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COST EFFECTIVE FORMULATION DEVELOPMENT OF ROSUVASTATIN IN COMPARED TO INNOVATOR BRAND & EVALUATION OF INTERCHANGEABILITY VIA IN-VITRO BIO-EQUIVALENCE STUDY

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ABSTRACT

Generic Rosuvastatin formulation has been developed which is comparatively cost-effective as well as bio-similar in efficacy in compared with the Brand drug **Crestor (**Rosuvastatin). Research shows that overpriced medicines causes huge national burden and health care expenses has gone out of control. A Study results shows that millions of adults patients skip over medications to buy due to their high cost (*Robin A. Cohen, Maria A. Villarroel, NCSH Researchers. 2013).*[1] Research also found that patients are used to save money on drugs costs and they asked doctors for lower-cost medications, buying prescription drugs from other countries and using alternative therapies. So, high drugs costs problems can be handled by development of cost-effective generic drugs with same therapeutic efficacy or bio-similar to brand name drugs. According to *US. FDA* - a generic medicine give the identical clinical benefit and works in the same way like other brand-name version drugs. This standard applies to all FDA-approved generic medicines in safety, dosage form, strength, quality, route of administration, and intended use"*(US FDA 2017).*[2] So, with the main focusing of cost-defective formulation development, we have tried to evaluate the overall quality of developed drugs from the points of - dosage form, therapeutic efficacy, strength, safety, route of administration, performance quality, characteristics and intended use. We have conducted an **In-Vitro Bio-Equivalence Study** to establish the bio-similarity

of **Generic Rosuvastatin** and we have achieved similar results like **Brand name Rosuvastatin- Crestor**. New developed **Generic Rosuvastatin** tablets found **therapeutically bio-equivalent** as the Brand name innovator and more cost-effective than brand drug.

KEYWORDS: Rosuvastatin, Formulation, Cost-Effectiveness, Bio-similarity, Direct Compression Method, Dissolution profile, Bio-equivance Study.

INTRODUCTION

People take drug in urgent necessity not for luxury; it's needed for life-saving. But sometimes medication does not come in any way for life saving when citizens cannot pay for that drug. Global healthcare expenditures have been increasing sharply, for what drug costs are major factors. Having regular easy access to health care is one of the most fundamental human rights, which includes easy access to secured and inexpensive prescription drugs. It is time to ratify the overall prescription drug policies that suitable for everyone, not just for the chief officials of the pharmaceutical industry. Recent market reports focused the growing cost of prescription drugs globally, which are outpaces in a number of disease areas, other health care expenses results in a non standard global accessibility of essential medicines (*berniesanders.com/issues/fighting-to-lower-prescription-drug-prices/*).[3]

According to *US FDA guideline* - **'**similarities of in-vitro bio-equivalence study results of new developed generics helps to demonstrate bio-equivalence of generics, which means a generic medicine give the identical clinical benefit and works in the same way like other brand-name version drugs. In other words, patients can take a low cost generic medicine as an identical substitute for its innovator brand-name counterpart'' (*US FDA guideline).*[4] Except this, there is a common psychology of peoples that high cost drug product manufactured by top pharmaceutical companies are better in quality compared with the low cost generics.

All of these facts directed our interest to prove the **Interchangeability of developed generic** that it has same quality as **Innovator / Brand name** product. Assessment of the quality of developed formulation was carried out with extraordinary emphasis on physico-chemical properties and comparative dissolution study due to their enormous importance in predicting bio-availability and product quality. The innovator brand is under patent

protection in the United States, Europe and major pharmaceutical markets and therefore highly expensive for patients in this region.

In today's world, globally overall healthcare expenses have been increasing aggressively where high drug costs are one of the most significant factor for this. Market researchers in this sector found that the brand-name drug or innovator drugs are highly expensive, recent public utterance has also highlighted the increasing expenses of prescription drugs worldwide *(Cathy, M. 2017).*[5] Pharma market based research literature's found that many drug manufacturers consistently launching high priced products, in addition with this, they are routinely raising the prices of existing generic drugs, including life saving prescription drugs (*Source: AHIP.ORG).*[6]

According to the *Institute for Healthcare Informatics IMS*, generic drugs significantly reduces the costs of medicines. Generic drugs enters the market at considerably lower prices than the innovator brands for which they are replaced and their costs go on with to fall in consequent years. This gives opportunity to payers and patients for savings, as well as the health-care system as a whole. Americans over the past decade paid of huge dollars for health care.*(QuintilesIMS Institute for Healthcare Informatics - IMS Health).*[7]

Its very natural that research and innovation of new drugs or pharmaceuticals are one of the most prominent nature of Pharma industries and they are incessantly developing new therapeutic entities, new generic drug formulations of existing innovator brand expensive drugs (*Petrova, E. 2013, USA*).[8] However presently some developed European countries implementing different types of policies for controlling brand-name drug or innovator brand prescription drug spending *(Gross, David J. et al, 1994).*[9]

Presently, pharmaceutical industries also experiencing tough most times due to keep balance with increased market expectations for lowering overall generic medication costs, also for near term patent expiration's of top selling drugs *(Kenneth I. Kaitin, 2010).*[10]

Researchers found that Generic drugs are always less pricey than brand name innovator drugs and the consumer can save money by choosing a generic version of any drug existing on the market *(Source: Generic Drug, ScienceDirect.Com).*[11]

In this research study, after justifying the present high market price of Rosuvastatin drug (Innovator / Brand Name Drug) we have decided to conduct further research approach to

develop a new bio-similar cost effective formulation of Rosuvastatin in compared to innovator brand. The evaluation of interchangeability of Rosuvastatin has been successfully carried out via in-vitro bio-equivalence study.

BACK-GROUND OF THE RESEARCH

On 2nd October 2017, An Action Plan for Drug Competition was announced in the Official blog of FDA (*Scott Gottlieb, M.D. Commissioner of the US Food and Drug Administration FDA)* to implement new policies that can build a platform where more competition can happen between generics and complex brand drugs. The purpose was to assist consumers / patients to improve their access to less expensive generic drugs, rather than highly expensive complex branded drugs. Also to assist generic makers to meet the requirements at various stages of manufacturing of generics such as product development, pre-submission of applications and review of applications. "Drug access is a matter of public health concern," *Gottlieb* said. enabling further generic drug competition, helps to lessen medicine prices, ensures more access, and advances in public health".[12]

There are a lot of reasons of why health care expenditures has gone out of control and become such an enormous national burden, together with over-testing, the aging and obesity problem of the common people, communication gap between health care professionals and lack of information about what treatments are most effective. With all these reason's she has been focused on a significant inherent reason that often goes unnoticed is the use of highly expensive branded drugs versus their cheaper, generic alternatives (*Catherine Rampell, June 4, 2012, economix.blogs.nytimes.com*).[13]

ProPublica, *New York City, USA* - nonprofit organization of investigative journalism for public interest, says that - **Brand-name medicines** are more expensive, but it don't have any impact on patient contentment. ***ProPublica*** worked to compare some patient reviews about generics and brands in different categories of drug including those drugs that prescribes to lower cholesterol. After analyzing the reviews of patients they have found that for each class of drug, a generic drug scored the best rank on each of the three questions than an expensive brand name drug. According to there report about cholesterol-lowering drugs of **Statin class drugs** like **Lipitor** & **Zocor** are now available as generics and are inexpensive in compared to the **Brand drug Crestor,** that is made by AstraZeneca, who are still in continuation to have patent protection and costs more than $230 for 30 pills at Costco. In-expensive generic alternatives of **Lipitor** & **Zocor** has the same user satisfaction score as the **Brand name**

drug Crestor (*Charles Ornstein, ProPublica, Nov. 21, 2015, published in uk.businessinsider.com*).[14]

For **Statins - the lipid lowering drugs**, the most important difference among **Generic** vs **Brand-name versions** is cost, as **generic Statins (Rosuvastatin)** are far inexpensive than **Brand-name versions (Crestor)**. But the price of **Brand-name versions** doesn't usually drop until different companies start making the **generic versions** drug. *(Deepak Bhatt, MD, MPH, Editor in Chief, Harvard Heart Letter, www.health.harvard.edu).*[15]

All investigative news's, reports, research findings discussed above ultimately encourages Pharma educators, researchers, manufacturers to conduct further research on developing cost-effective, bio-similar generics to play significant role in controlling national health care expenditures.

DATA SOURCES

Systematic searches of Peer-reviewed publications in Journals in NCBI Databases, Science Direct, PUBMED, FDA Official Blog, EMBASE database, NCBI News & Blog, MEDLINE database, IMS Institute for Healthcare Informatics, Harvard Health Edu Blog, UK Business Insider, NY Times, ProPublica - Investigative Statistical Reports, and International Pharmaceutical Abstracts published from January 1984 to 2017.

ROSUVASTATIN DRUG PROFILE

Rosuvastatin drug is a drug of **Anti-hyperlipidemic** class; the active ingredient is **Rosuvastatin calcium.** It is a widely prescribed **lipid or cholesterol-lowering drug,** used to decrease plasma cholesterol levels and prevent cardiovascular disease *(Adams, SP., et al 2014).*[16] It belongs to a class of drugs called **Statins.** It competitively inhibits HMG-CoA reductase. HMG-CoA reductase is an enzyme catalyzes the conversion of HMG-CoA to mevalonic acid, that defined as the rate-limiting step in cholesterol bio-synthesis.

Rosuvastatin is a competitive inhibitor of the enzyme HMG-CoA reductase, it has a mechanism of action similar to that of other statins class drugs.[17] Rosuvastatin calcium works by slowing down the production of cholesterol in the body, used to make lower level of cholesterol and fats in the blood. It helps to decrease the chances of developing heart disease type problems and strokes that is partly caused by high cholesterol levels.

Development of interchangeable formulation is one of the best and ideal methods to improve patient complacence and bio availability and to gives immediate relief. In the present circumstances alongside with the progress of various drug technologies, this kind of developments are extensively employed and show an acceptable outputs. There are a variety of methods to manufacture improved formulation which are traditional methods like wet granulation technique, direct compression method or moulding technique etc.

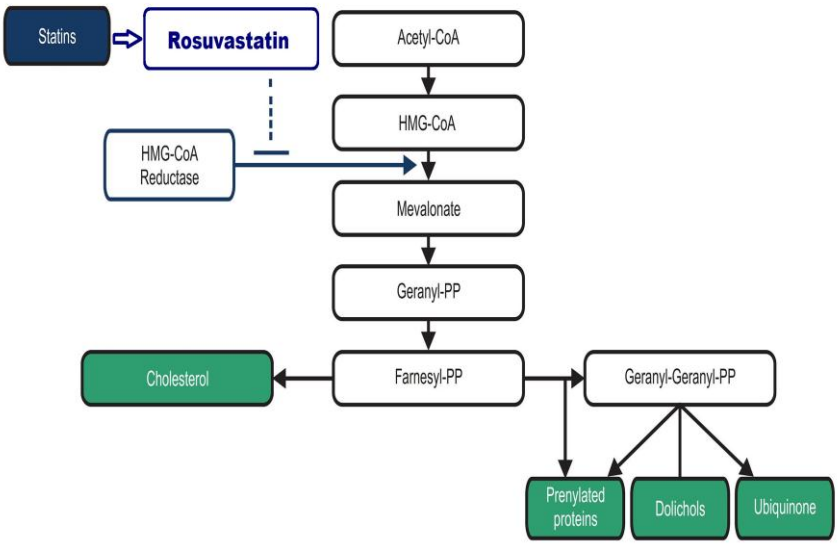

Figure 1: Rosuvastatin Mechanism of Action.

Picture Source: *scielo.br (http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0066-782X2015000400009)*

METHODS AND MATERIALS

For new formulation development of Generic Rosuvastatin, **Quality by Design (QbD)** principles has been applied to ensure that product quality is built in by design. According to ICH Q8 guideline - Quality by Design is a systematic risk-based, practical approach of pharmaceutical development that begins with predetermined objectives and gives emphasis to product and process understanding as well as process control, based on sound practical science and quality risk management. On the base of this we have designed the generic product formulation and the process to meet the pre-determined product attributes of safety, efficacy, dosage form, strength and quality. The details process of formulation development has been discussed in this paper.

In order to improve the physicochemical behavior and pharmacokinetics like innovator product, by using direct compression method by adjusting various concentration of Microcrystalline Cellulose, Lactose Monohydrade & Pregelatinized Starch. Physico-chemical analysis and comparative dissolution study has been conducted to estimate the quality of individuals formulation.

FORMULA DESIGN

Six trial formulations **(RF1, RF2, RF3, RF4, RF5, RF6)** with an average tablet weight of 126 mg were developed by direct compression method. In each formulation the excipients using with different ratios in considered to innovator drug formulation and with independent variables, they are: Micro-crystalline Cellulose (33.33-53.17) %, Lactose Monohydrade (17.86–27.77) %, Pregelatinized Starch (13.9-23.01) %. The Formulations are presented in **Table: 1.** The formulations were equivalent to the reference product with similarity factor (f2) and difference factor (f1) within the satisfactory range for both Rosuvastatin and developed formulation. **Formula number RF4** containing Microcrystalline Cellulose 41.27%, Lactose Monohydrade 23.81% & Pregelatinized Starch 19.05% were found to be the best formulation shows good physicochemical behavior and dissolution profile.

Table 1: Different Formula of Rosuvastatin tablets.

Ingredients	Quantities in mg per tablet					
	RF1	RF2	RF3	RF4	RF5	RF6
Rosuvastatin Calcium	10.42 mg	10.42 mg	10.42 mg	10.42 mg	10.42 mg	10.42 mg
Microcrystalline Cellulose	67.00 mg	62.00 mg	57.00 mg	52.00 mg	47.00 mg	42.00 mg
Lactose Monohydrate	22.5 mg	25.00 mg	27.5 mg	30.00 mg	32.50 mg	35.00 mg
Pregelatinized Starch	16.5 mg	19.00 mg	21.5 mg	24.00 mg	26.50 mg	29.00 mg
Crospovidone	2.40 mg	2.40 mg	2.40 mg	2.40 mg	2.40 mg	2.40 mg
Magnesium Stearate	0.82 mg	0.82 mg	0.82 mg	0.82 mg	0.82 mg	0.82 mg
Colloidal Anhydrous Silica	0.36 mg	0.36 mg	0.36 mg	0.36 mg	0.36 mg	0.36 mg
Hypromellose	3.00 mg	3.00 mg	3.00 mg	3.00 mg	3.00 mg	3.00 mg
Titanium dioxide,	2.00 mg	2.00 mg	2.00 mg	2.00 mg	2.00 mg	2.00 mg
Propylene glycol	1.00 mg	1.00 mg	1.00 mg	1.00 mg	1.00 mg	1.00 mg
Purified water *	qs	qs	qs	qs	qs	qs
Total Weight	126 mg	126 mg	126 mg	126 mg	126 mg	126 mg

* Used as coating solvent and not appear in finished product.

Equipment

Weighing balance (Satorius, England), Automatic Tablet Hardness Tester (8M, Dr Schleuniger, Switzerland), Tablet Disintegration Tester (Model: VDT-2, Veego, India), Veego Friabilator (VFT-2, India), Tablet Dissolution Tester (TDT-08L, Electrolab, India),

High Perfomance Liquid Chromatography (Shimadzu, Tokyo Japan), Oven drier (Memmert, Germany).

Pre-compressed Parameters

Bulk Density: Formulation blend was properly weighed and transferred to a measuring cylinder. After then the bulk volume was noted. Bulk density of blend was calculated by using the formula given below:

$$\text{Bulk Density} = \frac{\text{Mass of th Powder}}{\text{Bulk Volume}}$$

Tapped Density: The tablet blend was weighed properly and transferred to the measuring cylinder and subjected to 100 tappings. Then the volume was noted as tapped volume. Tapped density was measured by using the formula given below:

$$\text{Tapped Density} = \frac{\text{Mass of the Powder}}{\text{Tapped Volume}}$$

Carr's Index: Carr's index was calculated by using the following formula.

$$\text{Carr's index} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100$$

Hausner's Ration

Hausner's ratio is an index of ease of powder flow; it's calculated by following formula.

$$\text{Hausner's Ratio} = \frac{\text{Tapped Density}}{\text{Bulk Density}}$$

Post Compression Parameters

Weight Variation

In a weight variation test twenty tablets of manufactured formulation were selected randomly and the average weight was calculated. After then individual tablets were weighed properly and the weight was compared with an average weight.

Hardness test

The crushing strength (KgF) of tablet was determined with an Automatic Tablet Hardness Tester (8M, Dr Schleuniger, Switzerland). The force for crushing was applied to the edge of the tablet and increased gradually by moving the screw knob forward until the tablet was got broken. Ten tablets were selected randomly from each brand and the applied pressure was recorded at which each tablet crushed.[18]

Disintegration test

Six tablets from each new formulation were used for the test in distilled water at 37°C using a Tablet Disintegration Tester (Model: VDT-2, Veego, India). As stated by Alderborn, the disintegration time (DT) was defined as the time when no particle remained in the basket of the system.

Wetting Time

In wetting time a piece of tissue paper folded twice was placed in small petri dish (i.d = 6.5cm) containing 10mL of water, a new formulated tablet was placed on the paper and the required time for complete wetting of that tablet was measured. Three trails for each formulation were performed and standard deviation was also determined.

Friability test

Ten tablets from each new formulation were weighed properly and subjected to abrasion by using a Veego Friabilator (VFT-2, India), operated at 25 RPM for 4 minutes. The Friabilator apparatus was divided into two plastic chambers. During each revolution the tablets were subjected to fall from a distance of six inches to undergo shock. After 100 revolutions the tablets were weighed again. The final loss in weight of tablet indicated the friability.[19]

Assay

From 20 tablets, after determining the average weight and crush the tablet into fine powder and take a quantity of powder about 630 mg (equivalent to 50 mg of Rosuvastatin) in a 100 ml volumetric flask. After then we sdd about 60 ml mobile phase, sonicate for 15 minutes with gentle shake and dilute upto mark with mobile phase. Filter the solution through watman filter paper. Dilute 5 ml of this solution to 25 ml with mobile phase. Finally filter the solution with 0.45µ disk filter.

Comparative study

The dissolution test for this development works was undertaken using Tablet Dissolution Tester (TDT-08L, Electrolab, India) in 12 replicates for each developed formulation involving USP apparatus-II (paddle) at 50 RPM. The dissolution medium was 900 ml of sodium citrate buffer pH 6.6 which was properly maintained at 37 ± 0.5°C. In all the experiments, 20 ml of dissolution sample was withdrawn at 10, 20, 30 and 45 minutes and replaced with an equal volume to maintain an ideal sink condition. The samples were filtered

through. This is the final solution. The solution was then assayed by High-performance liquid chromatography.

The uniformity of tablet weight was analyzed with simple statistics while the dissolution profiles were analyzed by difference factor (f1) and similarity factor (f2).

$$f_1 = \left\{ \frac{\sum_{t=1}^{n} |R_t - T_t|}{\sum_{t=1}^{n} R_t} \right\} X100$$

$$f_2 = 50 \log \left\{ \left(1 + \frac{1}{n} \sum_{i=1}^{n} (R_t - T_t)^2 \right)^{-0.5} X100 \right\}$$

Here: "n" is the number of time points, "Rt" is the dissolution value of the reference product at time t and "Tt" is the dissolution value for the test product at time t. Similarity factor (f2) for the formulation has been accepted by FDA and the European Agency for the assessment of Medicinal Products by the Committee for Proprietary Medicinal Products (CPMP) to compare the dissolution profile. Two new formulated tablet dissolution profiles are considered similar and bio-equivalent, when f1 is between 0 and 15 and f2 is between 50 and 100.[20,28] **Table 4 & Figure 2** shows f2 values of different formulations in respect of the reference brand. It reveals for formulation RF1, RF2, RF3, RF4, RF5 & RF6, f2 value were more than 50. **So, their dissolution profile has been found similar to that of the reference innovator drug product and can be used interchangeably.**

RESULTS AND DISCUSSION

The pre-compression property study was presented in **Table 2,** Hausner's Index of all the formula lies between 0.46 - 0.53 which indicates that their flow was excellent which is in acceptable range. Angle of repose lies between 10.20 – 12.13, representing that they had an excellent flow. The post compression studies of tablets of Rosuvastatin are presented in **Tablet 3**. They reviled that all of the post compression parameters of tablet such as Weight Variation, Friability, Hardness, Wetting time, Disintegration time, Assay - all are within the acceptance ranges for individual tests. Up to certain concentration with varying in concentration of Microcrystalline Cellulose & adjusting Lactose Monohydrade & Pregelatinized Starch the Disintegration Time and Wetting time of tablet was decreased there after more or less remained same. Considering physico-chemical analysis of all the formulation, it is observed that formulation RF4 showed best results among 6 formulations

Table 2 & 3 as well as **best similarity** & **difference factor** in **Table 4**. The Qualitative comparison of formulation of Innovator Brand drug of Rosuvastatin and the new developed Generic Rosuvastatin has displayed in **Table 5**.

Table 2: Pre-formulation analytical studies of different formulations of Rosuvastatin tablets.

Formulation	Bulk density (g/cc) (Avg. ± S.D.)	Tapped density (g/cc) (Avg. ± S.D.)	Carr's index (Avg. ± S.D.)	Hausner's Index (Avg. ± S.D.)	Angle of Repose (Avg. ± S.D.)
RF1	0.19±0.01	0.23±0.02	8.40±0.12	0.53±0.02	10.75± 0.21
RF2	0.21±0.03	0.25±0.05	6.99±0.08	0.51±0.03	10.20± 0.16
RF3	0.19±0.01	0.23±0.02	8.40±0.16	0.53±0.07	12.13± 0.19
RF4	0.20±0.04	0.23±0.01	6.63±0.12	0.49±0.01	11.35± 0.23
RF5	0.19±0.03	0.21±0.02	4.20±0.07	0.46±0.03	10.73± 0.16
RF6	0.19±0.01	0.23±0.05	6.70±0.08	0.47±0.05	10.60± 0.11

Table 3: Post Compression analytical studies of different formulations of Rosuvastatin tablets.

Test Performed	RF1	RF2	RF3	RF4	RF5	RF6
	Results (Avg. ± S.D.)					
Weight Variation (mg)	126.11	125.19	125.23	126.10	127.83	125.96
Hardness (Kg/cm^2)	6.2 ±0.4	7.1 ±0.6	7.4 ±0.1	4.6 ±0.2	8.7 ±0.2	10.4 ±0.2
Friability (%)	0.17±0.03	0.13±0.03	0.10±0.04	0.09±0.06	0.07±0.05	0.05±0.05
Wetting time(sec)	22.2±0.3	24.1±0.4	20.31±0.3	30.3±0.4	50.4±0.7	59.4±0.3
Disintegration time (Min. Sec.)	4.0±0.3	5.1±0.2	5.5±0.2	2.2±0.4	6.3±0.3	8.4±0.2
Assay (%)	98.2	96.9	96.5	98.1	102.1	98.8

Table 4: Dissolution profile of formulated Rosuvastatin tablet and reference innovator sample in sodium citrate buffer pH 6.6.

Time (MIN)		0	10	20	30	45	Similarity factor (f2)	Difference factor (f1)
FORMULATION (average release)	RF1	0	77.37	91.15	90.93	90.28	44	12
	RF2	0	70.97	88.09	84.87	86.60	37	17
	RF3	0	88.41	92.49	92.69	93.84	56	7
	RF4	0	102.55	102.69	101.75	100.68	76	3
	RF5	0	79.73	90.85	94.22	94.75	48	9
	RF6	0	89.64	93.22	94.54	95.10	59	6
RI		0	98.57	99.39	99.88	99.18	-- --	

RI= Reference Innovator

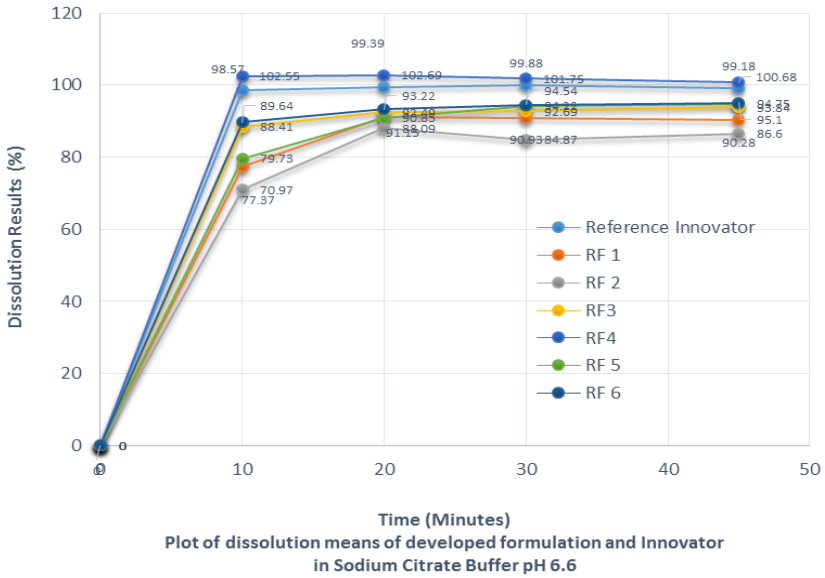

Figure 2: Graphical presentation of comparative dissolution study.

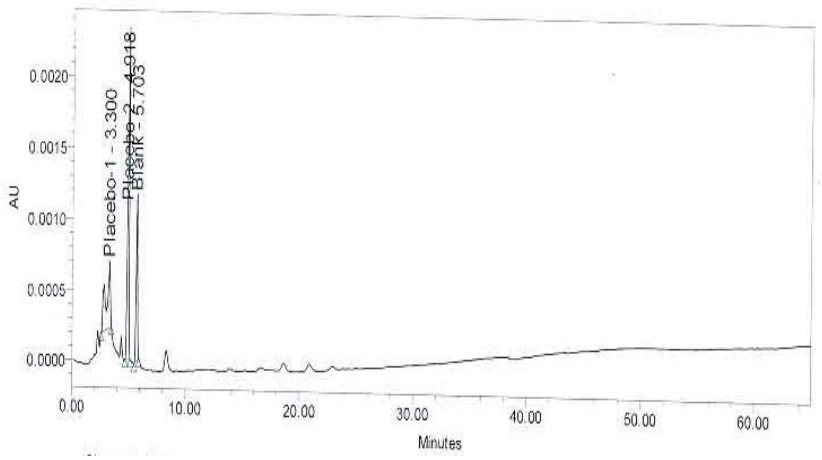

Figure 3: Chromatograms obtained from % Assay.

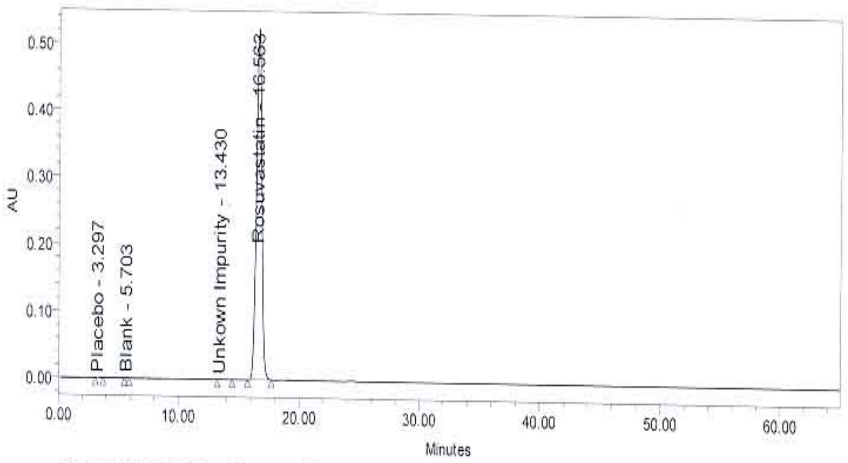

Table 5: Qualitative comparison of formulation.

Reference Innovator (Crestor Tablet 10 mg)	(Selected formulation RF4)
Rosuvastatin Calcium	Rosuvastatin Calcium
Microcrystalline Cellulose	Microcrystalline Cellulose
Lactose monohydrate,	Lactose Monohydrate
Crospovidone	Pregelatinized Starch
Magnesium stearate	Crospovidone
Tribasic Calcium Phosphate	Magnesium Stearate
Hypromellose, Triacetin, Titanium dioxide, Yellow ferric oxide and Red ferric oxide	Colloidal Anhydrous Silica
--	Hypromellose, Titanium dioxide, Propylene glycol, Purified water

CONCLUSION

The Formula number RF4 containing Microcrystalline Cellulose 41.27%, Lactose Monohydrade 23.81% & Pregelatinized Starch 19.05% was found to be the best formulation shows good physicochemical behavior and dissolution profile has been showed a similarity factor (f2) is 76, difference factor (f1) is 3 and good physico-chemical behavior both in granulation and post compression stage.

For the developed generic product **(**formulation RF4**)** the data of **Table 4 & Figure: 2 -** indicates that the product is likely to perform the same with the reference innovator since the computed f1 & f2 is within the acceptance level among 6 formulation. Therefore, it can be anticipated that these RF4 formulation can be considered **interchangeable** with brand name or innovator drugs. This study has showed that the **formulation RF4** can likely to be **bio-equivalent** to the **reference innovator** using Physico-chemical analysis and the in vitro dissolution profile. Finally we have developed the Cost Effective Formulation of Rosuvastatin In Compared To Innovator Brand & Its Interchangeability has been established through In-Vitro Bio-Equivalence Study.

REFERENCES

1. Robin A. Cohen, Maria A. Villarroel, NCSH Researchers. 2013, "Strategies Used by Adults to Reduce Their Prescription Drug Costs: United States, 2013" NCHS Data Brief No. 184, January 2015.
2. U.S. Food and Drug Administration, Published: 10/06/2017 , " Generic Drug Facts." www.fda.gov/drugs/resourcesforyou/consumers/buyingusingmedicinesafely/genericdrugs /UCM167991.htm

3. Fighting to Lower Prescription Drug Prices, (berniesanders.com/issues/fighting-to-lower-prescription-drug-prices/)
4. U.S. Food and Drug Administration, Published: 08/24/2017, "What are generic drugs? www.fda.gov/drugs/resourcesforyou/consumers/questionsanswers/ucm100100.htm
5. Cathy, M. 2017, "Addressing the challenge of high-priced prescription drugs in the era of precision medicine: A systematic review of drug life cycles, therapeutic drug markets and regulatory frameworks", PMCID: PMC5559086 doi: 10.1371/journal.pone.0182613
6. *AHIP.ORG,* "Why are high-cost drugs such a problem for the health care system?" www.ahip.org/issues/high-cost-drugs/
7. IMS Institute for Healthcare Informatics, January, 2016, "Price Declines after Branded Medicines Lose Exclusivity in the U.S.",
8. Petrova, E.(2014), "Innovation in the Pharmaceutical Industry: The Process of Drug Discovery and Development": Page: 19 - 81 , Springer New York.
9. Gross, David J. Ph.D., Ratner, J. Ph.D., Perez, J. B.B.A. and Glavin, Sarah L. Ph.D. "International Pharmaceutical Spending Controls: France, Germany, Sweden and the United Kingdom". Health Care Financ Rev. 1994 Spring; 15(3): 127–140. PMCID: PMC4193451
10. Kenneth I. Kaitin, 2010, "The Landscape for Pharmaceutical Innovation: Drivers of Cost-Effective Clinical Research" www.ncbi.nlm.nih.gov/pmc/articles PMCID: PMC3150117, NIHMSID: NIHMS238078
11. Generic Drug, from An Introduction to Pharmaceutical Sciences, 2011, (ScienceDirect.Com)
12. Scott Gottlieb, M.D, Commissioner of the U.S. Food and Drug Administration, October 2, 2017, "Reducing the Hurdles for Complex, Generic Drug Development", Official Blog FDA.
13. Catherine Rampell, June 4, 2012, "Cheap vs. Expensive Drugs", The NY Times. economix.blogs.nytimes.com
14. Charles Ornstein, Nov. 19, 2015, "Brand-Name Drugs Increase Cost But Not Patient Satisfaction". Propublica.org, uk.businessinsider.com
15. Deepak Bhatt, MD, MPH, Harvard Heart Letter, July, 2016, "Generic versus brand-name statins", Harvard Health Publishing, Harvard Medical School, www.health.harvard.edu
16. Adams, SP., Sekhon, SS, Wright, JM. (2014), "Lipid-lowering efficacy of Rosuvastatin." Cochrane Database Syst Rev., 2014 Nov 21; (11): CD010254. doi: 10.1002/14651858.CD010254.pub2.

17. Nissen SE, Nicholls SJ, Sipahi I, et al. (2006). "Effect of very high-intensity statin therapy on regression of coronary atherosclerosis: the ASTEROID trial" JAMA. 295(13): 1556 65. PMID 16533939. doi:10.1001/jama.295.13.jpc60002.
18. British pharmacopoeia, Medicines and Healthcare products Regulatory Agency (MHRA) of the United Kingdom.
19. United States Pharmacopoeia (USP) is the official pharmacopoeia of the United States, published gradually with the National Formulary as the USP-NF.
20. Oishi TS, Nimmi I, Islam SMA. Comparative in vitro Bioequivalence Analysis of Some Generic Tablets of Atorvastatin, a BCS Class II Compound. Bangladesh Pharm J, 2011; 14(1): 61-66.
21. Kumar P, Ganure AL, Subudhi BB, Shukla S, Upadhyay P. Design and comparative in-vitro and in-vivo evaluation of starch–acrylate graft copolymer based salbutamol sulphate sustained release tablets. Asian J Pharm Sci., 2015; 10(3): 239-246.
22. Nayak AK, Pal D. Comparative in vitro Bioequivalence Analysis of Some Ciprofloxacin HCl Generic Tablets. Int J Pharm Sci Res., 2010; 1(8): 51-57.
23. Karmoker JR, Joydhar P, Sarkar S, Rahman M. Comparative in vitro Evaluation of Various Commercial Brands of Amlodipine Besylate Tablets Marketed in Bangladesh. Asian J Pharm Hea Sci., 2016; 6(1): 1384- 1389.
24. Mangal M, Thakral S, Goswami M, Thakur N. Comparison study between various reported disintegration methods for fast dissolving tablets. African J Basic & Appl Sci., 2012; 4(4): 106-109.
25. Islam SMA, Islam S, Shahriar M, Dewan I. Comparative in vitro Dissolution study of Aceclofenac Marketed Tablets in Two Different Dissolution Media by Validated Analytical Method. J Appl Pharm Sci., 2011; 1(9): 87-92.
26. Popy FA, Dewan I, Parvin MN, Islam SMA. Evaluation of In vitro Equivalence for Tablets Containing the Poorly Water-Soluble Compound Atrovastatin. Dissolution Technology, 2012; 19(4): 30-33.
27. Karmoker JR, Sarkar S, Joydhar P, Chowdhury SF. Comparative in vitro equivalence evaluation of some Aceclofenac generic tablets marketed in Bangladesh. Pharma Innovation J., 2016; 5(3): 03-07.
28. Abbirami V, Sainithya P, Shobana A, Devi DR, Hari BNV. Review on In-vitro Bioequivalence Studies and its Methodologies. Int J Chem Tech Res., 2013; 5(5): 2295- 2302.