tapped density** | 0.61 | 0.66 | 0.69 | 0.63 | 0.61 | 0.66 | 0.69 | 0.63 | 0.63 |
| **Carr's index (%)** | 14.75 | 16.66 | 17.31 | 15.87 | 14.75 | 16.66 | 17.31 | 15.87 | 14.17 |
| **Hausner's Ratio** | 1.17 | 1.2 | 1.21 | 1.18 | 1.17 | 1.2 | 1.21 | 1.18 | 1.23 |
| **Angle of repose** | 29.69 | 28.06 | 27.58 | 28.44 | 29.69 | 28.06 | 27.58 | 28.44 | 26.54 |
| **Post – Compression parameters** | | | | | | | | | |
| **Hardness ($kg/cm^2$)** | 3.65±0.34 | 3.1±0.32 | 3.35±0.53 | 3.15±0.24 | 3.65±0.34 | 3.1±0.32 | 3.35±0.53 | 3.15±0.24 | 3.2±0.31 |
| **Friability (%)** | 0.54 | 0.71 | 0.69 | 0.74 | 0.54 | 0.71 | 0.69 | 0.74 | 0.71 |
| **Water absorption ratio (%)** | 59 | 63 | 73 | 75 | 59 | 63 | 73 | 75 | 72 |
| **Wetting time (seconds)** | 190 | 21 | 20 | 23 | 190 | 21 | 20 | 23 | 7 |
| **Disintegration time (seconds)** | 21 | 18 | 14 | 15 | 21 | 18 | 14 | 15 | 9 |
| **% release T5** | 74.41 | 84.3 | 88.7 | 85.33 | 74.41 | 84.3 | 88.7 | 85.33 | 95.74 |
| **Content uniformity** | 98.32 | 98.56 | 99.45 | 97.34 | 98.32 | 98.56 | 99.45 | 97.34 | 99.26 |

**Table 5: Summary of regression analysis for effect of X1 and X2 on Y1**

| **Regression Statistic** | | | **Regression Statistic** | | |
|---|---|---|---|---|---|
| **Multiple R** | 0.996278 | | **Multiple R** | 0.987412 | |
| **R Square** | 0.992569 | | **R Square** | 0.974983 | |
| **Adjusted R Square** | 0.990711 | | **Adjusted R Square** | 0.933288 | |
| **Standard Error** | 0.325669 | | **Standard Error** | 1.565179 | |
| **Observations** | 9 | | **Observations** | 9 | |
| **Coefficients** | | | **Coefficients** | | |
| **Coefficient** | Coefficient value | P - value | **Coefficient** | Coefficient value | P - value |
| **$B_0$** | 15.33333 | 0.000131 | **$B_0$** | 86.86222 | 5.34E-06 |
| **$B_1$** | -2.33333 | 0.000602 | **$B_1$** | 3.923333 | 0.008689 |
| **$B_2$** | -3.66667 | 0.000157 | **$B_2$** | 5.658333 | 0.003036 |
| **$B_{11}$** | 0.000785 | 1 | **$B_{11}$** | 0.076667 | 0.949132 |
| **$B_{22}$** | 0.00236 | 1 | **$B_{22}$** | -0.31833 | 0.792355 |
| **$B_{12}$** | -0.25 | 0.272228 | **$B_{12}$** | -0.6625 | 0.459431 |
| **Equation** | | | **Equation** | | |
| **Full Model:** $15.33 – 2.33X_1 – 3.66X_2 + (7.8 \times 10^{-4})X_{11} + (2.3 \times 10^{-3})X_{22} – 0.25X_1X_2$ | | | **Full Model:** $86.86+3.92X_1+5.65X_2+0.07X_{11}-0.31X_{22}-0.66X_1X_2$ | | |
| **Reduced Model:** $15.33 – 2.33X_1 – 3.66X_2$ | | | **Reduced Model:** $86.86+3.92X_1+5.65X_2$ | | |

**Table 6: Formulation and Evaluation of checkpoint batch.**

| Formulation Ingredient (mg) | Formulation Batch F10 |
|---|---|
| Drug complex | 10.65 |
| SSG | 6.88 |
| CCS | 7.35 |
| Camphor | 20 |
| Dibasic calcium phosphate | 10 |
| Talc | 3 |
| Magnesium stearate | 2 |
| Sucralose | 0.5 |
| MCC (Flocel) | 139.82 |
| Total | 200 |
| **Evaluation** | |
| Bulk density | 0.549 |
| Tapped density | 0.641 |
| Carr's index (%) | 14.28 |
| Hausner's Ratio | 1.16 |
| Angle of repose | 23.69 |
| Hardness () | 2.5 kg/cm2 |
| Friability | 0.79% |
| Water absorption ratio (%) | 78 |
| Wetting time (seconds) | 7 |
| Disintegration Time (seconds) | 11 |
| %Drug release T5 | 93.68 |
| Content Uniformity (%) | 99.27 |

**Table 7: Comparison between experimental and predicted values of response.**

| Response | Check point batch F10 | |
|---|---|---|
| | Experimental value | Predicted value |
| Disintegration time (sec) | 11 | 10.51 |
| % Drug release at 5 min | 93.68 | 94.02 |

**Table 8: Formulation comparison with marketed Product.**

| Test Parameters | F10 Batch | Crestor |
|---|---|---|
| Hardness (kg/cm2) | 2.5 | 3 |
| Friability (%) | 0.79 | 0.39 |
| Wetting time (sec) | 7 | 65 |
| In-vitro disintegration time(sec) | 11 | 286 |
| % Drug release at 5 min | 93.68 | 59.56 |

**Table 9: Test evaluation of checkpoint batch.**

| Volunteer | Pure drug | Optimized formulation |
|---|---|---|
| 1 | - | ++ |
| 2 | - | ++ |
| 3 | - | ++ |
| 4 | - | ++ |
| 5 | - | ++ |
| Bitterness graded from non-bitter (++), less bitter (+) and bitter (-) | | |

**Table 10: Result of short term stability study.**

| No. of weeks | Hardness (kg/cm2) | Disintegration time (sec) | % Drug release at 5 min |
|---|---|---|---|
| 0 | 2.5 | 11 | 93.68 |
| 1 | 2.5 | 11 | 93.09 |
| 2 | 2.5 | 11 | 92.87 |
| 3 | 2.5 | 12 | 92.56 |
| 4 | 2.5 | 12 | 91.33 |

**Table 11: Comparison of In-vitro drug release of F10 batch.**

| Time (min) | % Drug release of F10 Batch | |
|---|---|---|
| | Initial | After 4 Week |
| 0 | 0 | 0 |
| 1 | 63.11 | 62.39 |
| 2 | 70.58 | 69.79 |
| 3 | 79.27 | 76.45 |
| 4 | 87.85 | 86.75 |
| 5 | 93.68 | 91.33 |

**Table 12: Mean pharmacokinetic parameters after immediate release & reference concentration.**

| | Test product | | | Reference product | | |
|---|---|---|---|---|---|---|
| **Subject** | **Cmax (µg/mL)** | **Tmax (hr)** | **AUC 0 — ∞ (µgh/mL)** | **Cmax (µg/mL)** | **Tmax (Hr)** | **AUC 0 — ∞ (µg/hmL)** |
| **S1** | 3.13 | 0.6 | 12.1 | 2.86 | 1.3 | 12.7 |
| **S2** | 3.47 | 1.05 | 10.2 | 2.54 | 1.15 | 10.9 |
| **S3** | 3.34 | 0.8 | 10.4 | 2.73 | 1.2 | 10.6 |
| **S4** | 2.98 | 0.65 | 11.1 | 2.82 | 1.1 | 11.5 |
| **S5** | 3.08 | 1 | 10.7 | 2.79 | 1.5 | 10.3 |
| **S6** | 3.29 | 1.1 | 11.9 | 2.88 | 1.2 | 11.2 |

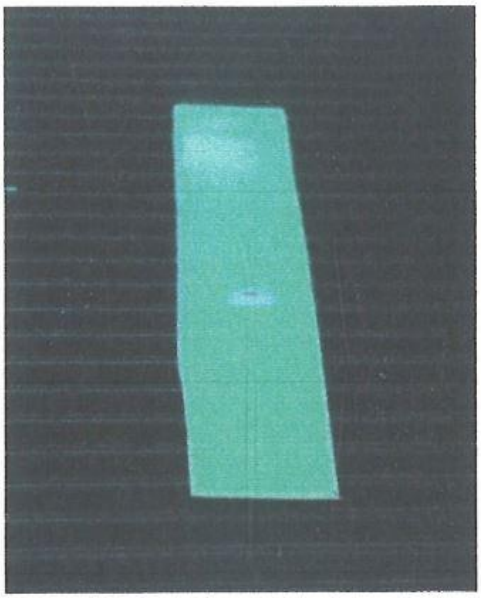

**Figure 1: HPTLC of rosuvastatin calcium.**

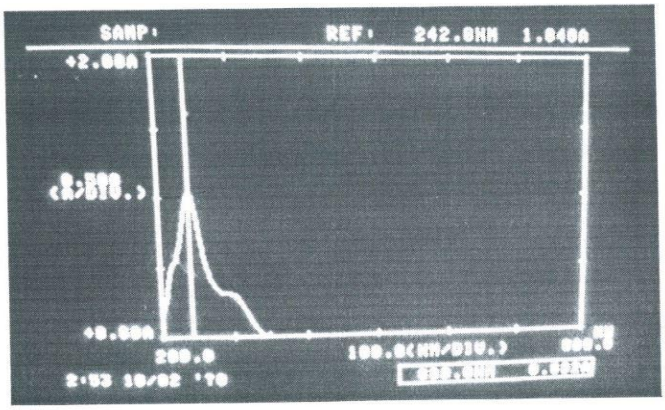


**Figure 2: Rosuvastatin calcium scanned in UV range (in phosphate buffer pH 6.8).**

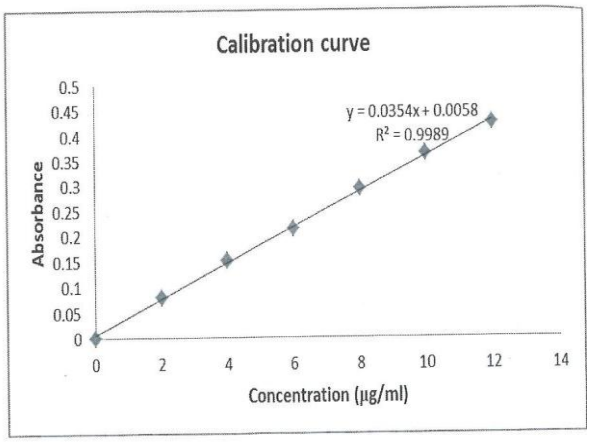


**Figure 3: Standard calibration curve of Rosuvastatin calcium**

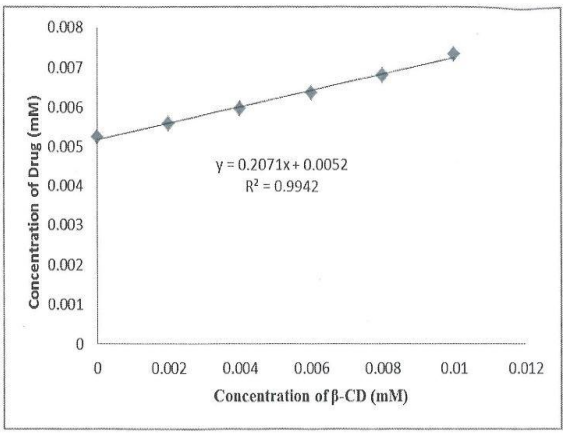


**Figure 4: Phase Solubility Diagram**

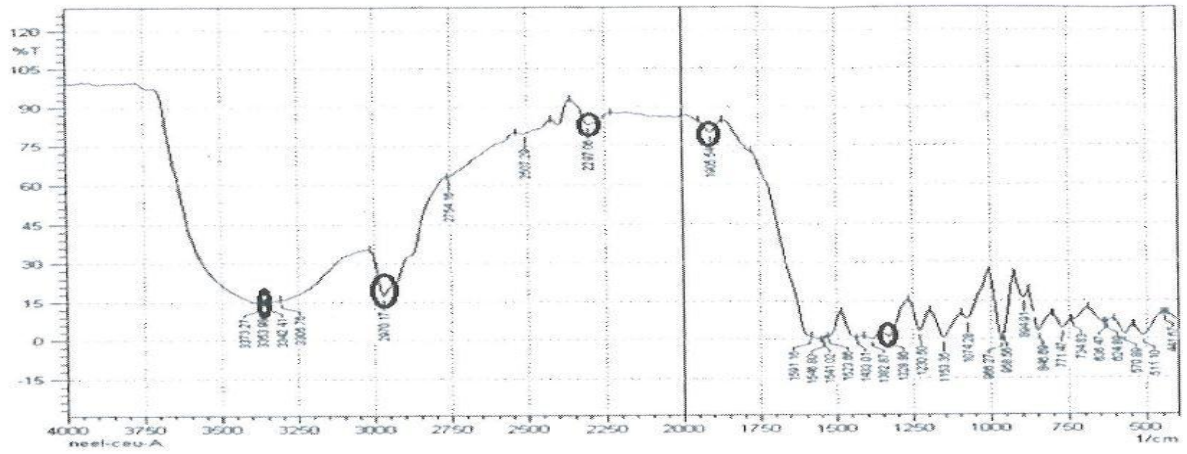


**Figure 5: FT – IR of Rosuvastatin Calcium.**

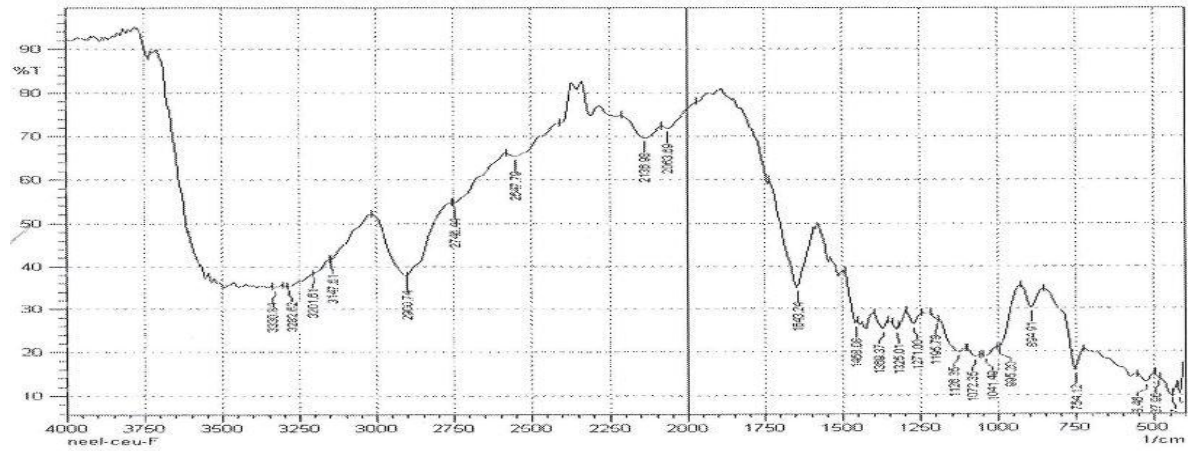


**Figure 6: FT – IR spectrum of drug complex and all excipients.**

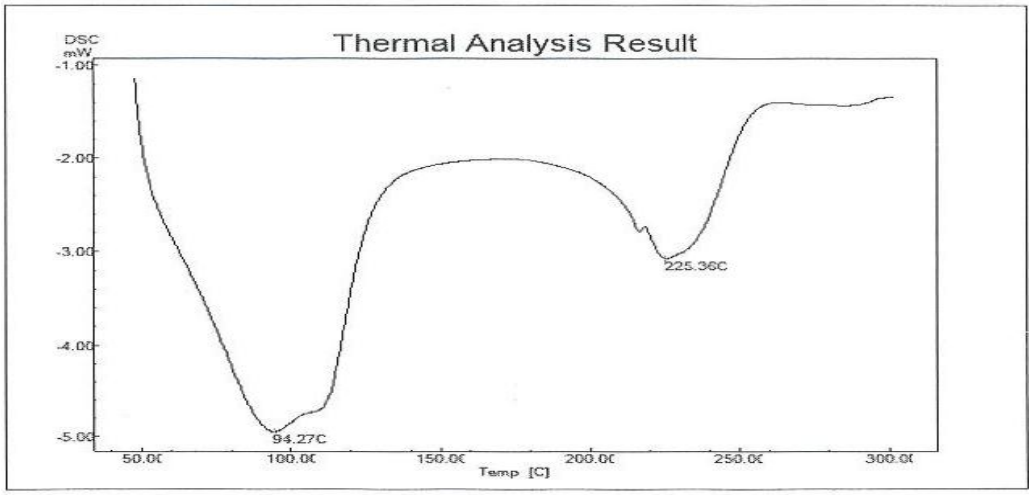


**Figure 7: DSC curve of drug-β-Cyclodextrin inclusion complex.**

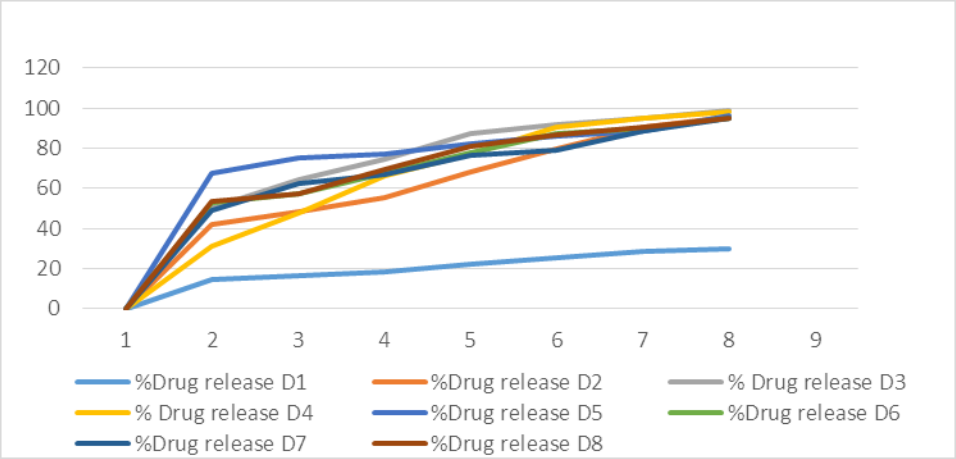


**Figure 8: Comparative dissolution profil inclusion complex.**

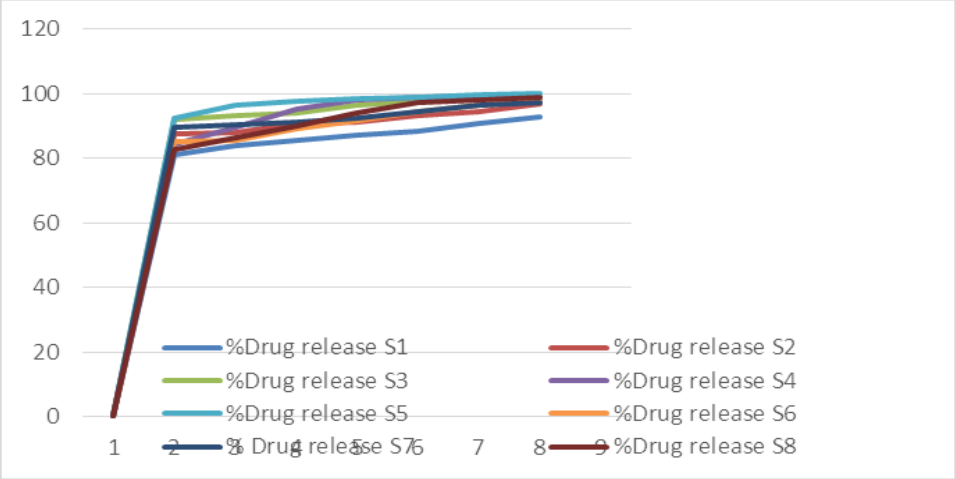


**Figure 9: Comparative dissolution profile of Batch S1-S8.**

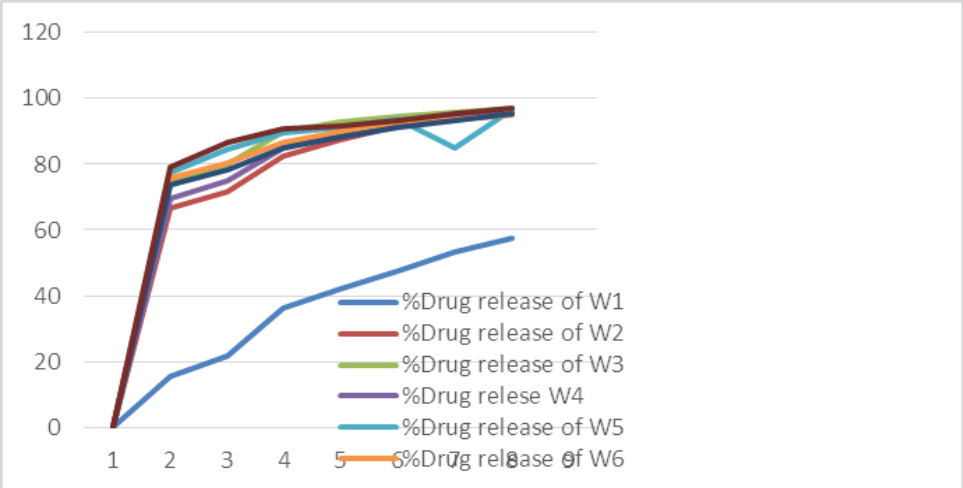


**Figure 10: Comparative dsoislution profile of batch W1-W8.**

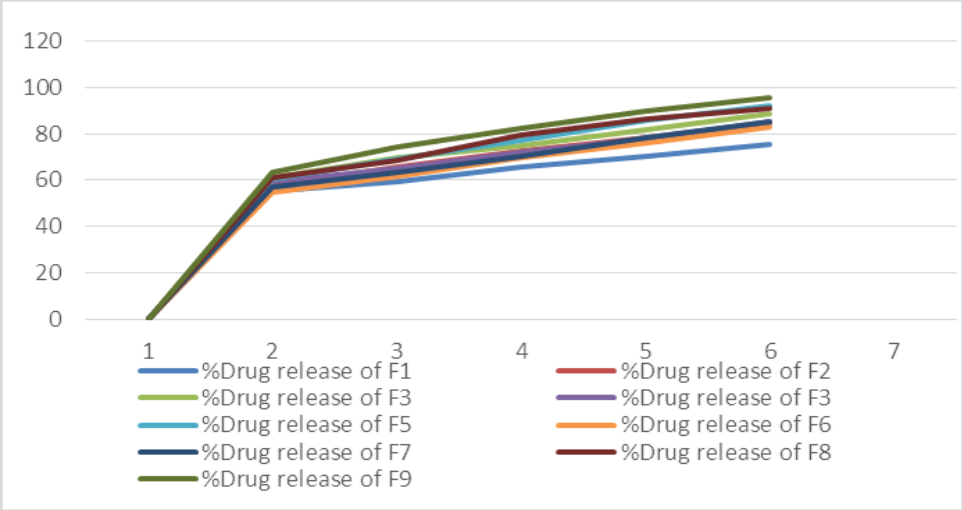


**Figure 11: Comparative dissolution profile of F1 to F9 batch.**

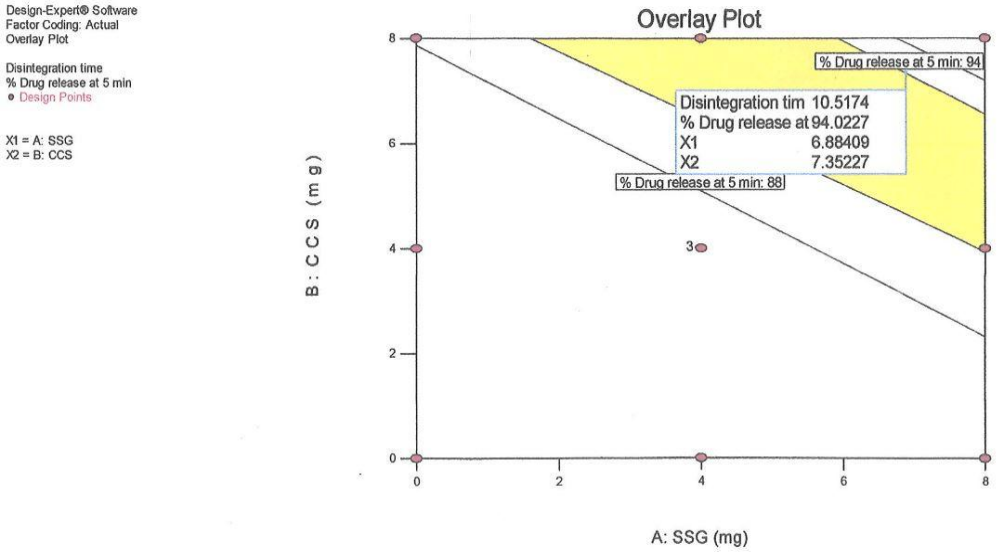


**Figure 12: Overly Plot of response variables.**

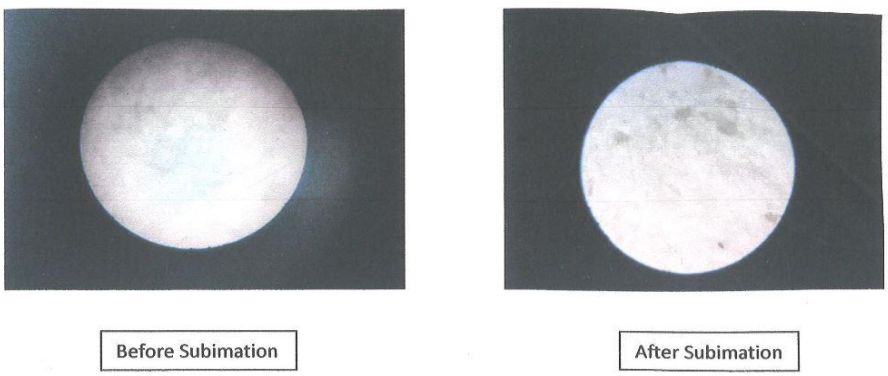


**Figure 13: Morphology of tablet before and after sublimation under microscope.**

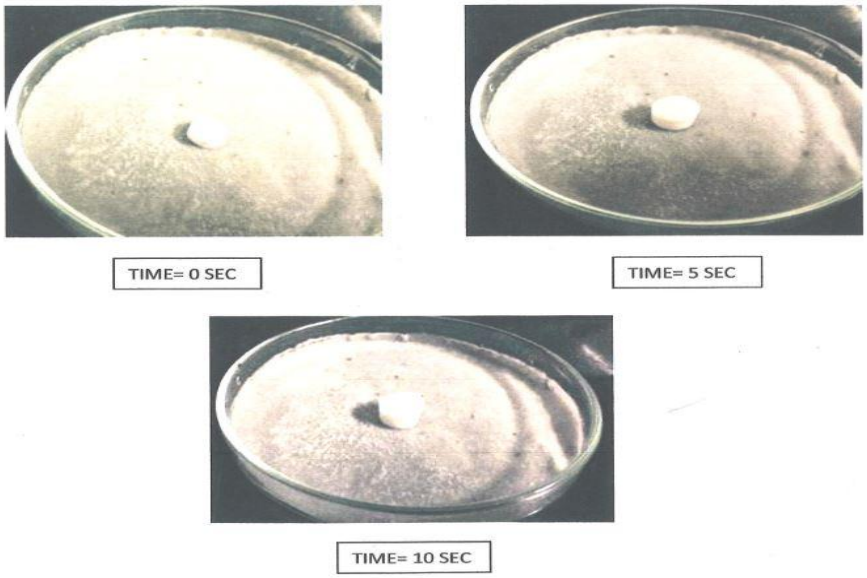


**Figure 14: Wetting time and water absorption by check poient batch tablets.**

## DISCUSSION

In previous, some experiments had been conducted systematically by some researchers for the formulation development of fast dissolving tablets of Rosuvastatin calcium. FDT of Rosuvastatin calcium of strengts 10 each were prepared by using direct compression methods with three supergisintegrants ,namely Croscarmellose sodium (CCS), Crosprovidone (CP) and Sodium starch glycolate(SSG). They have shown that friability affected significantly by the concentration of superdisintegrants and method of preparation. Combination of Crosprovidone (CP) and Sodium starch glycolate(SSG) showed least wetting ,disintegration and dispersion time. The tablet having Croscarmellose sodium (CCS) showed highest water absorption ratio.[31] The formulation containing 10% Crosprovidone (CP) and 5% Sodium starch glycolate(SSG)showed 55 sec disintegration time and greater rate of dissolution at 5 minutes which gave 99.89% drug release. Crosprovidone swell 4-10 folds in less than 10 seconds and has excellent swelling properties,on the other hand it showed lesser disintegration time than SSG. P.Muralidhar and his co-warkers have prepared mouth dissolving tablet of Rosuvastatin using natural superdisintegrants such as Banana powder, Plantago ovata mucilage powder and orange peel powder. The in vitro release studies showed that the formulation containing 7.5% Plantago ovata mucilage powder showed 97% of drug release at the end of 30 min and disintegrated within 15 sec due to its swelling.[32] Akbari et al prepared Rosuvastatin ODT by developing the solubilizind effect of HP-β-CD. Drug-CD complex were prepared by different techniques. The inclusion complex containing RST: HP-β-CD(1:1) was formulate into tablets using superdisntegrants namely SSG, CP and CCS by

direct compression and were evaluted. A significant improvement in the solubility of the drug was obtained due to the complex.[33] Bheemeshwara Rao k and his co-workers prepared immidiate release film-coted formulation of RSD using wet granulation, coating was done by fluid bed dryer. Different formulations were made by using a varying concentrstions of superdesintegrant Polyolasdone XL-10 and granulating fluids such as water, iso propyl alchol (IPA) Butyl hydroxy toluene (BHT) film coating was carried out using opadry pink 03K540019. The film coated RSD tablets showed best release profile.[34] P. Rohini and co-outhers had prepared14 tablets of Rosuvastatin calcium tablets using various superdisintegrants such as SSG, CCS, Ly coat Rs 720 and CP in different concentrations by direct compression technique. After evaluation it was reported that the formulation containing 8% superdisintegrant that is CP and SSG (1:1) gave 97% drug release in 5 minutes.[35] Netish Kumar Kundo and his colleagues made RSC tablets (10 mg) using various concentrations of crospovidone SSG, Kyron T-314 by wet granulation method among all, a tablet formulation contining 4.5% of CP gave 102.4% drug release in 30 minutes.[8]

In this work,step wise experiments were conducted to design and develop fast release tablets that disintegrate rapidly within the mouth with a view to improve ease of administration along with rapid onset action of time.

Prior to these trials, analystical method was developed. Here, the organoleptic characteristics of Rosuvastatin Calcium were fiest established. The melting point of Rosuvastatin caciulm was found to be 119 to 121$^0$C and visual observation was done on HPTLC plate, spot where obtained with Rf value 0.45 against the standard. This is shown in Figure 1.

In addition, standard calibration curve of rosuvastatin using UV spectroscopic measurements at maximum absorption 242nm (see Figure 2) in phosphate buffer pH 6.8 showed good reproducibility. This can be observed from the plotted calibration curve in Figure 3. This method was used in the study and the correlation coefficient for the standard curve was found to be closer to 1, at concentration range, 2 – 12µg/ml. Fourier Transform Infrared Spectroscopy shown in Figures 5 and 6 confirms good interaction between Rosuvastatin and superdisintegrants in the physical mixture. In order to set the baseline for our study for solubility, preliminary validation of phase solubility for Rosuvastatin Calcium was done by higuchi and connor's phase solubility studies as shown in Figure 4. As depicted from Figure 4, the slope value in diagram was less than 1, suggesting the formation of 1:1 M ratio complexes in solution. Successful complex formation by kneading method was achieved as

shown in Figure 7. Rosuvastatin calcium showed a endothermic peak at 119˚C corresponding to its melting range. The DSC of the drug complex showed diminished peak which confirms the complex formation. Table 1 show the selection criteria used for binder selection. The Polyvinylpyrrolidine (PVC) at concentration 10% (in PVA) showed better result and was selected for preparing further batches.

Infrared spectra of Rosuvastatin Calcium, drug complex and drug with other excipients were obtained using Fourier transform infrared (FTIR) spectroscopy. The –C=O stretching of COOH and CH stretching of aromatic group at 2970 $cm^{-1}$ and 3330 to 3360 $cm^{-1}$ respectively confirms the presence of drug without any interaction and the peaks at 1907 $cm^{-1}$, 2297-2300 $cm^{-1}$ 1328 $cm^{-1}$ show a major peaks of drug. All above peaks are also present in drug-excipient mixture, which shows about no drug-excipient incompatibility. While the FT-IR of drug complex showed change in major peak confirming formulation of inclusion complex.

**This was observed from**

Table 2,which shows comparison of direct compression, wet granulation and sublimation method. The batch D1 to D8 of the fast release tablets were prepared by direct compression using different combination of super-disintegrants. Batch S1 to S8 of fast release tablets were prepared by sublimation method using different combination of super-disintegrants while batch W1 to W8 were prepared by wet granulation method. Comparison of evaluation parameters such as wetting time, disintegration time and % drug release at 5min as depicted from Figures 8, 9,10, 11 showed that tablets prepared with sublimation methods were better compared to tablets prepared by direct compression and wet granulation, while % friability and hardness of the tablets prepared by wet granulation showed better results compared to that of sublimation method and direct compression. The data of disintegration time and % Drug release at 5 minute of tablets prepared by direct compression and wet granulation didnt show marked differences. However, introduction of sublimation agent in direct compression method increased the pore in tablets resulting in rapid disintegration time. Dissolution profile of tablets prepared by sublimation method in Figure 8 showed that the tablets with Crospovidone had least results and combination of other disintegrants with crospovidone produced less release. Hence further batches were prepared by sublimation method using Sodium Starch Gylcolate and Croscarmellose Sodium in combination employing $3^2$ factorial design.

A $3^2$ factorial design was adopted to predict an optimized formulation. Table 3 shows design layout and evaluation of factorial design batches. Nine batches were prepared as per the design layout and evaluated. From the dissolution profile of the tablets from batch F1 to F9 it can be interpreted that the F8 batch which consist of 8% Sodium starch glycolate and 4% Croscarmellose Sodium showed greater release of drug compared to other batches.

The evaluation data were tabulated as in Table 4. The values for angle of repose were found in the range of 26.54 to 29.69' and that of bulk densities and tapped densities of various formulations were found to be in the range of 0.52 to 0.62 (gm/cc) for pre-compression. Carr's index of the prepared blends was in the range of 14.17% to 17.31% and hausner's ratio in the range of 1.17 to 1.23 for pre-comression. From these findings it was confirmed that the parameters of the powder blends had good flow properties for further sublimation test analysis. Post-Compression parameters were tested and tabulated as shown in Figure 7. Hardness of all the nine batch were in the range of 3.1 to 3.65 ($kg/cm^2$) while friability loss was found to be between 0.54 and 0.74%. Other parameters such as water absorption ratio (%), wetting time (seconds), disintegration time (seconds) and % release T5 showed very good correlation in all batches. The drug content was found to be higher than 97.34%. From these results, hardness and friability loss confirmed significant mechanical strength of the tablets.

Coefficient with one factor represent the effect of that particular factor on responses while the coefficient with more than one factor and those with second order terms represent the interaction between those factors and the quadratic nature of the phenomena, respectively. Positive sign infront of the terms indicates synergistic effect while negative sign indicates antagonistic effect upon the responses. For response Y1 (disintegration time) reduced mathematical model was evolved omitting the insignificant terms ($p>0.05$) by adopting multiple regression analysis. The main effect X1, and X2 were found significant as P value was less than 0.05. For response Y2 (% Drug release at 5min) the main effect X1 and X2 were found significant as P value was less than 0.05 (table 5).

The optimization was performed using design expert 9.0.4 by superimposing the contour plots of the response Y1 and Y2 and locating the region of optimal surface common to both the plots as shown in figure 12. The overly plot of the responses generates an optimized area, as per desired criteria. The disintegration time (Y1) was set to less than 30 sec an % of drug release at 5 min (Y2) values in the range of 88 to 94%. These specifications satisfy the

requirements of an orodispersible tablet for rapid disintegration and sufficient mechanical strength. The overly plot of the responses generates an optimized area as per the desired criteria. The disintegration time (Y1) was set to less than 13 sec and % drug release at 5 min (Y2) values in the range of 88 to 94 %. These specifications satisfy the requirements of an orodispersible tablet for rapid disintegration and sufficient mechanical strength. It can be concluded that by adopting a systematic formulation approach, one can reach to an optimum point in the shortest time with minimum efforts. The study showing on table 6 about % compressibility, angle of (Θ) and Hausner's ratio of power blend showed good flow properties. The smaller value of angle of repose and Hausner's ratio indicates good flow properties.

The check point batch showed similar results as compared to the predicted values and therefore the validity of developed model was confirmed (table 7).

The comparison of Formulated Rosuvastatin calcium tablets were compared with marketed product crestor tablet (5mg) manufactured by Astrazeneca, Banglore, as shown in Table 8.

Volunteers in the age group of 20 to 25 years performed taste evaluation of Rosuvastatin fast release tablet. The study protocol was explained to each volunteer. Tablet containing drug equivalent to 5 mg of Rosuvastatin Calcium will held in the mouth for 15 seconds by each volunteer and then spit out. Bitterness level was recorded against pure drug as seen in Table.9. As depicted from table 9, all the volunteers reported pleasant mouth feel and none reported bitterness for the optimized formulation.

The average peak plasma concentration obtained for the drug and fast release tablet, indicated an increase in the extent of absorption (AUC) in Table 12. The decrease in the Tmax values indicated faster absorption from optimized formulation and increase in the Cmax values indicated higher attainable plasma drug concentrations with the same dose of the drug. The higher values of PK parameters (AUC, Cmax, and Tmax) showed enhancement in bioavailability of Rosuvastatin calcium by formulation fast dissolving tablet.

## CONCLUSION

Present work was design to develop fast release tablets that disintegrate rapidly within the oral cavity hence improving an ease of administration along with rapid onset action of time. Out of a variety of approaches used to formulate fast release tablets, direct compression and

sublimation utilized with Rosuvastatin calcium. This drug was chosen as it was considered being more effective than traditional statins for the treatment of hypercholesterolemia. Further, the drug was complexed with β-cyclodextrin to enhance solubility, which was evaluated by higuchi and connor's phase solubility studies. Sublimation method showed the best results among all methods employed with the use of croscermellose sodium and sodium starch glycolate and camphor. A 32 full factorial design was employed to create an optimized batch (F10) which in turn showed disintegration time 11 second and 93.68 % drug release at 5 minutes. It was concluded from our study that drug complex can be used to increase the solubility and sublimation method can be employed to produce fast release tablets of Rosuvastatin calcium. It was also confirmed in this study that the amount of superdisintegrates can be optimized using a factorial design.

## ABBREVIATIONS

%=percentage,Min=Minute,Sec=Second,Mg=Milligram,Ml=Milliliter,µg=Microgram, Mm=Millimeter,$\lambda_{max}$=Wavelength of maximum absorbance, ˚C=Degree Celsius, Conc=Concentration, Abs.=Absorbance, Temp=Temperature, Ɵ=Angle of repose, $D_b$=Bulk density, $D_t$=Tapped density,CI= Compressibility index, H=Hausner's ratio,DC=Directly compressed, MCC=Microcrystalline cellulose, SD=Standard deviation, %DR=Percentage of drug release, RH=Relative Humidity, RPM=Rotation Per Minute, BCS=Biopharmaceutics Classification System, DSC=Differential Scanning Calorimetry, UV=Ultra Violet, FTIR= Fourier transform Infra-red spectroscopy, ODT=Oral-dispersible tablet, CAS=Chemical Abstract Service,AUC=Area under curve, MDT=Mean dissolution time, MAT=Mean absorption time, CP=Crospovidone, SSG=Sodium Starch Glycolate, CCS=Croscarmellose sodium, IPA=Isopropyl alcohol, BHT=Butyl hydroxyl toluene, RSC=Rosuvastatin Calcium, SNEDDS=Self emulsifying drug delivery system.

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