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BIOEQUIVALENCE MODULATION WITH MODIFIED STARCH IN ORODISPERSIBLE TABLETS IN COMPARISON TO MARKETED CONVENTIONAL TABLETS OF ROSUVASTATIN CALCIUM

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ABSTRACT

Poor solubility and permeability of slightly soluble drug, Rosuvastatin calcium, often expose a problem of low bioavailability (absolute bioavailability 20%) as its dissolution and permeation are the rate limiting factors, so it becomes a challenge to improve dissolution and permeability of Rosuvastatin calcium oral conventional solid dosage forms. The dissolution profile and bioequivalence modulation of oral solid dosage form depend mostly on its formulation excipients and method of manufacture. Considering that *in vitro* dissolution studies can simulate *in vivo* bioequivalence of the therapeutically equivalent branded and generic versions of the same API, the present study had been targeted to explore bioequivalence modulation and justify interchangeability of marketed oral drug products by comparing the multipoint *in vitro* dissolution profile, per cent cumulative drug release (%CDR), dissolution efficiency (%DE) and the similarity factor (f_2) among different commercially marketed formulations of Rosuvastatin Calcium 5 mg tablets along with the Orodispersible tablets of Rosuvastatin Calcium (5 mg) formulated with modified Starch by solid dispersion technique. In the present study modified Starch (Starch-5-phosphate) was prepared in the laboratory by reaction of starch with di-sodium hydrogen orthophosphate, anhydrous at elevated temperatures (>130^0 C) and the product was found to be white, crystalline, non-hygroscopic powder, insoluble in water and aqueous fluids in acidic and alkaline pHs as well. It has no pasting or gelling property when heated at 100^0 C in water for 30 min. As starch phosphate exhibited good swelling (> 400%) in water, it was evaluated as disintegrant in tablet formulations. Orodispersible Tablets of Rosuvastatin Calcium 5 mg were prepared by direct compression method using starch phosphate with PEG as solid dispersion in the ratio of Rosuvastatin calcium : PEG 6000 : Starch-5-phosphate in the ratio of 1:1:1 (F1cc), 1:2:5 (F4cc) and 1:1:9 (F5cc) and were evaluated. The dissolution efficiency **(%DE_5)** obtained in Orodispersible tablet formulations were found as **84.22%** (F1cc), **88.11%** (F4CC) & **89.19%** (F5cc) in comparison to **29.40%** & **25.20%** for **CRESTOR & ROSUVAS** (Branded commercial tablet formulations) justifying that Rosuvastatin solid dispersion with starch-5-phosphate as significantly better alternative than commercially marketed oral tablets of Rosuvastatin Calcium with faster dissolution and improved bioavailability. Furthermore, the results of the study revealed that **ROZUCOR** & **ROSUVAS** have been found bioequivalent and interchangeable with **CRESTOR** (*Innovator Brand*) having similarity factor **(f2 value) > 50**; whereas **ROSUMAC** & **ZYROVA** have not been found bioequivalent and interchangeable with **CRESTOR** (*Innovator Brand*) having similarity factor **(f2 value) < 50**. Incidentally, all the formulated Orodispersible tablets were found bioequivalent & interchangeable.

KEYWORDS: Bioequivalence, Dissolution efficiency, Orodispersible, starch-5-phosphate, solid dispersion.

INTRODUCTION

The oral route of drug administration is the most common and preferred method of delivery due to convenience and ease of ingestion. From an adult patient's perspective, swallowing a dosage form is a comfortable and a familiar means of taking medication. Although the oral route of administration is preferred, for many drugs it can be a problematic and inefficient mode of delivery for a number of reasons. Limited drug absorption resulting in poor bioavailability is paramount amongst the potential problems that can be encountered when delivering *via* the oral route.[1] Drug absorption from the gastrointestinal tract can be limited by a variety of factors with the most significant contributors being poor aqueous solubility and/or poor membrane permeability of the drug molecule. When delivering a drug product orally, it must first get dissolved in gastric and/or intestinal fluids before it can permeate the membranes of the gastrointestinal tract to reach systemic circulation.[1,4] Therefore, a drug with poor aqueous solubility might typically exhibit dissolution rate limited absorption and a drug with poor membrane permeability

will typically exhibit permeation rate limited absorption. Hence, two areas of pharmaceutical research that focus on modulating the bioavailability from oral solid dosage forms include: (i) enhancing solubility and dissolution rate of poorly water-soluble drugs and (ii) enhancing permeability of poorly permeable drugs. So, a solid dispersion technology is used to improve the dissolution characteristics of poorly water soluble drug and modulate its oral bioavailability.

Incidentally, European Pharmacopoeia has used the term Orodispersible tablets and Indian Pharmacopoeia has used the term Dispersible tablets that disperse readily within 3 min in the mouth before swallowing. However, United States of Food and Drug Administration (USFDA) defined Sublingual tablet as Uncoated tablet containing medicinal substance or active pharmaceutical ingredient which disintegrates rapidly within specified time limit as per individual monograph, usually before 2 – 3 minutes when placed upon the tongue.

Rosuvastatin is a specific and competitive inhibitor of HMG-CoA reductase, the rate limiting enzyme that converts 3-hydroxyl-3-methyl glutaryl coenzyme A to mevalonate, a precursor of cholesterol, it increases the catabolism of LDL and inhibits the hepatic synthesis of VLDL and increases the synthesis of HDL. Rosuvastatin calcium is a white amorphous powder that is sparingly soluble in water. Peak plasma concentration could be reached by 3-5 hours following oral dosing.[1] It has got elimination half-life of 19 hours and 88% of it has the tendency to protein binding. Rosuvastatin is highly susceptible to light, moisture and low pH environment. In acidic environment, it undergoes conversion into lactone through intramolecular esterification which takes place between carboxylic acid and hydroxyl groups that are present on β and δ carbons in this compound. This phenomenon reduces the stability of the compound and reduces the shelf-life.[2] To overcome this, most of the marketed immediate release Rosuvastatin tablets are film/enteric coated. Its oral absorption is dissolution rate limited and it requires enhancement in solubility and dissolution rate for increasing its oral bioavailability. Several techniques such as micronization, cyclodextrin-complexation, use of surfactants and solubilizers, solid dispersion in water soluble and dispersible carriers, use of salts, prodrugs and polymorphs which exhibit high solubility, micro emulsions and self-emulsifying micro and nano-disperse systems have been used to enhance the solubility, dissolution rate and bioavailability of poorly soluble drugs. Among these various approaches, solid dispersions in water dispersible excipients are a simple, industrially useful approach for enhancing the solubility, dissolution rate and bioavailability of poorly soluble drugs.[3] Starch phosphate is one of the modified starches used in the frozen food industry. It is produced by phosphorification of free hydroxyl groups of anhydro glucose units of starch molecule.

OBJECTIVE OF THE PRESENT STUDY

The US Food and Drug Administration approve generic forms of brand name drugs if they show bio-equivalence as well as standards in drug content. Bio-equivalence is calculated based on three pharmacokinetic parameters:

a. The maximum concentration in the blood (C_{max}).
b. The time at which the maximum concentration is reached (T_{max}).
c. The extent of drug administration (Area under the concentration versus time curve {AUC}).

Bio-equivalence (BE) studies focus on the drug release from the formulation and subsequent absorption into the systemic blood circulation which consist of both *in-vivo* and *in-vitro* studies. According to US Pharmacopeia, necessary *in-vitro* tests are assay, content uniformity and dissolution studies. The dissolution profile comparison is more precise than others to characterize the drug product. The similarity in *in-vitro* dissolution behaviour of oral dosage forms has long been sought from the perspective of both bioavailability and quality control considerations as key pre-requisite to be systemically effective. Variable therapeutic responses to therapeutically equivalent drug products have been reported with so called branded and generic products and batch to batch inconsistencies have also been reported. Different products with the same amount of API have shown distinct differences in their therapeutic effects. The reasons may be either due to the differences in rate and extent of absorption, or difference between the purity of active ingredients, type of excipients, proportion between them and the manufacturing variables such as the influence of mixing method and granulation procedure as well as coating parameters. Therefore these are serious issues to the prescribing physicians that various branded generic substitutions may have different bioavailability and could not be used interchangeably.

Dissolution is extremely important for all conventional solid oral dosage forms and can be the rate limiting step for the absorption of drug administered orally especially for class II drugs in BCS classifications i.e. low solubility and high permeability. The dissolution profile comparison is more precise than others to characterize the drug product. On the other side, *in-vitro* dissolution profile is the most frequently used in-vitro variable parameter to generate IVIVC. Furthermore, dissolution efficiency (DE%) is defined as the area under the dissolution curve up to a certain time (t), expressed as a percentage of the area under the rectangle described by 100% dissolution in the same time. The comparison of DE% of several formulations simultaneously can be theoretically related to the comparison among mean plasma concentration-time curve obtained after deconvolution of the *in-vivo* data. The similarity factor (f_2) is also used to determine whether any selected branded formulation under test is similar to the therapeutically equivalent reference product (usually called an innovator) with the same API to allow interchangeability between the therapeutically equivalent

products. An f_2 value higher than 50% means that the average difference between both dissolution profiles is less than 10% at all sampling points indicating similarity of the two branded therapeutically equivalent products.

The objective of the present work is to formulate immediate release Orodispersible tablets of Rosuvastatin calcium with starch-5-phosphate as solid dispersion for the enhancement of solubility and modulating bioequivalence by improving its dissolution efficiency, preventing intramolecular esterification and by comparing *in vitro* dissolution profile with marketed formulations of Rosuvastatin calcium 5 mg tablets.

Criteria for Orodispersible Drug Delivery (Mouth dissolving) System[4]

- No requirement of water to swallow, but should dissolve or disintegrate in the mouth in matter of seconds.
- Be compatible with taste masking.
- Be portable without fragility concern.
- Have a pleasant mouth feel.
- Leave minimum or no residue in the mouth after oral administration.
- Exhibit low sensitive to environmental condition as temperature and humidity.

Salient features of Orodispersible Drug Delivery (Mouth dissolving) System[5]

- Ease of administration to the patient who cannot swallow, such as elderly, stroke victims, bedridden patients, patient affected by renal failure and patient who refuse to swallow such as paediatric, geriatric and psychiatric patients.
- No need of water to swallow the dosage form.
- Rapid dissolution in salivary fluid and absorption of the drug in buccal capillary vessels, which will produce quick onset of action.
- Pre-gastric absorption can result in improved bioavailability and as a result of reduced dosage; improve clinical performance through a reduction of unwanted effects.
- Good mouth feel property helps to change the perception of medication as bitter pill particularly in paediatric patient.
- The risk of chocking or suffocation during oral administration of conventional formulation due to physical obstruction is avoided, thus providing improved safety.

Limitations of Mouth Dissolving Tablets[6]

- The tablets usually have insufficient mechanical strength. Hence, careful handling is required.
- The tablets may leave unpleasant taste and/or grittiness in mouth if not formulated properly.

MATERIALS

Rosuvastatin calcium was obtained as a gift sample from Hygeia Pharmaceuticals, Kolkata, INDIA. Starch IP and Di-sodium hydrogen orthophosphate anhydrous (AR) have been supplied by B.D. Pharmaceuticals, WB and Loba Chemie Pvt. Ltd., INDIA, respectively.

Other excipients used in tablet formulation like Mannitol, Cross carmellose (Balaji Drugs), talc, magnesium stearate were of standard Pharmacopoeial grade and all chemical reagents, solvents were of analytical grade.

Table 1: LIST OF MATERIALS

Sl. No.	Materials	Source
1	Rosuvastatin calcium	Hygeia Pharmaceuticals, Kolkata, INDIA
2	Methanol	S D Fine Chem. Ltd., Mumbai
3	PEG 6000	Balaji Drugs, Surat, INDIA
4	Starch IP	B.D. Pharmaceuticals, Howrah, WB, INDIA
5	Di-sodium Hydrogen Orthophosphate anhydrous	Loba Chemie Pvt. Ltd., INDIA
6	Potassium Dihydrogen Phosphate	Merck Specialities Pvt. Ltd., INDIA
7	Dipotassium Hydrogen Phosphate	Merck Specialities Pvt. Ltd., INDIA
8	Mannitol	Balaji Drugs, Surat, INDIA
9	Cross-carmellose	Balaji Drugs, Surat, INDIA
10	Triton X 100	Loba Chemie Pvt. Ltd., INDIA
11	Cholesterol test kit	Span Diagnostic Ltd, India
12	HDL-Cholesterol test kit	Span Diagnostic Ltd, India
13	Triglycerides test kit	Span Diagnostic Ltd, India

Details of commercially marketed Rosuvastatin calcium 5 mg tablets used in the study

	ROZUCOR	ROZUMAC	ROSUVAS	ZYROVA	CRESTOR
Mfg. by	Torrent Pharmaceuticals Ltd.	Macleods Pharmaceuticals Ltd.	Ranbaxy Laboratories Ltd.	Zydus Cadilla Healthcare Ltd.	AstraZeneca Pharma India Ltd.
Batch no	2M77A002	HRN401C	2593163	GN2929	CL0008
Mfg. Date	04/2014	03/2014	02/2014	11/2013	06/2014
Exp. Date	03/2016	02/2016	01/2016	10/2015	05/2017
MRP	Rs.65.00	Rs.42.35	Rs.72.00	Rs.82.40	Rs.66.10

METHODOLOGY

- **Method of preparation of Orodispersible formulations[7]**

Various techniques can be used to formulate Orodispersible tablets. Direct compression is one of the techniques which require the incorporation of a super-disintegrant into the formulation, or the use of highly water-soluble excipients to achieve fast tablet disintegration. Direct compression does not require the use of water or heat during the formulation procedure and is the ideal method for moisture and heat-labile medications. Conventional equipment, commonly available excipients and a limited number of processing steps are involved in direct compression. Also high dosages can be accommodated and final weight of tablet can easily exceed that of other production methods. Directly compressible tablet's disintegration and solubilisation depend on single or combined action of disintegrant, water soluble excipients and/or effervescent agent. Disintegration efficacy is strongly affected by tablet size and hardness. Large and hard tablets have disintegration time more than that usually required. As consequences, products with optimal disintegration properties often have medium to small size and /or high friability and low hardness.

- **Determination of absorption maxima:** Absorption maxima or the wavelength at which absorption takes place. For accurate analytical work it is important to determine the absorption maxima of the substance under study.

Equipments

Double beam UV-VIS Spectrophotometer; Shimazdu – model UV1800-240v.

- **Preparation of standard calibration curve of Rosuvastatin calcium (RS) in Methanol**

Accurately weighed 10mg of Rosuvastatin Calcium was dissolved in 10ml of methanol (conc. 1000µg/ml). From this solution 1ml was pipetted out into 10ml volumetric flask and volume was made up to 10ml with methanol (conc. 100µg/ml). From this solution 1ml was pipetted out into 10ml volumetric flask and volume was made up to 10ml with methanol (conc. 10µg/ml). The solution containing 10µg/ml of Rosuvastatin calcium in methanol was scanned over the range of 200-400nm against respective solutions as blank using double beam UV spectrophotometer. The maximum absorbance obtained in the graph was considered as λ_{max} for the pure drug. The solution exhibited UV maxima at 242nm. From this stock solution (conc. 100µg/ml), several concentrations like 0.5µg/ml, 1µg/ml, 1.5µg/ml, 2µg/ml, 2.5µg/ml were prepared and volume in each was made up to 10ml with methanol, subsequently absorbance was measured at 242 nm.

- **Preparation of standard calibration curve of Rosuvastatin calcium (RS) in pH 6.8 Phosphate Buffer**

Accurately weighed 10mg of Rosuvastatin Calcium was dissolved in 10ml of methanol (conc. 1000µg/ml). From this solution 1ml was pipetted out into 10ml volumetric flask and volume was made up to 10ml with pH 6.8 phosphate buffer (conc. 100µg/ml). From this solution 1ml was pipetted out into 10ml volumetric flask and volume was made up to 10ml with pH 6.8 phosphate buffer (conc. 10µg/ml). The solution containing 10µg/ml of Rosuvastatin calcium in pH 6.8 phosphate buffer was scanned over the range of 200-400nm against respective solutions as blank using double beam UV spectrophotometer. The maximum absorbance obtained in the graph was considered as λ_{max} for the pure drug. The solution exhibited UV maxima at 242nm. From this stock solution (conc. 100µg/ml), several concentrations like 0.5µg/ml, 1µg/ml, 1.5µg/ml, 2µg/ml, 2.5µg/ml were prepared and volume was made up to 10ml with phosphate buffer. Then the absorbance was measured at 242 nm spectrophotometrically.

Table 2: Standard curve data of Rosuvastatin Calcium in Methanol

Concentration (in mcg/ml)	Absorbance at 242 nm
5	0.097
10	0.174
15	0.266
20	0.354
25	0.436
30	0.513

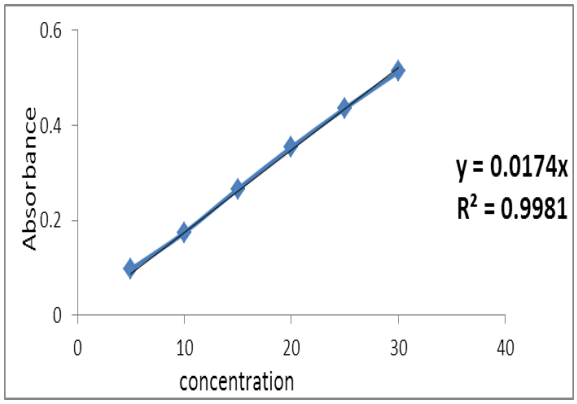


Fig 1: Standard curve of Rosuvastatin Calcium in Methanol

Table 3: Standard curve data of Rosuvastatin Calcium in pH 6.8 Phosphate Buffer

Concentration (in mcg/ml)	Absorbance at 242 nm
5	0.169
10	0.295
15	0.446
20	0.62
25	0.766
30	0.908

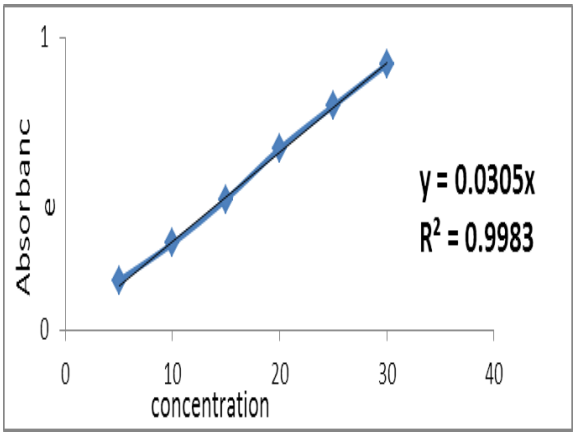


Fig 2: Standard curve of Rosuvastatin Calcium in pH 6.8 Phosphate Buffer

➢ **Saturation solubility studies**

A quantity of 5 mg of Rosuvastatin calcium (RS) was weighed and transferred into different conical flasks. 20ml of different dissolution media were transferred into individual conical flask and were closed appropriately. All the conical flasks were placed in a REMI incubator shaker. The shaker was allowed to operate at 50 rpm at 37±1°C for 24 hours. Then the conical flasks were removed from the incubator shaker and the samples were filtered by using Whatman filter paper. The clear solution obtained by filteration was suitably diluted with appropriate dissolution media and the absorbance values were noted at 242 nm by using corresponding dissolution media as blank solutions.

➢ **Preparation of Starch-5-Phosphate**[8]

Starch-5-Phosphate was prepared based on the method of *Choi et al* with some modifications. Starch IP (100g) and Di-sodium hydrogen orthophosphate anhydrous AR (30g) were suspended in 100 ml of water and continuously stirred for 20 min. This starch slurry was then filtered and the wet starch slurry was conditioned for a period of 12 hours at room temperature (25±2° C). To enhance phosphorylation, this mixture was heated in a forced air oven at a temperature 130° C for 3 hours. The product obtained after cooling was ground and sieved and kept in desiccators.

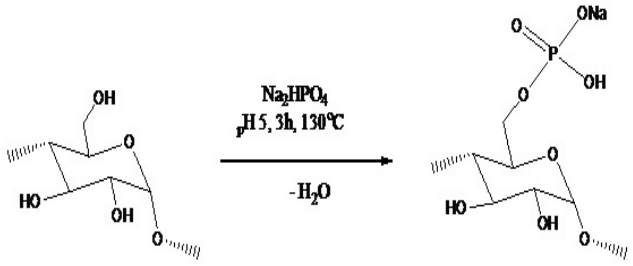


Fig. 3: Phosphorification of Starch IP to produce Starch-5-phosphate

➢ **Characterization of Starch-5-Phosphate**

The Starch-5-Phosphate prepared was evaluated for the following:

Solubility

Solubility of starch phosphate was tested in purified water, aqueous buffers of pH 1.2, 4.5, and 7.4 and organic solvents such as alcohol, acetone and petroleum ether.

Ph

The pH of a 1% w/v slurry was measured.

Melting Point

Melting point was determined by using melting point apparatus.

Viscosity

Viscosity of 1% w/v slurry in water was measured using Ostwald Viscometer.

Swelling Index

Starch-5-phosphate (200 mg) was added to 10 ml of water and light liquid paraffin taken in two different graduated test tubes and mixed. The dispersion in the tubes was allowed to stand for 12 h. The volumes of the sediment in the tubes were recorded. The swelling index of the material was calculated as follows.

$$\% \text{ SI} = \frac{\text{Vol of sediment in water - Vol of sediment in liq.paraffin}}{\text{Vol of sediment in liq parafiin}}$$

Test for gelling property

The gelling property (gelatinization) of starch & starch phosphate prepared was evaluated by heating a 7% w/v dispersion in water at 100^0 C for 30 min.

Moisture absorption

The hygroscopic nature of starch phosphate was evaluated by moisture absorption studies in a closed desiccator at 84% RH and room temperature.

Particle size

Particle size analysis was done by sieving using standard sieves.

Density

Density (g/cc) was determined by liquid displacement method using benzene.

Bulk density
Bulk density (g/cc) was determined by tapping method in a graduated cylinder.

Angle of repose
Angle of repose was measured by fixed funnel method.

Compressibility index
Compressibility index (CI) was determined by measuring the initial volume (Vo) and final volume (V) after hundred tapping of a sample of starch phosphate in a measuring cylinder. CI was calculated using equation:

$$\% \, \mathbf{CI} = \frac{\mathbf{Vo} - \mathbf{V}}{\mathbf{Vo}} * \mathbf{100}$$

Table 4: Physical properties of Starch-5-phosphate prepared

Properties	Result
Solubility	Insoluble in all aqueous and organic solvents tested
pH (1% w/v aqueous dispersion)	7.27
Melting point	Charred at 210°C
Viscosity (1% w/v aqueous dispersion)	2.15 cps
Swelling index	400
Gelling property	No gelling and swollen particles of Starch-5-phosphate separated from water.
Density	1.567 gm/cc
Bulk density	0.534 gm/cc
Angle of Repose	23.05°
Compressibility Index	15%

- **Preparation of Solid Dispersion by Solvent Evaporation method**

Poorly soluble Rosuvastatin calcium was first incorporated into a carrier polymer polyethylene glycol (PEG 6000). Rosuvastatin calcium was taken and dissolved in few ml of methanol in a beaker. To the methanolic solution, specified amount of PEG 6000 and Starch-5-phosphate was added in different ratio and the mixtures were heated on a water bath at about 40^0 C with continuous stirring until the solvent got evaporated. Then the mixtures were dried in a vacuum drier at 55^0 C and dried materials were sieved through 100# sieve. Then finally collected samples were stored separately in amber coloured glass containers and were hermetically sealed. Then the mixture was stored at ambient conditions.

- **Estimation of Rosuvastatin Calcium in Solid Dispersions**

Samples of solid dispersions of Rosuvastatin Calcium from different batches were taken at random and were weighed separately, transferred individually each into a 50ml volumetric flask to which 20ml of methanol was added. All the flasks were placed in a REMI incubator shaker. The shaker was allowed to operate at 50 rpm at 37±1° C for 24hours. Then the flasks were removed from the incubator shaker and the volume of each was made up to 50 ml by adding methanol. The samples were then filtered by using Whatman filter paper. The clear solution obtained by filtration was suitably diluted with 6.8 pH phosphate buffer and the absorbance was measured at 242nm.

- **Estimation of pre-compression parameters of powder**

The pre-compression parameters such as tapped density, bulk density, compressibility index, Hausner ratio and angle of repose were evaluated for the pre-compression blends.

Table 5: Pre-compression parameters of Rosuvastatin Calcium Orodispersible tablet

Formulation	Angle of Repose (θ)	Bulk Density (gm/cc)	Tapped Density (gm/cc)	Compressibility Index	Hausner's ratio
F1cc1	30±0.22	0.5±0.01	0.606±0.02	17.5±0.56	1.212±0.03
F1cc2	35±0.24	0.51±0.02	0.666±0.04	23.07±0.68	1.305±0.01
F4cc1	38±0.28	0.5±0.01	0.606±0.02	17.5±0.56	1.212±0.03
F4cc2	36±0.24	0.5±0.01	0.606±0.02	17.5±0.56	1.212±0.03
F5cc1	40±0.32	0.44±0.04	0.555±0.05	20±0.62	1.261±0.02
F5cc2	42±0.36	0.46±0.04	0.540±0.04	23.95±0.75	1.173±0.05

- **Preparation of Rosuvastatin Calcium Tablets with Solid Dispersion**

Among the solid dispersions prepared and based upon the dissolution studies performed, optimized dispersions were selected for further preparation as Orodispersible tablets. The solid dispersions prepared by solvent evaporation method with Rosuvastatin to PEG 6000 to Starch-5-phosphate in the ratio of **1:1:1 (F1), 1:2:5 (F4) and 1:1:9 (F5)** were further compressed as tablets. The tablets were prepared by direct compression process in controlled environment. The average weights of all the batches of tablet formulations were maintained

uniformly by using directly compressible Mannitol as diluents and Crosscarmellose as superdisintegrant. All other excipients were individually weighed, passed through sieve no. 60#. The powder mixture was then lubricated with 1% Talc and Magnesium stearate and directly compressed as matrix tablets using MINIPRESS I (RIMEK) 10-station rotary tablet compression machine using a set of 6mm flat-faced punch & die. Compositions of various tablet formulations are given in Table-6.

- **Estimation of post-compression parameters of Rosuvastatin tablets**

The physical parameters such as uniformity of weight, hardness, friability, disintegration time and drug content were evaluated for the prepared batches of tablets as per the Indian Pharmacopoeial Standards as shown in Table-6.

Table 6: Composition of different formulations by Direct Compression

Ingredients (mg)	F1cc1	F1cc2	F4cc1	F4cc2	F5cc1	F5cc2
Drug	1000	1000	1000	1000	1000	1000
PEG	--	--	2000	2000	1000	1000
Starch-5-phosphate	5050	5550	5000	5000	9000	9000
Mannitol	11000	11000	9050	9550	6050	6550
Aspartame	500	500	500	500	500	500
Sodium saccharin	300	300	300	300	300	300
Talc	300	300	300	300	300	300
Magnesium stearate	300	300	300	300	300	300
Vanilline	50	50	50	50	50	50
Cross-carmellose	1500	1000	1500	1000	1500	1000
Total weight	20000	20000	20000	20000	20000	20000

Table 7: Post-compression parameters of Rosuvastatin Calcium Orodispersible tablet

Formulation	Average weight (mg)	Hardness (kg/cm^2)	Disintegration time (min)	Drug content (mg)
F1cc1	101±0.81	3±0.11	2.40	5.97
F1cc2	100±0.75	3±0.13	2.51	5.82
F4cc1	101±1.17	3±0.11	3.00	5.48
F4cc2	102±1.24	3±0.11	3.20	5.66
F5cc1	103±1.17	3.5±0.14	4.30	5.91
F5cc2	102±2.16	4±0.17	3.40	6.01

- ***In-vitro* drug release study**

The *in-vitro* dissolution studies of Rosuvastatin Calcium immediate release sublingual tablets were carried out in USP Type-II dissolution test apparatus. The drug release study was carried out in 900ml phosphate buffer (pH 6.8) as the dissolution medium with agitation speed 75rpm, maintained at 37±0.5°C. At predetermined time intervals, aliquot of 10ml of samples was withdrawn and filtered by Whatmann filter paper. The volume withdrawn at each interval was replaced with same quantity of fresh dissolution medium. The samples were analyzed for cumulative drug release by measuring the absorbance at 242nm in UV spectrophotometer.

- **Dissolution Efficiency**

The dissolution efficiency (DE%) of a pharmaceutical dosage form is defined as the area under the dissolution curve up to a certain time (t) expressed as a percentage of the area of the rectangle described by 100% dissolution in the same time. This concept was proposed by Khan and Rhodes and is calculated by the equation:

$$DE\,\% = \int_0^t [y.dt / y100.t] * 100$$

Where, **y** is the percent drug release as the function of time t. **y100** is 100% drug release and t is the total time of drug release.

The amount of drug present in the sample was calculated with the help of appropriate calibration curve constructed from reference standards. The dissolution profiles of formulations are shown in below.

Table 8: Composition of different batches of RSV Orodispersible tablets

Per Tablet Ingredients (mg)	F1cc	F1cc1	F1cc2	F4cc	F4cc1	F4cc2	F5cc	F5cc1	F5cc2
Rosuvastatin Calcium (RSV)	10	10	10	--	--	--	--	--	--
RSV+PEG+Starch-5-phosphate	--	--	--	80	80	80	110	110	110
Starch-5-phosphate	60.5	50.5	55.5	--	--	--	--	--	--
Mannitol	110	110	110	100.5	90.5	95.5	70.5	60.5	65.5

Aspartame	5	5	5	5	5	5	5	5	5
Sodium saccharin	3	3	3	3	3	3	3	3	3
Talc	3	3	3	3	3	3	3	3	3
Magnesium stearate	3	3	3	3	3	3	3	3	3
Vanilline	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Cross-carmellose	5	15	10	5	15	10	5	15	10
Total weight	200	200	200	200	200	200	200	200	200
	Physical Mixture			SD with Drug:PEG:Starch-5-Phosphate = 1:2:5			SD with Drug:PEG:Starch-5-Phosphate = 1:1:9		

[F1 = Physical mixture 1:1:1; F4 & F5 = Solid dispersion in 1:2:5 (F4) and 1:1:9 (F5)]

Table 9: %CDR of different marketed brands of Rosuvastatin Calcium 5 mg tablets

TIME(min)	ROZUCOR	ROZUMAC	ROSUVAS	ZYROVA	CRESTOR
5	20.40	19.20	19.80	18.60	25.20
10	27.00	25.80	30.60	26.40	33.60
15	31.80	31.20	48.60	30.60	42.00
20	45.00	39.00	55.80	37.20	57.00
25	57.60	47.40	63.60	48.60	68.40
30	77.40	68.40	76.80	66.60	79.80
45	92.40	78.00	90.60	80.40	87.00
60	97.80	89.40	96.60	94.20	94.80
	No of Time Points where %CDR >70% at 30 mins				

Table 10: %CDR of different formulated batches of Rosuvastatin Calcium 5 mg tablets

TIME (min)	F1cc	F1cc1	F1cc2	F4cc	F4cc1	F4cc2	F5cc	F5cc1	F5cc2
0	0	0	0	0	0	0	0	0	0
5	94.64	76.11	88.79	96.33	85.80	93.15	106.62	90.67	95.10
10	95.40	96.86	96.83	97.76	99.04	99.19	109.23	99.68	99.26
15	95.40	100.40	98.06	97.76	102.67	102.95	113.41	100.95	101.36
20	100.77	102.03	96.80	99.20	104.52	104.43	113.94	102.24	102.22
25	100.77	102.54	100.69	100.16	105.27	105.48	115.51	103.13	102.98
30	100.38	105.15	102.08	100.16	107.13	106.25	119.69	104.93	103.62
45	101.53	107.08	102.92	101.12	107.52	107.64	119.69	106.10	105.56
60	102.30	109.01	105.45	104.95	108.28	108.01	120.73	107.63	106.82

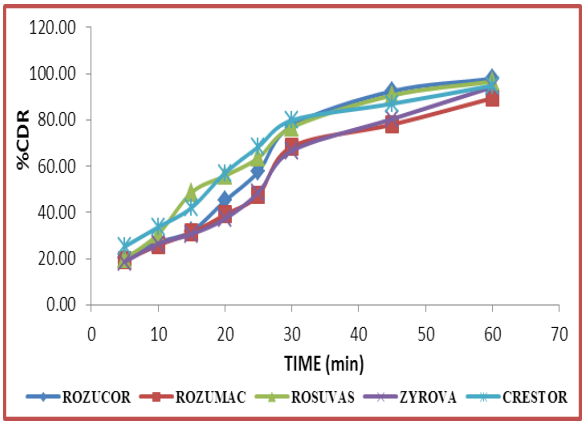


Fig 4: %CDR of different marketed brands of Rosuvastatin Calcium 5 mg tablets

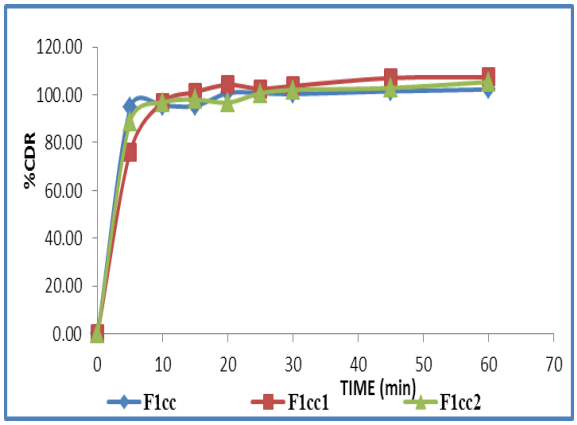


Fig 5: %CDR of F1 formulated tablets of Rosuvastatin Calcium 5 mg

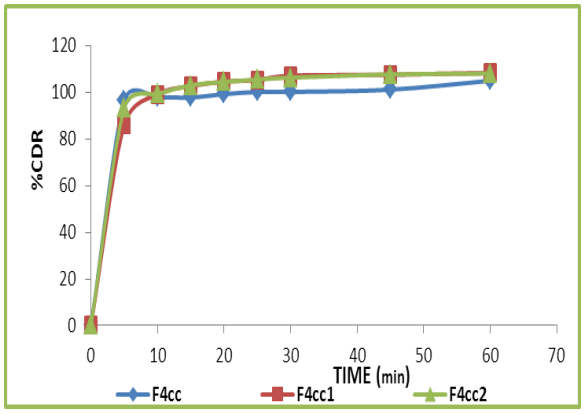


Fig. 6: %CDR of F4 formulated tablets of Rosuvastatin Calcium 5 mg

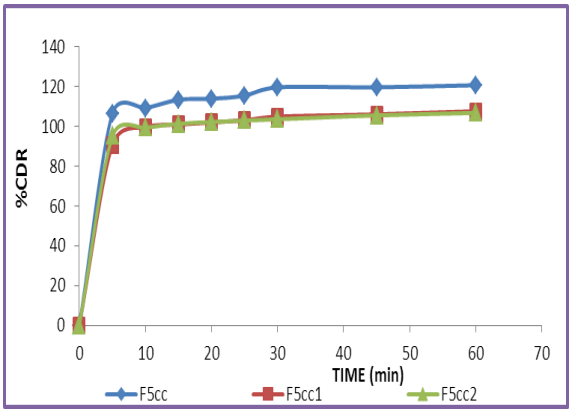


Fig. 7: %CDR of F5 formulated tablets of Rosuvastatin Calcium 5 mg

Table 11: AUC of different marketed brands of Rosuvastatin Calcium 5 mg tablets

Area Under the Curve (AUC) of %CDR vs. Time					
AUC= 0.5*{(CDR1+CDR2)*(t2-t1)}					
Time (min)	**ROZUCOR**	**ROZUMAC**	**ROSUVAS**	**ZYROVA**	**CRESTOR**
5	118.50	112.50	126.00	112.50	147.00
10	147.00	142.50	198.00	142.50	189.00
15	192.00	175.50	261.00	169.50	247.50
20	256.50	216.00	298.50	214.50	313.50
25	337.50	289.50	351.00	288.00	370.50
30	1273.50	1098.00	1255.50	1102.50	1251.00
45	1426.50	1255.50	1404.00	1309.50	1363.50

Table 12: % Dissolution Efficiency of marketed brands of Rosuvastatin Calcium tablets

% Dissolution Efficiency					
DEtmax= AUC/(Ymax*tmax)					
%DEmax	**ROZUCOR**	**ROZUMAC**	**ROSUVAS**	**ZYROVA**	**CRESTOR**
DE_5	**23.70**	**22.50**	**25.20**	**22.50**	**29.40**
DE_{15}	**30.50**	**28.70**	**39.00**	**28.30**	**38.90**
DE_{30}	**77.50**	**67.80**	**83.00**	**67.65**	**83.95**
DE_{45}	**83.37**	**73.10**	**86.53**	**74.20**	**86.27**

Table 13: AUC of F1 formulated batches of Rosuvastatin Calcium tablets

Area Under the Curve (AUC) of %CDR vs. Time			
AUC= 0.5*{(CDR1+CDR2)*(t2-t1)}			
Time (min)	**F1cc**	**F1cc1**	**F1cc2**
0	236.59	190.26	221.98
5	475.10	432.41	464.07
10	477.01	493.13	487.23
15	490.42	506.08	487.13
20	503.83	511.43	493.71
25	502.87	519.21	506.93
30	1514.37	1591.68	1537.48
45	1528.74	1620.66	1562.72

Table 14: AUC of F4 formulated batches of Rosuvastatin Calcium tablets

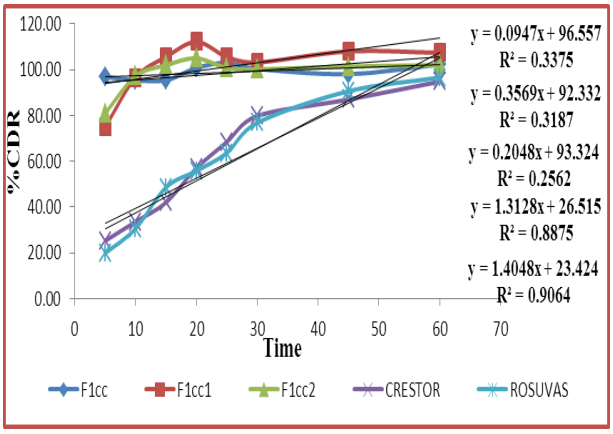
Area Under the Curve (AUC) of %CDR vs. Time			
AUC= 0.5*{(CDR1+CDR2)*(t2-t1)}			
Time (min)	**F4cc**	**F4cc1**	**F4cc2**
0	240.81	214.50	232.88
	485.22	462.11	480.85
10	488.82	504.27	505.36
15	492.41	517.97	518.46
20	498.40	524.49	524.79
25	500.80	531.02	529.33
30	1509.58	1609.87	1604.18
45	1545.53	1618.50	1617.35

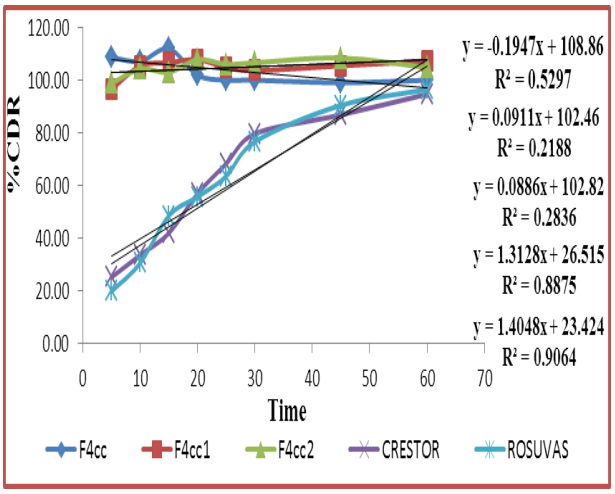
Table 15: AUC of F5 formulated batches of Rosuvastatin Calcium tablets

Area Under the Curve (AUC) of %CDR vs. Time			
AUC= 0.5*{(CDR1+CDR2)*(t2-t1)}			
Time (min)	**F5cc**	**F5cc1**	**F5cc2**
0	266.55	226.68	237.74
5	539.63	475.88	485.88
10	556.62	501.58	501.53
15	568.38	507.48	508.94
20	573.61	512.93	513.00
25	587.98	520.16	516.51
30	1795.30	1582.73	1568.87
45	1803.14	1602.98	1592.88

Table 16: % DE of F1, F4 &F5 formulated tablets of Rosuvastatin Calcium 5 mg

% Dissolution Efficiency					
$\%DE_{max}$	DEtmax= AUC/(Ymax*tmax)				
	F1cc	**F1cc1**	**F1cc2**	**CRESTOR**	**ROSUVAS**
DE_5	96.2	85.8	89.1	29.4	25.2
DE_{15}	112.7	111.1	110.9	38.9	39.0
	F4cc	**F4cc1**	**F4cc2**	**CRESTOR**	**ROSUVAS**
DE_5	108.1	101.1	101.7	29.4	25.2
DE_{15}	126.4	121.0	120.2	38.9	39.0
	F5cc	**F5cc1**	**F5cc2**	**CRESTOR**	**ROSUVAS**
DE_5	107.9	100.5	100.8	29.4	25.2
DE_{15}	128.7	117.9	119.9	38.9	39.0





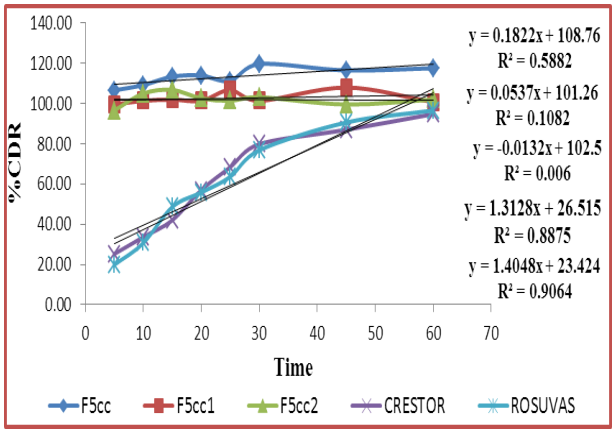
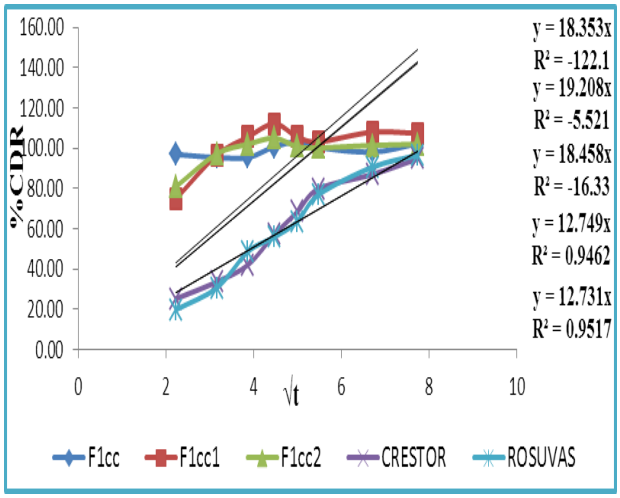
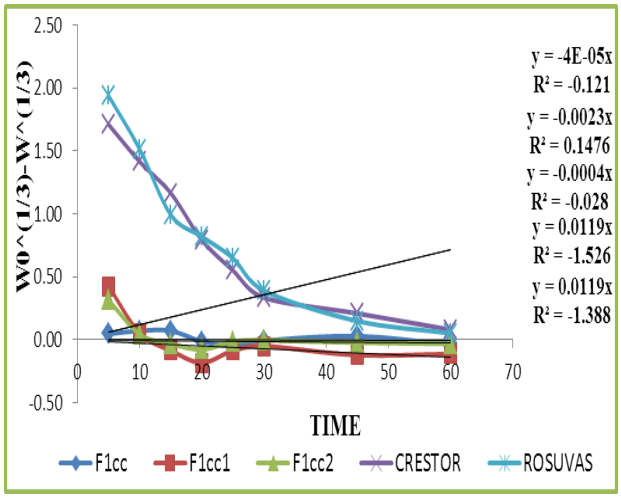
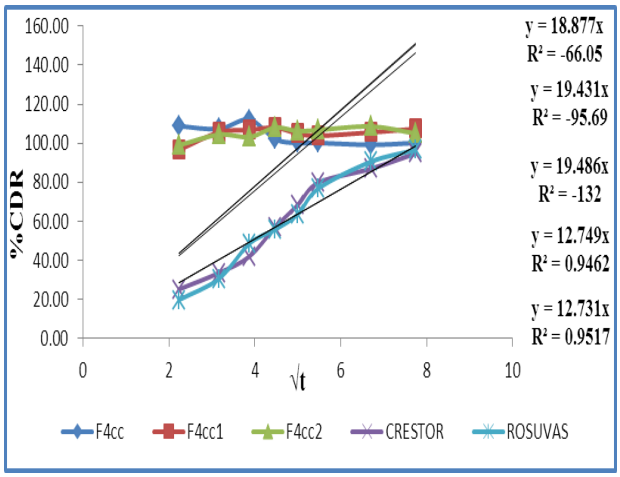
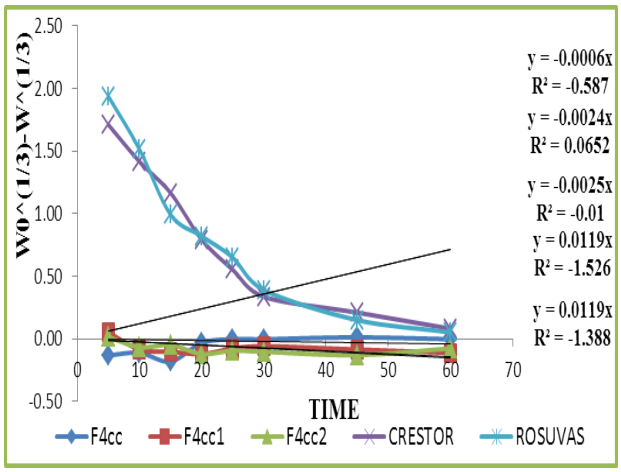


Fig 8: Comparison of % cumulative drug released from F1, F4 & F5 formulations with marketed brands of Rosuvastatin Calcium 5 mg tablets at various time intervals by ZERO ORDER RELEASE









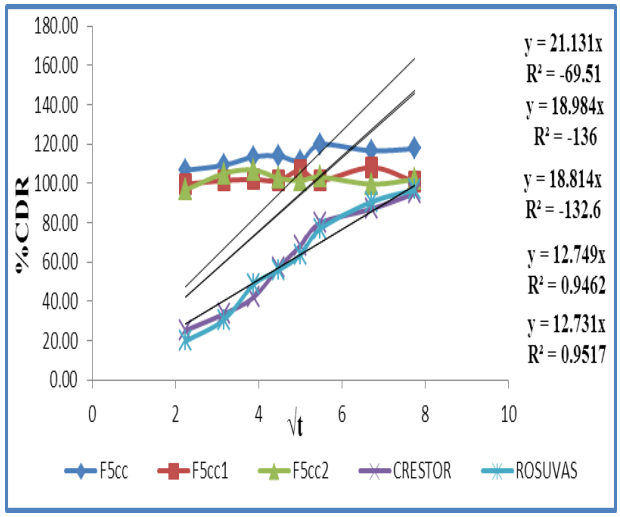


Fig 8: Comparison of % cumulative drug released from F1, F4 & F5 formulations with marketed brands of Rosuvastatin Calcium 5 mg tablets at various time intervals by HIGUCHI MODEL

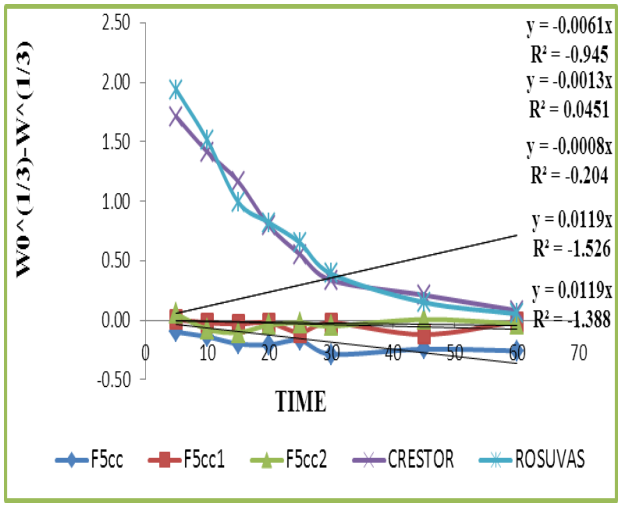
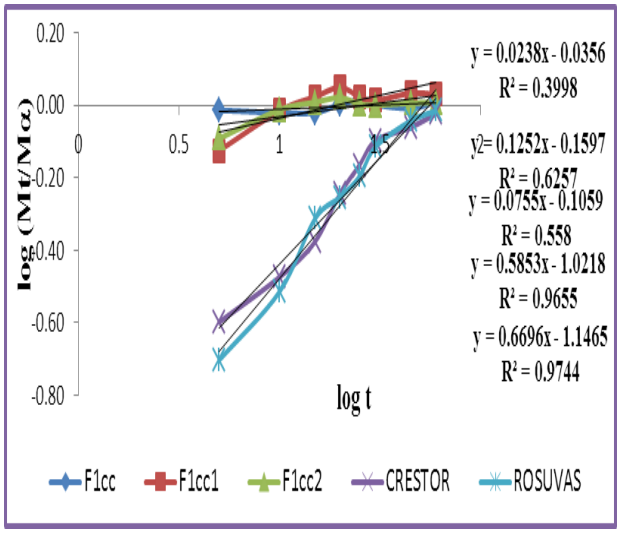
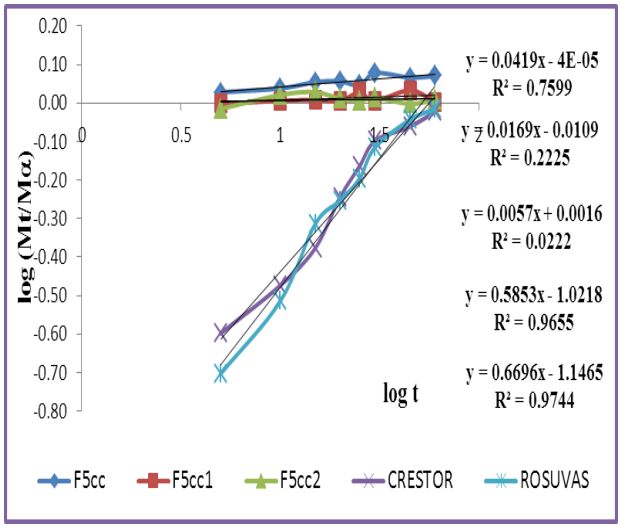


Fig 8: Comparison of % cumulative drug released from F1, F4 & F5 formulations with marketed brands of Rosuvastatin Calcium 5 mg tablets at various time intervals by HIXON-CROWELL MODEL





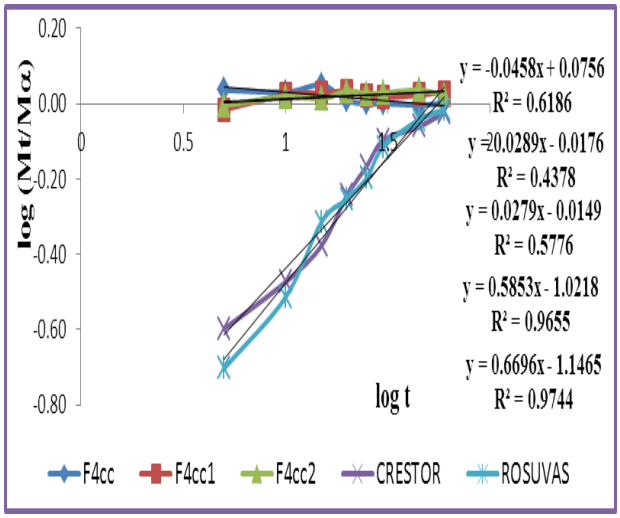


Fig 9: Comparison of % cumulative drug released from F1, F4 & F5 formulations with marketed brands of Rosuvastatin Calcium 5 mg tablets at various time intervals by KORSMEYER-PEPPAS MODEL

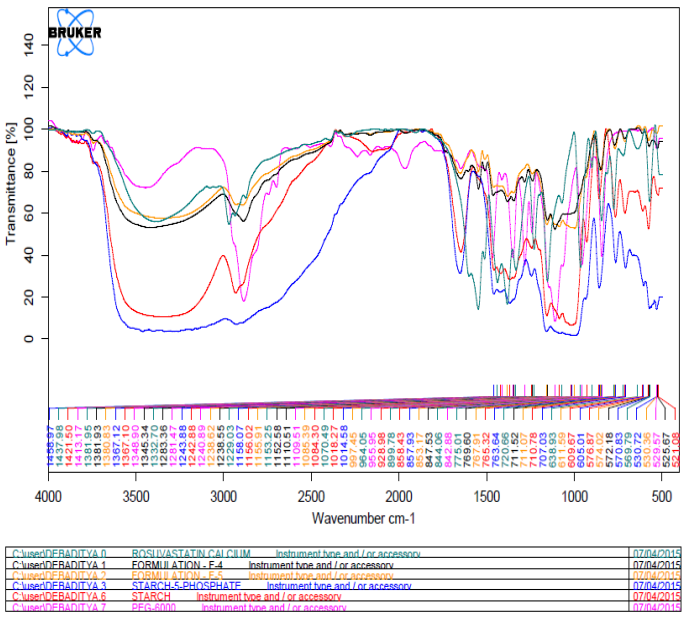


Fig 10: Compatibility study of Rosuvastatin drug & excipients with Optimised formulation F4 by FT-IR STUDY

DISCUSSION

Saturated solubility studies revealed that rosuvastatin showed maximum solubility in pH 6.8 phosphate buffer as medium among the different media used. The drug concentration was measured at 242nm using UV spectrophotometer for all the dissolution media. Solid dispersions were prepared by incorporating poorly soluble rosuvastatin into PEG 6000 by solvent evaporation method as per the composition shown in Table-2. All dispersions were prepared under similar conditions to avoid batch to batch variations. The dispersions were found to be uniform in their characteristics.

The dissolution studies of rosuvastatin as pure drug and its solid dispersions were performed in pH 6.8 phosphate buffer by using paddle method. The dissolution rate of all the solid dispersions were found to be rapid than compared to its pure drug rosuvastatin. Formulation F4 prepared by solvent evaporation method in drug to polymer ratio 1:2was found to release the drug rapidly than the other solid dispersions. It was found that as polymer concentrations increases the drug release also increases.

The solid dispersions were further directly compressed as tablets. All the tablets were compressed under identical conditions to avoid processing variables. The ratio of drug and polymer were maintained constant while the super disintegrant concentration was varied. The physical parameters such as weight uniformity, hardness, drug content, dispersion time were evaluated for prepared tablets (Table-4).

The rate of dissolution of tablet formulations was rapid when compared to the marketed tablet of rosuvastatin. Formulations F4 and F5 prepared by solvent evaporation method with cross carmellose was found to release the drug rapidly than the other tablet formulations i.e. 100% of the drug released within 5min was suitable as fast dissolving tablet.

CONCLUSION

The present study has shown that it is possible to increase the dissolution rate of poorly water soluble drug rosuvastatin by preparing solid dispersions with super disintegrants like cross carmellose and mannitol. The solid dispersions exhibit faster dissolution characteristics as compared to plain drug. This was due to solubilising effect of the carrier or crystallization of drug entrapped in molecular state by the carrier. Solid dispersions in the drug to polymer ratio 1:2 released the drug rapidly than the pure drug and other dispersions. Based on the study it has been revealed that the % CDR has touched 100% at 5 minutes for the formulated products (F4 & F5) with dissolution efficiency (DE_5), found to be 101.1% & 100.5% in comparison to 29.4% & 25.2% for CRESTOR & ROSUVAS (branded products). Further the disintegration time for F4 & F5 sublingual tablet formulations shows around 3 minutes compared to 1 hour in case of branded products as referred. Further the designing of sublingual tablets contrary to the oral swallow able tablets of Rosuvastatin calcium marketed by different pharma companies may lead to a new arena so that hepatic first pass metabolism could be avoided with increased buccal capillary absorption and improved bioavailability due to comparative faster dissolution.

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