WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.453
Volume 13, Issue 13, 1549-1582. Research Article ISSN 2277–7105

ROSUVASTATIN CALCIUM-EXCIPIENT COMPATIBILITY STUDIES FOR ADVANCED DRUG DELIVERY SYSTEMS DEVELOPMENT

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Article Received on
30 May 2024,

Revised on 20 June 2024,
Accepted on 01 July 2024

DOI: 10.20959/wjpr202413-33126

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ABSTRACT

The safety, efficacy, quality and stability of a formulation are major concepts of any API development process. In API development process, a detailed characterization of the API and other formulation components is usually carried out during the preformulation stage. The main objective of the present study was to the preformulation studies were performed to know the physico-chemical and mechanical properties of Rosuvastatin calcium for formulation development of FDTs. The drug-excipient compatibility studies were conducted to characterize the drug Rosuvastatin present in Fast Dissolving Drug Delivery System FDDs. Preformulation, formulation and evaluation of Rosuvastatin to avoid problems associated with conventional delivery system such as limited permeation, low dissolution and bioavailability and also to improve bioavailability and hypocholesteremic effect in blood vessels. In the present study that the compatibility was assessed by, FTIR spectroscopy, and melting point apparatus, precompression parameters and powder flow properties. Results showed that physical

mixtures of Rosuvastatin calcium and various excipients as mannitol, microcrystalline cellulose as diluents, and sodium starch glycolate, croscarmellose sodium, and crospovidone as superdisintegrants and PEG6000, tween80 and sodium lauryl sulfate as wetting agents were evaluated for preformulation studies parameters. It was concluded that the drug Rosuvastatin calcium was found to be compatible with various excipients which were selected for the formulation development of the Rosuvastatin calcium FDTs. Formulation scientist from his experience and knowledge have to significantly in the preformulation study stage and is an important factor in the ADDS (Advanced Drug Delivery Systems) product development process.

KEYWORDS: Rosuvastatin calcium, Compatibility, Excipients, Development, Superdisintegrants, Preformulation, Formulation.

INTRODUCTION

Pre-formulation Studies[1-100]

The safety, efficacy, quality and stability of a formulation are major concepts of any API development process. In API development process, a detailed characterization of the API and other formulation components is usually carried out during the preformulation stage. Formulation scientist from his experience and knowledge have to significantly in the preformulation study stage and is an important factor in the ADDS (Advanced Drug Delivery Systems) product development process.

One of the objectives of this study is to development of drug delivery systems by building scientific pharmaceutical research information depend on formulation scientists to join the knowledge and experience as well as experimental and practical results of this study with regard to information in previous studies, and approved references. It was found to be that the most important concepts and basics of preformulation studies such as definitions, methods, conclusion, idea, and types of pharmaceutical analysis techniques using in evaluation of preformulation studies parameters, in this study that we focused on developing drug delivery systems and linking the formulation development to establish the basics of pharmaceutical research in studying the drug-excipient compatibility, dug with various excipients, which is important for the safety, effectiveness, quality, formulation, stability, bioavailability, and pharmacokinetics of the drug etc.

Preformulation research were evolved in 1950. It is defined as the phase of research and development in which preformulation studies characterize physical and chemical properties of a drug molecule in order to develop safe, effective, bioavailability and stable dosage form. In preformulation studies, physicochemical properties of drug molecules are characterized either alone or in combination with excipients. Preformulation is the first step in the rational formulation of an active pharmaceutical ingredient (API).

Preformulation Study Includes: Determination of physical chemical properties of API substance with the goal of developing a new drug which is safe stable and efficacious, each API, has intrinsic chemical and physical properties that were considered prior to the development of pharmaceutical formulation, the purpose of preformulation study is to generate useful information for the formulator in the development of stable and bioavailable dosage form, inappropriate preformulation study results in poor stability of active ingredients increase the overall cost of development and increased development time, preformulation studies help to fortify the pharmaceutical scientific foundation of the guidance, provide regulatory relief and conserve resources in the drug development and evaluation process, enhance public safety standards, improve product quality, promote the implementation of new technologies, aids policy development and regulatory decision making and after compiling all data it is transferred to the development pharmacist and for the day work on formulation of dosage form.

Table 1: Biopharmaceutical Classification System (BCS).

BCS -Class	Solubility	Permeability
Class-I	High	High
Class-II	Low	High
Class-III	High	Low
Class-IV	Low	Low

Preformulation Study Objectives: To establish the Physico-chemical parameters of a new API entity, determine its kinetics and stability, establish its compatibility with common excipients, it provides insights into how drug products should be processed and stored to ensure their quality, estimate problem may arise during formulation that is stability problem poor *in-vivo* dissolution, poor bioavailability, to interpret BCS classification of drugs and its significance and develop optimal drug delivery system. As shown in Table 1.

Drug-Excipient Compatibility Study: The primary objective of this investigation was to identify a stable storage condition for API in solid state and identification of compatible

excipients for its formulation. Incompatibilities are major concerns in formulation development. Selection of the proper excipient during preformulation studies is of prime importance.

Dosage Forms: DF contain API and pharmaceutical excipients, which are intended to generate an ideal formulation and manufacturability of pharmaceutical products, thereby enabling a much safer and more effective administration. Pharmaceutical excipients are ideally inactive and have no impact on the stability or therapeutic effect of the active ingredient. On the other hand, there are studies that have presented that some pharmaceutical excipients are just allegedly described as inactive ingredient. Some pharmaceutical excipients have the capacity to affect API, efficacy by affecting its pharmacokinetics. Excipients can affect the physical and chemical form of pharmaceuticals by several factors such as hydrogen bond interaction, polymorphic conversion, and others. Accordingly, drug-excipient compatibility should be conducted so as to determine any drug-excipient interactions that may obstruct the stability, bioavailability, and manufacturability of pharmaceutical dosage forms.

Importance of Drug-Excipient Compatibility

Studies of active pharmaceutical ingredient (API)-excipient compatibility represent an important study in the preformulation stage of the development of new dosage forms, stability of the dosage form can be maximized, any physical or chemical interaction between API, and excipient can affect bioavailability and stability of drug, it helps to avoid the surprise problem, by performing drug excipient compatibility studies (DECS) we can know the possible reaction before formulating final dosage form, DECS data is essential for IND (investigational new drug) submission, and now, USFDA has made it compulsory to submit DECS data for any new coming formulation before its approval.

The potential physical and chemical interactions between an API, and the excipients can affect the chemical nature, the stability and bioavailability of the former and, consequently, its therapeutic efficacy and safety, solid dosage forms are generally less stable than their API components and despite the importance of API-excipient compatibility testing, there is no universally accepted protocol to assess such interactions.

Pharmaceutical Excipients: Excipients are additive substances used to improve the bulkiness, disintegration, dissolution rate, and bioavailability of a formulation etc. Different dosage

forms like powders, granules, capsules, tablets, oral liquids, injectable products, implants, eye products, nasal products, inhalers, topical creams, ointments, gels, transdermal patches and suppositories etc, contains different types of excipients. To make it acceptable and compatible various pharmaceutical excipients are added in pharmaceutical dosage form for their direct therapeutic action, manufacturing process, to protect, support or enhance stability, for bioavailability or patient compliance. These must be physiologically and chemically stable, must not have any incompatibility with the API, and must meet the standards of regulatory requirements.

Evaluation of Drug-Excipient Compatibility

The compatibility study of API and excipients is important to predict the stability of the API, in the final pharmaceutical product. It's the first time that API was compatible with excipients promoted physical and chemical compatibility studies was achieved by thermal and non-thermal methods. As a part of preformulation study, a compatibility study of API with the other excipients was carried out using physical blends in analytical techniques for the evaluation of drug-excipient interactions. The most commonly used pharmaceutical analytical techniques include, thermal techniques such as Differential Scanning Calorimetry (DSC), Thermogravimetric Analysis (TGA), Isothermal Microcalorimetry (IMC) and Hot stage microscopy (HSM) etc, and non-thermal techniques such as UV-Visible Spectrophotometric (UV), Infrared, Near-Infrared and Raman Spectroscopy (FT-IR), (NIR), Powder *X*-Ray Diffraction (PXRD), Solid-State Nuclear Magnetic Resonance Spectroscopy (ssNMR), Microscopic techniques: Scanning Electron Microscopy (SEM), Chromatographic techniques: Thin Layer Chromatography (TLC), and High-Performance Liquid Chromatography (HPLC) etc.

Preformulation Parameters: According to dosage form of API, mainly solid state, particle size, shape, pKa, pH determination, common ion effect, temperature, partition coefficient, solubility studies, dissolution rate, melting point, powder flow properties, crystallinity, polymorphism, hygroscopicity, stability study and drug-excipient compatibility etc. While other dosage forms according to important of preformulation parameters used in study before start in development of formulation.

Drug-excipient compatibility and formulation stability is not depended on API only but also its affected by excipient. Excipient play important role in dosage form but side by side it also increases compatibility problem so proper selection of excipient is very important in

development of formulation. Incompatibility can be result mainly in any of following changes: Changes in organoleptic properties, changes in dissolution performance, decrease in potency, and increase in degradation rate etc.

Drug excipient physicochemical characterization is a systematic approach towards design of therapeutically active and stable dosage forms. The rapid advancements in novel drug delivery systems development have led to an interest by formulation scientists in the role and functionality of the excipients.

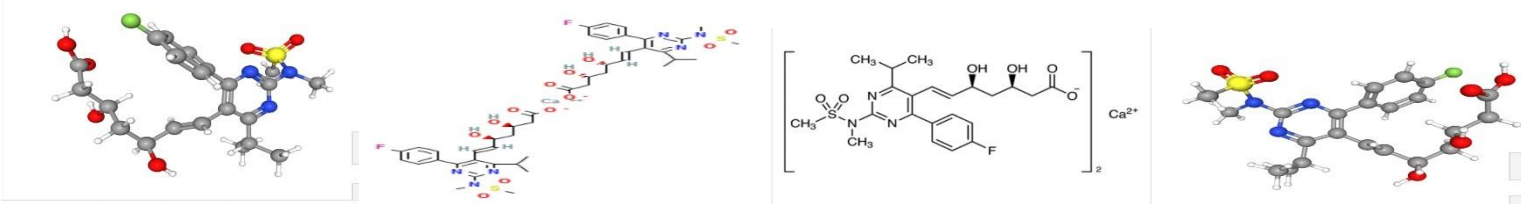
In the present study, it was proposed to drug-excipient compatibility studies of Rosuvastatin calcium, with commonly different excipients using for formulation development of fast dissolving tablets FDTs.

MATERIALS AND METHODS

Rosuvastatin Calcium was obtained as a gift from (Yemen-Egyptian Pharmaceutical Industry Company - Yemen). While Mannitol, Microcrystalline Cellulose (Avicel), Croscarmellose Sodium, Crospovidone, Sodium Starch Glycolate, Sucralose, Magnesium Stearate, Sodium Lauryl Sulfate, PEG 6000, Tween80, Orange Flavor, Methanol, Ethanol, Buffer Solutions, and other materials were obtained as a gift from (Modern Pharmaceutical Industry Company-Yemen).

Evaluation of Drug–Excipient Compatibility Studies Methods[48-171]

Table 2: Rosuvastatin Calcium Data.

Characterization of Rosuvastatin Calcium			
			
Rosuvastatin Calcium Structure and 3D Conformer			
Chemical Structure	bis[(E)-7-[4-(4-fluorophenyl)-6 isopropyl-2-[methyl(methylsulfonyl)amino] pyrimidin-5-yl]-(3R,5S)-3 ,5 dihydroxyhept-6-enoic acid] calcium salt.	**Appearance**	White amorphous powder
Chemical Formula	$C_{44}H_{54}CaF_2N_6O_{12}S_2$	**Solubility**	Sparingly soluble in water and methanol
Molecular Weight	1001.1 g/mol	**BCS**	Class-II Drug
Action and Use	HMG Co-A reductase inhibitor; lipid-regulating drug.	**Duration of Treatment**	Chronic
Pharmacokinetics of Rosuvastatin calcium			

Absorption	The absolute bioavailability of Rosuvastatin is approximately 20%. peak plasma concentrations of Rosuvastatin were reached 3 to 5 hours following oral dosing. Both peak concentration (Cmax) and area under the plasma concentration-time curve (AUC) increased in approximate proportion to Rosuvastatin dose. the extent of absorption as assessed by Cmax, AUC.	**Distribution**	88% bound to plasma proteins mostly albumin. Mean volume of distribution at steady-state is approximately Vd =134 L
Metabolism	10% metabolized by cytochrome P450 2C9 In clearance 50% cytochrome P450 3A4	**Excretion**	After oral dose, approximately 10% of total body clearance was via the renal route, and 90% by the hepatic route excreted unchanged in feces. After an intravenous dose, approximately 28% of total body clearance was via the renal route, and 72% by the hepatic route.
The Elimination Half-Life (T1/2)	Half-life: 19 hr.	**Availability**	Tablets: 5 mg, 10 mg, 20 mg, 40 mg.

Table 3: Pharmaceutical Excipients Data.

Nonproprietary Name	Chemical Name	Functional Category	Concentration%	Solubility	Incompatibilities	Notes
Crospovidone (PVPP)	1-Ethenyl-2-pyrrolidinone homopolymer	Tablet disintegrant.	2–5%	Practically insoluble in water	Compatible with most organic and inorganic pharmaceutical ingredients.	Hygroscopic powder
Croscarmellose Sodium (Ac-Di-Sol)	Cellulose, carboxymethyl ether, sodium salt, crosslinked	Tablet and capsule disintegrant.	0.5-5% 10-25%	Insoluble in water	Incompatible with strong acids or with soluble salts of iron and some other metals such as aluminum, mercury, and zinc.	White or grayish-white powder
Sodium Starch Glycolate (Explotab)	Sodium carboxymethyl starch	Tablet and capsule disintegrant.	2–8%	Gives a translucent suspension in water	Incompatible with ascorbic acid.	Very hygroscopic
Microcrystalline Cellulose (Avicel PH)	Cellulose	Adsorbent, suspending agent, tablet and capsule diluent; tablet disintegrant.	5–20% 20–90%	Practically insoluble in water	Incompatible with strong oxidizing agents.	Crystalline powder
Mannitol	Mannitol	Diluent,	10–90%	Freely	Incompatible with	Crystalline

(Emprove)		plasticizer, sweetening agent, tablet and capsule diluent, therapeutic agent, tonicity agent.		soluble in water	may be salted out by potassium chloride or sodium chloride. Sodium cephapirin. xylitol infusion and may form complexes with some metals such as aluminum, copper, and iron.	powder
Magnesium Stearate (magnesium salt)	Octadecanoic acid magnesium salt	Tablet and capsule lubricant.	0.25 - 5.0%	Practically insoluble in water	Incompatible with strong acids, alkalis, and iron salts.	Greasy
Sucralose (SucraPlus)	,6-Dichloro-1,6-dideoxy-b-D-fructofuranosyl-4-chloro-4-deoxya-D-galactopyranoside	Sweetening agent.	0.03–0.24%	Freely soluble in water	---	Crystalline powder

According to Rosuvastatin calcium and excipients data as shown in Tables 2and 3, it was selected that the different excipients to preformulation study with Rosuvastatin in the present study.

Table 4: The Equipment's Used.

Sr. No.	Equipment's
1	**Fourier Transform Infrared Spectrophotometer**
2	**UV/VIS Spectrophotometer**
3	**Melting Point Tester**
4	**Moisture Tester**
5	**Density Tester**
6	**pH Meter**
7	**Electronic Balance**

Determination of The Organoleptic Properties

The organoleptic properties of the API substance were assessed: physical appearance, for Rosuvastatin calcium was inspected and assessed.

UV-Visible Spectrophotometric Method

Preparation of Calibration curve Solutions

Preparation of citrate buffer (pH6.6): prepare a solution of 14.7 g/L of sodium citrate dihydrate and 0.33 g/L of anhydrous citric acid; adjust, if necessary, with sodium citrate or

citric acid to a citrate buffer (pH 6.6) (USP). Preparation of Rosuvastatin standard stock solution: Accurately weight quantity equivalent to 100mg of Rosuvastatin to 100 ml volumetric flask then add 25 ml of acetonitrile, vigorously mix or sonicate the flask to dissolve the material and then complete the volume with distal water. Finally, 1ml of the solution transferred to 100ml volumetric flask and diluted with the solution.

Determination of λ Max for Rosuvastatin Calcium

The standard solution of Rosuvastatin calcium was scanned in the range of 200-800 nm and the λ max was determined.

Calibration Curve of Rosuvastatin Calcium

The standard calibration curve graph was obtained by preparing aliquots of standard solution of Rosuvastatin calcium in citrate buffer (pH 6.6) and the absorbance at 242 nm was measured after suitable dilution using UV/Visible spectrophotometer.

appropriate aliquots were pipette out from standard stock solution into the series of volumetric flask and the volume was made up to the mark with concentration range 0.002-0.04 µg/ml of Rosuvastatin calcium. Solutions of different concentrations were analyzed 242 nm against blank solution and absorbance were recorded. The calibration curve was plotted between concentration and absorbance.

Preformulation Studies

Preformulation studies are initiated to define the physical and chemical properties of the agent. The key goals of preformulation studies are to ensure the delivery of drug product with acceptable stability, bioavailability, and manufacturability.

Melting Point Determination of Rosuvastatin Calcium

Melting point of pure Rosuvastatin was determined by open capillary method. The capillary tube was closed at one end by fusion and was filled with Rosuvastatin by repeated tapings. The capillary tube was placed in a digital melting point apparatus. The instrument was set to automatically increase the temperature of the heating bath. The rise in temperature was viewed through screen . The temperature at which the drug started melting was recorded.

Drug-Excipient Compatibility Studies

A physical mixture including Rosuvastatin calcium and excipient was created in a 1:1 ratio, and it was subjected to analytical techniques such as FTIR spectroscopy. FTIR, of both pure

drug and physical mixes were obtained, and the spectra of the both drug and mixture of excipient with drug were compared to look for any incompatibilities.

FTIR Spectroscopy Study

FTIR study KBr-disc method was used to record the FTIR spectra and KBr pellets were made in 1:100 ratio of sample and KBr. FTIR spectra was recorded using FTIR spectrum in a range of 4000-400cm^{-1}. Different functional groups of test compound for distinctive vibrational frequencies are identified using FTIR spectroscopy. FTIR spectra were used for the investigation of interaction in the physical mixture of API and excipient through shifting of peaks to lower or higher wavenumbers and appearance or disappearance of characteristic peaks of functional groups for pure API in physical mixture. FTIR spectroscopic study was performed to check the compatibility between API, and different excipients in amount (5mg:5mg) as ratio (1:1) as shown in Table 5. The FTIR spectra of a API alone and API with excipients were obtained by KBr method and compared with the standard FTIR spectrum of the pure API. Infrared spectrophotometer is not only used for determining the compatibility of excipients with the APIs, but also for API identification.

Preparation of IR Samples

The sample was determined by the disc method. Triturate 5mg of the substance to be examined with 300-400 mg of finely powdered and dried potassium bromide R or potassium chloride R. Each excipient was mix with Rosuvastatin equally then of potassium bromide is added to the mixture. Carefully grind the mixture, spread it uniformly in a suitable die, and submit it to a pressure of about 800 MPa (8 t·cm^{-2}). Then the tablets were inserted to the device and the Infrared spectra was recorded at mild-infrared light in wavenumber range of 4000 cm^{-1} to 400 cm^{-1}. After that the spectra were compared with the reference.

Table 5: Samples of Rosuvastatin Calcium and Different Excipients for Compatibility Studies.

Sr.No	Component(s)	Amount(5mg:5mg)
1	Rosuvastatin	1
2	Rosuvastatin and Crospovidone	(1:1)
3	Rosuvastatin and SSG	(1:1)
4	Rosuvastatin and SLS	(1:1)
5	Rosuvastatin and MCC	(1:1)
6	Rosuvastatin and Tween 80	(1:1)
7	Rosuvastatin and Orange Flavor	(1:1)
8	Rosuvastatin and Sucralose	(1:1)

9	Rosuvastatin and PEG	(1:1)
10	Rosuvastatin and CCS	(1:1)
11	Rosuvastatin and Mannitol	(1:1)
12	Rosuvastatin and Mg. Stearate	(1:1)

Preparation of Rosuvastatin Formulations

Table 6: Composition of Rosuvastatin Calcium Formulations.

Ingredients	Formulation Amount %							
	Formulation Code							
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**
Rosuvastatin Calcium	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Microcrystalline Cellulose	48.25	48.25	48.25	48.25	58.25	47.25	45.25	46.75
Mannitol	32	32	32	32	32	32	30	30.5
Crospovidone	10	---	---	5	---	5	5	5
Croscarmellose Sodium	---	10	---	5	---	5	5	5
Sodium Starch Glycolate	---	---	10	---	---	---	---	---
Sucralose	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75
Sodium Lauryl Sulfate	---	---	---	---	---	2	---	---
PEG 6000	---	---	---	---	---	---	5	---
Tween 80	---	---	---	---	---	---	---	3
Magnesium Stearate	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Orange Flavor	6	6	6	6	6	6	6	6

The active ingredients were mixed with superdisintegrants (crospovidone, croscarmellose and sodium starch glycolate) avicel and mannitol for 5 min. Solution of sucralose in ethanol was added to the powder mixture. Eight formulations were prepared by combining all these ingredients in different quantities. [In F6, F7, F8. Sodium lauryl sulfate, PEG6000 and tween80 was add as wetting agent to enhance the solubility of Rosuvastatin. Finally, orange flavor and magnesium stearate were added in this mixture and mixed for further 5 min. Formulations of Rosuvastatin have been prepared and evaluated by parameters of pre-compression studies as shown in Table 6.

Evaluation of Pre-Compression Parameters of Formulations

Bulk Density

Bulk density (ρb) was determined by placing pre sieved drug excipients mixture into a graduated cylinder and measuring the volume (Vb) and weight (M).

$\rho b = M/Vb.$

Tapped Density

The measuring cylinder containing a known quantity of blend was tapped for a fixed number of taps. The minimum volume (Vt) occupied in the cylinder and the weight (M) of the drug

excipients mixture was measured. The tapped density (ρt) was calculated using the following formula. ρt = M/Vt.

Angle of Repose

Angle of repose (**θ**) was determined using funnel method. The drug excipients mixture was poured through a funnel that can be raised vertically until a maximum cone height (h) was obtained. The radius of the pile (r) was measured and the angle of repose was calculated. **θ** = tan -1 (h/r). As shown in Table 7.

Carr's Index

Carr's Index or % compressibility is helpful to determine flow properties of powder mixtures, which is calculated as follows:

C = (ρt–ρb)/ρt X 100 Where, ρt - Tapped density, ρb -Untapped bulk density.

Hausner's Ratio

Hausner's ratio is an index of ease of powder flow; it is calculated by the following formula. Hausner's ratio = ρt\ ρb Where, ρt - Tapped density ρb - Bulk density. As shown in Table 8.

Table 7: Powder Flow Properties.

Description of Flow	Angle of Repose (θ)
Excellent	≤25
Very Good	25 – 30
Good	31 – 35
Fair	36 – 40
Passable (but flow aid might be needed)	41 – 45
Poor (agitation or vibration needed)	46 – 55
Very Poor	>56

Table 8: Powder Flow Properties.

Description of Flow	Carr's Index (%)	Hausner Ratio
Excellent	≤10	1.00 – 1.11
Good	11 – 15	1.12 – 1.18
Fair	16 – 20	1.19 – 1.25
Passable	21 – 25	1.26 – 1.34
Poor	26 – 31	1.35 – 1.45
Very Poor	32 – 39	1.46 – 1.59
Very, Very Poor	>40	>1.60

RESULTS AND DISCUSSION

Preformulation Studies

Characterization of Rosuvastatin Calcium

The important objective for characterization of Rosuvastatin Calcium is to know identity, purity, and characteristic of the drug. Rosuvastatin calcium was identified and its purity assessed using organoleptic properties and a variety of analytical methods, including FTIR, UV-Visible spectroscopy and melting point apparatus.

Physical Identification of Rosuvastatin Calcium

Rosuvastatin calcium is White to off white colored powder.

Characterization of Rosuvastatin Calcium by UV Spectroscopy

Solubility study of Rosuvastatin calcium was showed that the Rosuvastatin calcium pH dependent solubility and is highly soluble at citrate buffer pH (6.6).

The absorption maximum (λmax) of Rosuvastatin calcium was observed to be 242nm.

Calibration Curve of Rosuvastatin Calcium

The calibration curve of Rosuvastatin calcium was prepared in citrate buffer (pH 6.6). This solution was scanned at a range of 200-400 nm wavelengths. The corresponding scan spectrum curve was noted and the wavelength having highest absorbance is noted as λmax, 242 nm. The plot of different concentrations of Rosuvastatin calcium versus absorbance was found to be as shown in Table 9 and Figure 1. A graph of absorbance versus concentration was plotted which indicated in compliance to Beer's law in the concentration range 0.002 - 0.04 µg/ml. Standard plot of Rosuvastatin was plotted by taking absorbance on Y-axis and concentration (µg/ml) on X-axis; the plot is shown in Figure 1. The standard calibration curve of Rosuvastatin calcium in citrate buffer pH 6.6 showed good correlation with regression value of R^2= 0.99994.

Table 9: Calibration Curve of Rosuvastatin Calcium in Citrate Buffer (pH 6.6).

Sr.No	Concentration µg/ml	Absorbance
1	0.00	0.00
2	0.002	0.0865
3	0.004	0.1525
4	0.005	0.1979
5	0.01	0.3895
6	0.02	0.7971
7	0.04	1.6077

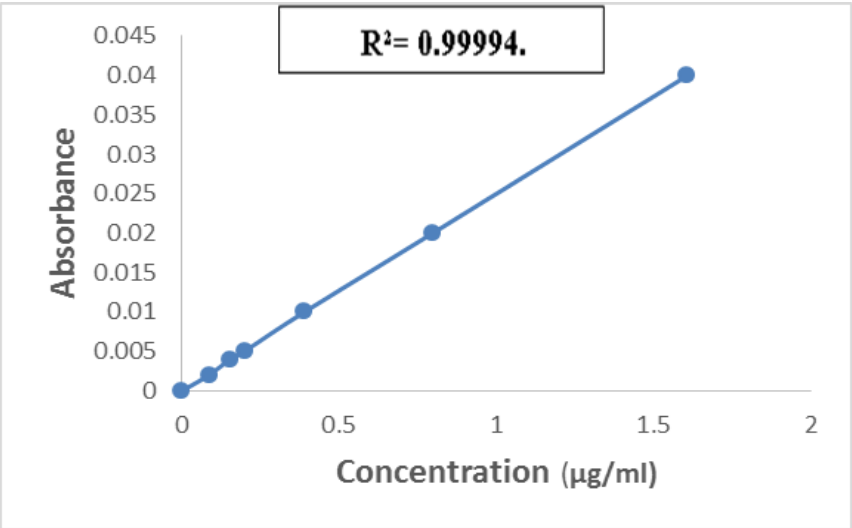


Fig. 1: Standard Calibration Curve of Rosuvastatin Calcium in Citrate Buffer (pH 6.6).

Melting Point Determination of Rosuvastatin Calcium

Melting point of Rosuvastatin calcium was observed to be 157℃. Reported melting point of rosuvastatin calcium is (156-160 C°). The melting point range of Rosuvastatin calcium was identical to reference melting point stated in BP (156-160 C°).The sample started to melt at 156 C°, and turned into liquid at 157 C°, as shwon in Table 10, indicating that the sample used is pure. That reading has stated in melting point apparatus.

Table 10: Melting Point Results of Rosuvastatin Calcium.

Test	Temp Rang Analyzed (Melting)	Results
Test I Rosuvastatin	(156-160 C°)	157 C°
Test II Rosuvastatin	(156-160 C°)	157 C°

Characterization of Rosuvastatin Calcium by FTIR

Spectrophotometry FTIR spectra of pure Rosuvastatin calcium was recorded on an IR Spectrophotometer. The FTIR spectrum of pure Rosuvastatin calcium showed an absorption band at reveals certain characteristic peaks at 3301 cm^{-1}, 1550 cm^{-1}, 1506 cm^{-1}, 1390 cm^{-1}, 1330 cm^{-1}, 1229 cm^{-1}, 1067 cm^{-1}, 841 cm^{-1} and 770 cm^{-1} as shown in Figure 2.

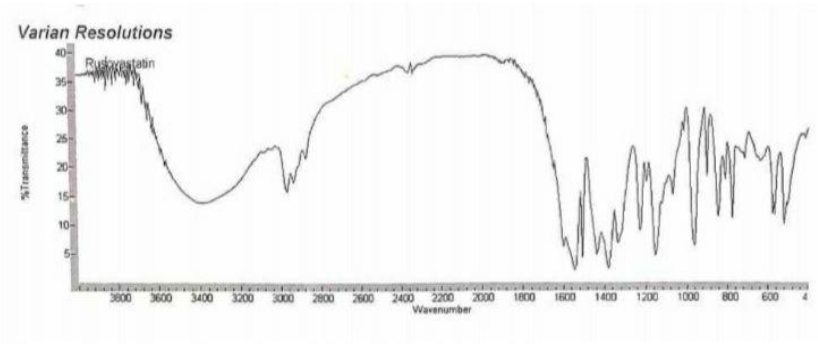


Fig. 2: FT-IR Spectrum of Rosuvastatin Calcium.

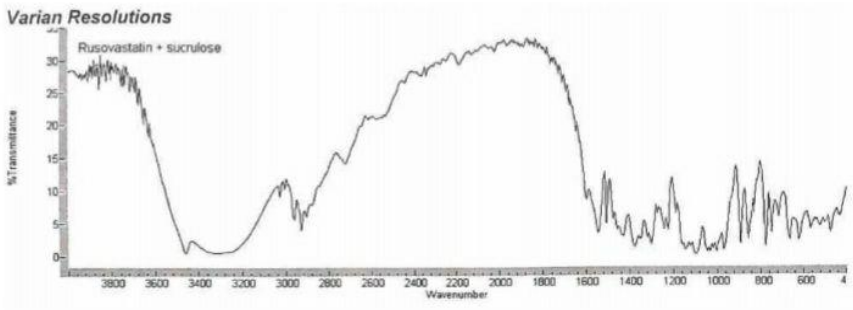


Fig. 3: FT-IR Spectrum of Rosuvastatin Calcium and Sucralose.

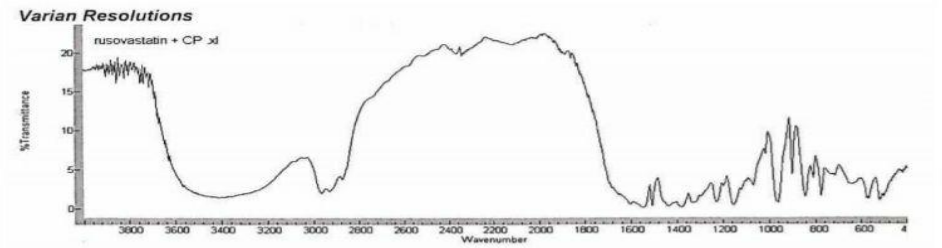


Fig. 4: FT-IR Spectrum of Rosuvastatin Calcium and Crospovidone.

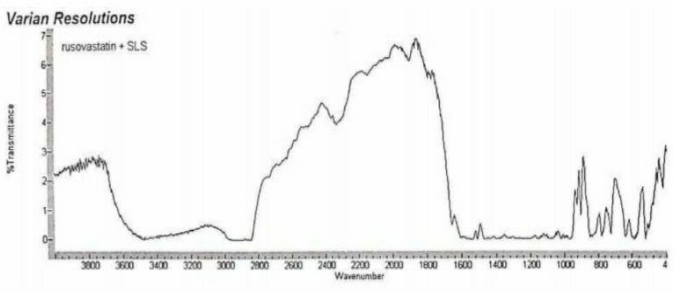


Fig. 5: FT-IR Spectrum of Rosuvastatin Calcium and SLS.

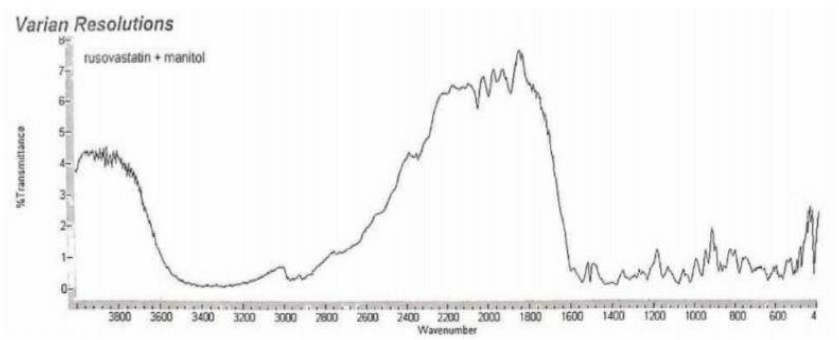


Fig. 6: FT-IR Spectrum of Rosuvastatin Calcium and Mannitol.

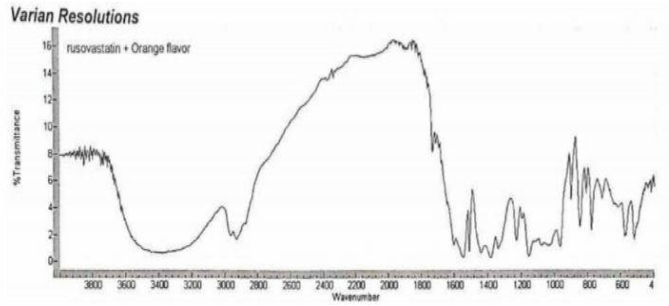


Fig. 7: FT-IR Spectrum of Rosuvastatin Calcium and Orange Flavor.

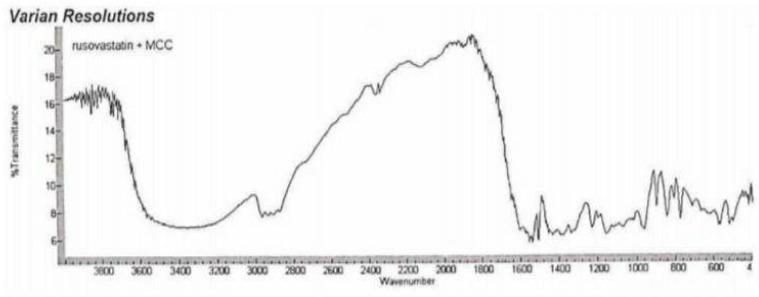


Fig. 8: FT-IR Spectrum of Rosuvastatin Calcium and MCC.

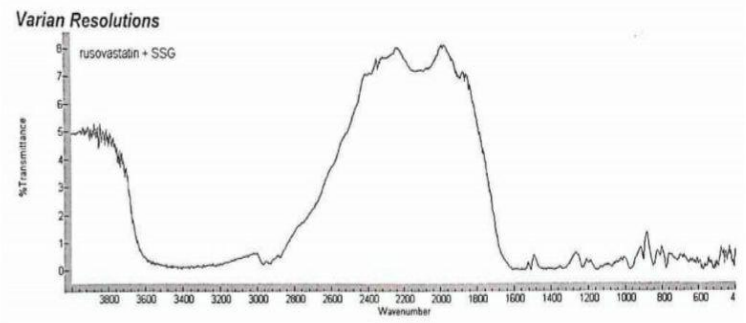


Fig. 9: FT-IR Spectrum of Rosuvastatin Calcium and SSG.

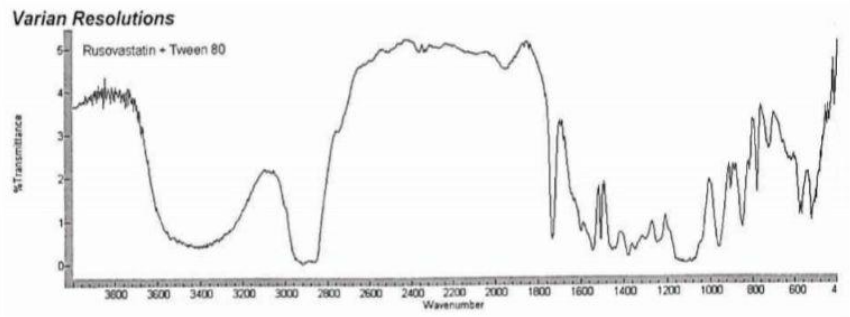


Fig. 10: FT-IR Spectrum of Rosuvastatin Calcium and Tween 80.

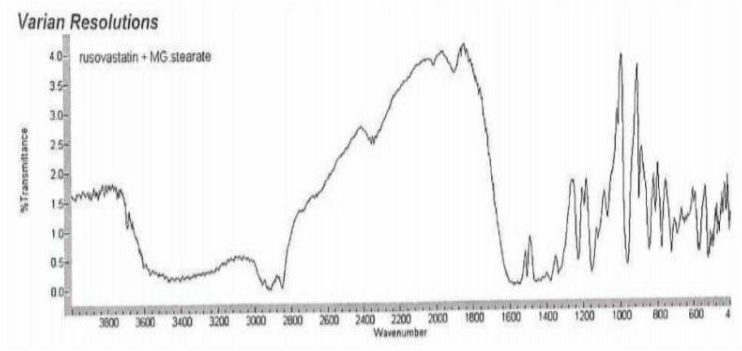


Fig 11: FT-IR Spectrum of Rosuvastatin Calcium and Mg. Stearate.

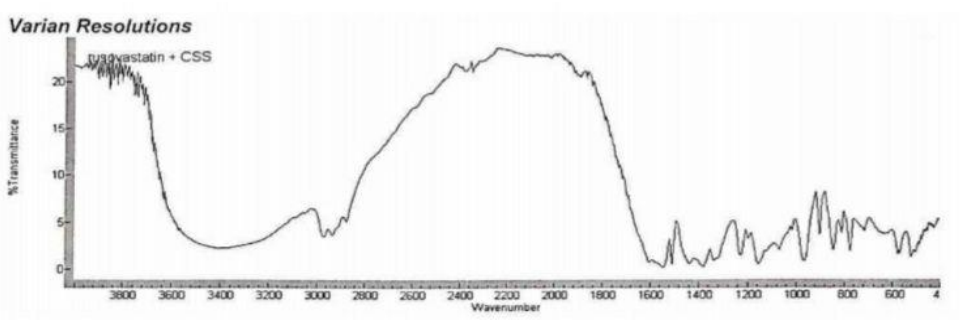


Fig. 12: FT-IR Spectrum of Rosuvastatin Calcium and CCS.

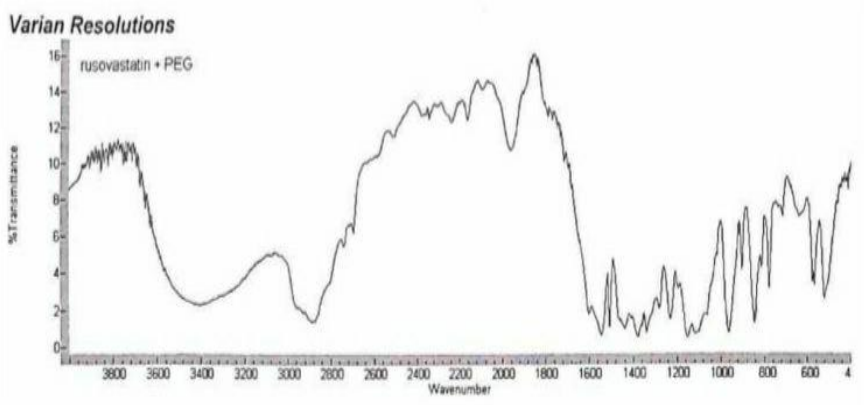


Fig. 13: FT-IR Spectrum of Rosuvastatin Calcium and PEG.

Drug-Excipient Compatibility Studies

It was noted that, under room temperature and humidity conditions, there was no color change or lump formation in any of the drug-excipient mixtures. Based on the observations

made, it was determined that there was compatibility between the drug and the excipients used in the experimental study.

Drug-excipient compatibility study is essential part of preformulation step for the development of new drug. Physical mixture of drug and excipient (1:1) were prepared and compatibility studies were carried out using FTIR Spectroscopy.

Compatibility Study of Rosuvastatin Calcium Utilizing FTIR Spectroscopy

Rosuvastatin calcium and excipients absorption bands were identified and interpreted in the spectra. The FTIR spectra of physical mixtures of Rosuvastatin calcium and excipients reveal no interaction between drug and excipients. The FTIR studies from the spectra confirmed the absence of any chemical interaction between the Rosuvastatin calcium and the excipients as shown in Figures 2-13.

Evaluation of Pre-Compression Parameters of Formulation

Pre-compression studies were evaluated for the prepared powders and their flow properties, the results for the blends of formulations were shown in Tables 11 and 12.

Table 11: Preformulation Parameters of Powder Flow Properties.

Formulation Code	Angle of Repose	Flowability	Carr's Index	Flowability	Hausner's Ratio	Flowability
F1	30°	Excellent	23.96 %	Passable	1.315	Passable
F2	23.83°	Excellent	20.39 %	Fair	1.256	Fair
F3	26.8°	Excellent	20.35 %	Fair	1.256	Fair
F4	28.14°	Excellent	20.50 %	Fair	1.258	Fair
F5	29.32°	Excellent	19.54 %	Fair	1.243	Fair
F6	34°	Excellent	22.28 %	Passable	1.287	Fair
F7	23.05°	Excellent	19.05 %	Fair	1.235	Fair
F8	35°	Good	19.42 %	Fair	1.241	Fair

Table 12: Preformulation Parameters of Powder Flow Properties.

Formulation Code	App.Wt G	App.Vol ml	Tapp.Wt g	Tapp.Vol ml	App.D g/ml	Tapp.D g/ml	Voids	Porosity%	Bulkness ml/g
F1	19.18	55	19.18	38	0.349	0.505	0.31	31	2.87
F2	19.58	44	19.58	35	0.445	0.559	0.20	20	2.25
F3	19.62	44	19.62	35	0.446	0.561	0.20	20	2.24
F4	19.28	44	19.28	35	0.438	0.551	0.20	20	2.28
F5	19.32	46	19.32	37	0.42	0.522	0.20	20	2.38
F6	19	45	19	35	0.422	0.543	0.22	22	2.36
F7	19.44	42	19.44	34	0.463	0.572	0.19	19	2.36
F8	19.44	46	19.44	37	0.423	0.525	0.20	20	2.36

All eight prepared formulations of Rosuvastatin calcium were evaluated for pre-compression studies, i.e., angle of repose, bulk density, tapped density, compressibility index, and Hausner's ratio. The pre-formulation studies were conducted to know the flow properties of formulations. The flowability of the prepared formulation mixture is important which in tum is important for the uniformity of tablets mass and in vitro drug dissolution. For direct compression, the flowability of the formulation mixture is important which in tum is significant for the uniformity of mass of the tablets. The flow of the formulation mixtures was analyzed before compression to tablets. The angle of repose of all formulations lied between 23.05°and 35° indicating excellent and very good powder flow property of all formulations except F6 and F8 which have good flow properties according to the official criteria.

The bulk and tapped densities of all formulations lied between 0.349 g/ml to 0.463 g/ml and 0.505 g/ml to 0.572 g/ml, respectively, which were used to determine compressibility index. The compressibility index lied between 19.05% and 23.96% indicating that the F1 and F6 was having passable flow properties and other formulations were having fair flow property results. Hausner's ratio of all formulations lied between 1.241 and 1.315 which showed that all the formulations were having fair flow properties except F1 which have passable flow properties when compared with standard values.

CONCLUSION

The compatibility studies of physical mixtures of Rosuvastatin calcium with different used excipients such as mannitol, microcrystalline cellulose as diluents, and sodium starch glycolate, croscarmellose sodium, and crospovidone as superdisintegrants and PEG6000, tween80 and sodium lauryl sulfate as wetting agents were investigated by FTIR it was detected that there was no variation or minor deviation in the characteristic peaks in FTIR spectroscopy. The Rosuvastatin calcium formulations prepared were evaluated for precompression parameters and powder flow properties which were found to be within limits. It was concluded that the drug Rosuvastatin calcium was found to be compatible with various excipients which were selected for the formulation development of the Rosuvastatin calcium FDTs. Formulation scientist from his experience and knowledge have to significantly in the preformulation study stage and is an important factor in the ADDS (Advanced Drug Delivery Systems) product development process.

ACKNOWLEDGEMENT

The authors are thankful to Yemen-Egyptian Pharmaceutical Industry Company -Yemen and Modern Pharmaceutical Industry Company-Yemen for their support and facilities.

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