Research article

Formulation, development and evaluation of immediate release rosuvastatin calcium tablet

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ABSTRACT

Rosuvastatin belongs to the statin medication class, which is used to treat excessive cholesterol and prevent heart disease. The Biopharmaceutical Classification System classifies it as class II. The goal of this project is to create 10 mg Rosuvastatin instant release pills using several types of materials. To boost the drug's bioavailability, superdisintegrants were used to speed up the disintegration and dissolution of Rosuvastatin calcium. Cited research work aims to formulate an immediate release tablet of Rosuvastatin for the treatment of hypercholesterolemia, hyperlipoproteinemia, and atherosclerosis. The present work used a cost-effective wet granulation process to create an immediate release formulation of Rosuvastatin calcium. All of the batches were manufactured, and the granules were evaluated for pre-compression properties such as loss on drying, bulk density, tapped density, and compressibility index. Disintegration time and assay were determined to be within acceptable parameters, as were weight fluctuation, thickness, hardness, and friability of tablets. The effect of several superdisintegrants on in vitro dissolutions in 6.8 PH phosphate buffer was investigated. The final formulation was chosen based on the dissolution profile; dissolution studies revealed that formulations F2 and F4 released 80 percent of the medication within 15 minutes. Two different formulations of Rosuvastatin Calcium 5.199 and 10.398 mg employing immediate-release tablets were successfully generated using Crospovidone, Meglumine, and Comprecel 112D+. The tablets showed complete drug release in 60 minutes and fair flow characteristics when compared to the innovators' product.

Keywords: Immediate-release tablets, Rosuvastatin, Dissolution, Film coating tablets

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INTRODUCTION

Drug substances are rarely given alone. They are administered or provided as part of a formulation with one or more non-medicinal ingredients. Physical, chemical, and biological aspects must all be considered when designing and formulating a dosage form. The majority of medication compounds are given in milligram doses, which are much too small to be weighed with anything other than a sensitive prescription scale or an automated analytical balance. There is various type of dosage form according to the route of administration. There are orals, topical, parenteral, etc. out of this oral route is most preferably used [1].

A tablet is a pharmaceutical dosage form made up of a mixture of active ingredients that are usually powdered and crushed or compacted into a solid. It is the most common dose form, with tablets accounting for 70% of all medicines prescribed. According to the Indian Pharmacopoeia, it is a compressed solid dosage form containing drug or drugs in combination. A tablet should have a stylish design and be devoid of flaws such as chips, cracks, and discoloration. It should be strong enough to endure mechanical shock during the packaging process. They are unit dosage forms with the broadest range of capabilities of any oral dosage form. Two classes of drugs are administered orally in a tablet dosage form [2]. To make the best tablets, it's crucial to use the right excipients. In dosage forms such as tablets and capsules, excipients determine the weight of the finished product. The rate of disintegration, dissolution/release of the medicine, moisture protection, and storage stability are all key aspects in the medicine's stability and effectiveness. Two major classifications of additives by function include those which affect the tablet and those which do not. The primary purpose of the granulation using the direct compression method is to produce a free-flowing and compressible flow. A liquid is added to a powder in a vessel during the wet granulation process, and moisture may be present if the powder is not dried properly and correctly. Dry granulation has a
long history and can be an effective tool in the correct scenario. The wet granulation technique uses the same preparation and finishing operations (screening or screening or mixing) as the two previous granulation techniques. For more than 150 years, coatings on the surface of medicinal solid-dose forms have been employed. Coating technologies are still widely used in the pharmaceutical manufacturing industry [3].

The film coating process comprises covering a suitable substrate with thin polymer-based coatings. It's possible to utilize a continuous film or a physical deposition of the coating material on the tablet substrate. An ideal film coating material should have the following characteristics: free water solubility, gradual water solubility, and the ability to generate a beautiful result. A variety of polymers have been investigated for use in film coating. To dissolve or disperse the polymers or other additives used in drug delivery before delivering them to the surface substrate is the main function of a solvent system. Water, ethanol, and other chemicals are the most commonly used solvents, either alone or in combination. Plasticizers are essential for polymeric film coatings to function properly. Aqueous latex dispersions have a one-of-a-kind film-forming mechanism. During subsequent evaporation, the residual water is squeezed out, and the latex particles flow together and solidify to form a homogeneous film. Due to inadequate film development, individual latex particles may be visible in a densely packed configuration. There may be variations in the permeability and dissolution rate profile throughout this time. The term "continuous" refers to the bulk of today's film-coating processes. Layers make up the majority of film coatings [4].

Cholesterol, triglycerides, and phospholipids are the body's major lipids. Abnormal plasma lipids can increase the risk of coronary, cerebrovascular, and peripheral vascular artery disease. The liver secretes very-low-density lipoproteins (VLDL) into the bloodstream, which are mostly triglycerides (TGs) and some cholesteryl esters (CHE). The CHE is deposited in atheromas and xanthomas. LDL circulates in plasma for a long time, and the need for cholesterol to be released into the bloodstream or removed in the bile as cholesterol/bile determines its uptake into the liver and other tissues. VLDL is acted upon by endothelial cells which take back half of the immediate density lipoprotein (IDL) and the other half is taken back by liver cells [5-6].

The goal of the stated research is to prepare and evaluate a rosuvastatin film-coated tablet for the treatment of hypercholesterolemia, hyper-lipoproteinemia, and atherosclerosis. In this research work, a formulated dosage forms are compared with innovator formulation. Stability testing of optimized formula according to ICH was also been performed. The prepared tablets contain 5 mg and 10 mg of active drug.

**MATERIALS AND METHODS**

Rosuvastatin Calcium was a gift sample from Zydus Cadila Healthcare Limited, Mumbai. All the chemicals and reagents including Lactose Monohydrate USP (DMV Fontera), Microcrystalline Cellulose Comprecel 102+® (Migniti Chemical Co. Ltd.), Crospovidone USP (BASF South East Asia Pvt. Ltd.), Meglumine USP ((BASF South East Asia Pvt. Ltd.), The Magnesium Stearate USP (MallinKrott) utilized in this research was an analytical grade. All the working chemicals and reagents were kept in suitable storage conditions.

Direct compression was used to make immediate-release tablets of Rosuvastatin utilizing different concentrations of Crospovidone, Meglumine, and Comprecel 102+® in different combinations utilizing a 32-factorial design. The concentrations of these excipients required to achieve the desired drug release were chosen as independent variables.

**Drug- Excipient Compatibility Study**

Compatibility studies were carried out to investigate and predict physicochemical interactions between drug substance and excipients by creating compatibility blends with different excipient-to-drug ratios based on a tentative average weight. For a month, these mixtures were kept at 40°C with a relative humidity of 75%. The drug-to-excipient ratio is used in the range of 1:1 to 1:10. The samples were compared to a control sample kept at 40°C for 7, 14, and 30 days to check any physical properties had changed. The most powerful way for finding drug functional groups is FTIR spectrometry, which determines chemical compatibility. The potassium bromide disc (pellet) method was used in this investigation [7-8].

**Evaluation of Flow properties of Prepared Granules**

**Angle of repose**

The angle of repose of API powder was determined using the funnel method. The angle of repose is the maximum angle that can be achieved between the surface of a pile of powder and the horizontal plane [9]. The funnel was filled with the precisely weighed powder combination. The height of the funnel has been adjusted to 2.5 cm above the surface level. Allow for free flow of the powder mixture through the funnel and onto the surface. The powder cone's diameter is measured, and the process is repeated three times, yielding an average value [10].

The equation is used to calculate the angle of repose:

$$\text{Angle of Repose (θ)} = \tan^{-1}\left(\frac{h}{r}\right)$$

Where, $h = \text{height of pile}$, $r = \text{radius of the base of the pile}$, and $θ = \text{angle of repose}$. 
Bulk density determination

The bulk density of a substance is the mass to volume ratio of an untapped powder sample (including inter particulate void volume). The powder (W) is weighed and placed in a graduated measuring cylinder, which is used to determine the volume (V₀). The formula used to compute bulk density is given below:

\[ \text{Bulk density (BD)} = \frac{W}{V₀} \]

Where, \( W \) = Weight of powder,
\( V₀ \) = Volume of powder.

Tapped density determination

Mechanically tapping a graduated cylinder carrying the sample until minimal more volume change is noticed yields the tapped density. The powder sample equal to 25 gms under examination was screened via sieve No.18, and a 100 mL graduated cylinder was filled with the weight of the sample. The mechanical tapping of the cylinder was done at a nominal rate 500 times using a tapped density tester, and the tapped volume \( V_f \) was recorded. \( V_f \) is tapped volume when the difference between two tapping volumes is less than 2%. The tapped density, Hausner’s ratio, and Carr’s Index were calculated using the blend volume. The unit of bulk density and tapped density is g/ml.

The formula used to calculate tapped density is given below:

\[ \text{Tapped density (TD)} = \left( \frac{W}{V_f} \right) \]

Where, \( W \) = Weight of powder,
\( V_f \) = Volume of powder.

Carr’s index

Compressibility is a term used to describe Carr’s index. It’s a measure of the powder’s compressibility. It is indirectly connected to relative flow rate, cohesiveness, and particle size.

The formula for calculating Carr’s index was:

\[ \text{Carr’s Index (%) = } \left( \frac{\text{Tapped Density} - \text{Bulk Density}}{\text{Tapped Density}} \right) \times 100 \]

Hausner’s ratio

The ratio of tapped density to bulk density is used to calculate Hausner’s ratio, which reveals the flow qualities of the powder.

\[ \text{Hausner’s Ratio} = \frac{\text{Tapped density}}{\text{Bulk density}} \]

Preparation of Rosuvastatin Calcium Tablets

Rosuvastatin Calcium, Crospovidone, MCC (Comprecel 112D+®), Meglumine and Lactose Monohydrate was co-sifted through # 40 sieve. Blended for 15 minutes with the sifted material in the double cone blender. Sift magnesium stearate through sieve 60 # and lubricate above blend for 3 minutes in a blender. A 12-station rotary tablet machine with an 8-mm flat punch and B tooling was used to compress the mixture \(^{[11]}\). As stated in Table 1, each tablet includes 5.199 or 10.398 mg Rosuvastatin calcium equivalent to 10 mg Rosuvastatin, as well as additional medicinal components.

| Ingredient (mg)       | F1     | F2     | F3     | F4     |
|-----------------------|--------|--------|--------|--------|
| Rosuvastatin Calcium  | 5.199  | 5.199  | 10.398 | 10.398 |
| Crospovidone          | 7.5    | 3.75   | 3.75   | 7.5    |
| Meglumine             | 3      | 3      | 3      | 3      |
| Comprecel 02+®        | 31     | 31     | 31     | 31     |
| Lactose Monohydrate   | 101.801| 105.551| 99.972 | 96.602 |
| Magnesium Stearate    | 1.5    | 1.5    | 1.88   | 1.5    |
| Average Wt. (mg)      | 150    | 150    | 150    | 150    |

Composition of film coating and preparation of film-coated tablets

Opadry II Pink® and Opadry II Yellow® coating solutions were used to coat direct compression tablets, and the weight of each tablet was allowed to increase by 5 mg using these coating solutions as shown in table 2 \(^{[12]}\).

| Ingredient (mg)       | Std. (qty./tabl.) mg |
|-----------------------|----------------------|
| Core Tablet 5 mg      | 150                  |
| Core Tablet 10 mg     | 150                  |
| Opadry II Pink®       | 5                    |
| Opadry II Yellow®     | 5                    |
| Water                 | 45                   |
| Average Wt. (mg)      | 155                  |

Coating parameter

Weighed quantities of Opadry II pink® or Opadry II yellow® was added in water under continuous stirring for 15-20 min. The tablets were loaded in a pan and start the coating. Continue the process till the tablet weight is gained by 5 mg/tablet.

The tablets were coated using Neo Cota. With inlet temperature 55-57°C, bed temperature 38-40°C and exhaust temperature 35-37°C. The pan speed was kept 5rpm with a spray rate of 1gm/min, a tube used in the coating machine was 1 mm with a 0.8 mm gun. The actual weight of each tablet (prepared using direct compression method) was 150 mg and the target weight (after coating) was expected to 155 mg. Tablet de-dusting time was 1 min.

The coated tablets were dried for 10-15 minutes at 55°C inlet temperature. A Vernier caliper (Mitutoyo 500-196-30-Advanced) was used to measure the thickness of the tablets, and average values were calculated using 20 tablets from each batch.

Evaluation of Uncoated Tablets

Thickness

A Vernier caliper (Mitutoyo 500-196-30-Advanced) was used to measure the thickness of the tablets, and average values were calculated using 20 tablets from each batch.

Weight uniformity

Each pill in a batch should be the same weight, and weight deviations should be within the pharmacopeia’s authorized acceptable range. A Mettler Toledo AB analytical balance, model AB104-S, was used to determine weight uniformity. The weight variation was determined using a sample of ten pills.

Hardness

The strength of the tablet is determined by its hardness. A hardness tester (Erweka, TBH 425) was used to determine the hardness of 10 tablets from each batch.
Friability

A friability test equipment was used to determine the friability of 10 tablets for each formulation (Electrolab, EF-2W).

Disintegration

The disintegration test was conducted using the disintegration tester (Electrolab, ED-2L), which consists of a basket rack comprising six plastic tubes that are open at the top and covered at the bottom with a 10-mesh screen. A 37°C bath of adequate liquid, preferably a 1L beaker, is used to submerge the basket [14].

In-vitro dissolution test

The Electro lab apparatus II was used to conduct dissolution tests on the manufactured tablets. Dissolution was carried out in 900 mL of pH 6.8 phosphate buffer at 37±0.5°C and 100 rpm. The dissolving apparatus was coupled to an auto sampler (UV spectrophotometer Shimadzu, UV1900i) that was configured to remove and replenish 10 ml of the dissolution media at 0, 5, 10, 15, and 30 minutes. When measured at 242 nm, around 80% of the medication should be released within 15 minutes.

A 900 mL phosphate buffer solution with a pH of 6.8 is employed as a dissolving media. A Type II USP (Paddle type) apparatus was used with 900 cc of dissolving solution and a rotation speed of 75 rpm at a temperature of 37 ±0.5°C [15].

Drug Release Kinetics (Dependent Model Method)

The drug release kinetics is controlled by one or more mechanisms that are dependent on the matrix composition, shape, production process, and drug release dissolution media. This can be explained using mathematical models based on the model's desired or required forecasting capacity and accuracy [16].

Stability testing for selected formulations

Drug stability refers to a formulation's capacity to stay within its physical, chemical, therapeutic, and toxicological parameters while in a certain container. Stability testing enables prescribed storage settings, retest periods, and shelf lives to be specified by revealing how the quality of a drug substance or drug product varies over time as a result of various environmental factors such as temperature, humidity, and light.

The standards for stability testing of novel drug products are specified by the FDA and ICH as a technical prerequisite for the registration of pharmaceuticals for human use. The main goal of the stability study is to assess the stability of the optimized formulation at various temperatures and humidity levels [17].

RESULTS AND DISCUSSION

Pre-formulation studies

Drug were tested for various parameters in pre-formulation studies including description, solubility, loss on drying, melting point, water content by Karl Fisher method, Drug identification, and λmax identification. The pre-formulation parameters including description, solubility, loss on drying, melting point, water content, drug identification and identification of λmax were performed and checked against certificate of analysis issued by supplier and was found to be satisfactory when compared with Pharmacopoeial standards.

Drug-excipient interaction

According to the drug-excipient compatibility analysis, the chosen excipients are compatible with the drug, when samples were tested in 1:1 to 1:10 ratio.

Evaluation of Granules

Angle of repose, bulk density, tapped density, compressibility index, and Hausner's ratio were all measured in the granules of all formulations. The evaluation parameters are summarized in Table 3. All of these findings show that the granules are free-flowing.

In-process Quality Control Tests for uncoated tablets

The average weight of the tablets was revealed to be between 149.710.47 and 151.470.61 mg. 3.610.37 to 3.700.54 mm in thickness, 4.870.42 to 6.170.85 kPa in hardness, and 0.003 to 0.08 percent in friability the disintegration time of the pills was discovered to be between 40 and 55 seconds. All these parameters are summarized in table 6. The drug release was found in the range of 95.47 to 102.13%, performed using dissolution test (as mentioned in table 4). All formulations have a consistent thickness, the tablet hardness was satisfactory, and the percentage friability for all formulations was less than 1%, indicating that friability was within the acceptable range. Within batches of various tablet formulations, good and homogeneous drug content (>95%) was observed.

In-process Quality Control Tests for coated tablets

The research work aimed to match the dissolution profile with that of the innovator products. Aliquots were collected and analyzed for drug release at various time intervals viz. 0, 5, 10, 15, 20, 30, 45 and 60 minutes.

Table 5, shows drug release from prepared formulations F1, F2, F3, F4, and innovator products.

In Innovative Tablets

A comparative dissolution profile of formulation batch F1, F2, F3, F4, and innovator products is shown in figure 1.
Drug Release Kinetics (Dependent Model Method)

Mathematical models are used to investigate the kinetics and mechanism of drug release from tablets. Based on the correlation coefficient (r) value, many models choose the model that best fits the release data. The model with the highest "r" value is thought to be the most accurate match for the publicly available data. The mathematical models are the zero-order release model, first-order release model, Hixson-Crowell release model, Higuchi's release model, and Korsmeyer-Peppas release model. Table 6 shows the kinetics and mechanisms of drug release.

Table 6: Drug Release Kinetics using various mathematical models

| Formulation | Correlation coefficient | K Value (mg/hr) |
|-------------|-------------------------|-----------------|
|             | Zero-order  | First-order  | Hixson-Crowell | Higuchi  | Peppas  |               |
| F1          | 0.9253      | 0.9984       | 0.8741         | 0.8624   | 0.9878  | 2.89          |
| F2          | 0.9132      | 0.9949       | 0.8687         | 0.8832   | 0.9881  | 3.14          |
| F3          | 0.9214      | 0.9897       | 0.8836         | 0.8924   | 0.9869  | 3.11          |
| F4          | 0.9421      | 0.9947       | 0.8728         | 0.8742   | 0.9783  | 3.17          |
| Innovator   | 0.9327      | 0.9941       | 0.8921         | 0.8973   | 0.9878  | 3.03          |

Stability Testing

Stability testing was performed on the formulations as per ICH recommendations. During the study time, the tablets did not display any physical alterations, such as color change, friability, or hardness. After 30 days, the drug content was found to be above 97 percent. This suggests that the formulations were rather stable under rapid storage. However, it will take two years to establish the produced product in real-time for stability tests.

The drug-excipient interaction investigation revealed that all selected excipients are compatible with the medicine and their presence has no effect on Rosuvastatin efficacy. For the formulation of Rosuvastatin instant release tablets using the direct compression method, to make Rosuvastatin formulation more cost-effective.

CONCLUSION

Using Crospovidone, Meglumine, and Comprigel 112D®®, several trials of Rosuvastatin Calcium 5.199 and 10.398 mg using immediate-release tablets were effectively created.

Pharmacopoeial and non-Pharmacopoeial testing were performed on the pills. According to the findings, F2 was found to be the best formulation for 5 mg strength, and F4 was shown to be the best formulation for 10 mg strength among all Rosuvastatin Calcium formulations. The results were good when a reproducible batch formula of 5 mg strength was applied to a 10 mg strength of Rosuvastatin Calcium.

When compared to the innovators’ product, the formulations (F2 and F4) showed entire drug release in 60 minutes and fair flow characteristics. The formulations F2 and F4 follow first-order kinetics, and the Korsmeyer-Peppas exponential coefficient 'n' > 1 suggests that Super case II transport was responsible for the release.

CONFLICT OF INTEREST

The authors have no conflicts of interest regarding this investigation.

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