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Liquisolid Technique for Enhancement of Dissolution Properties of Rosuvastatin

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ABSTRACT:
The Aim of the study was to enhance the solubility of Rosuvastatin plain drug by using liquisolid compact and formulate at capsules containing such solubility enhanced Rosuvastatin content. The solubility of drug enhanced by using polyethylene glycol 600 and microcrystalline cellulose in liquisolid formulation. Evaluated the plain drug rosuvastatin and drug loaded liquisolid compact by using different analytical test like FTIR, DSC and XRD, which shows all the observed data were as same as reported in official books and literature and matched with standards. The capsules were formulated by using simple excipients such as microcrystalline cellulose, ethyl cellulose, PEG 600 and colloidal silicon dioxide of liquisolid compact. The liquisolid compact containing microcrystalline cellulose shows more solubility than the liquisolid compact containing ethyl cellulose. Release of drug from capsule of containing liquisolid compact which shows enhance the dissolution rate than the plain drug i.e. increase the dissolution of drug.The release of LS 1 formulation shows that almost similar compare to LS of PG , LS of PEG 200 and also the marketed formulation. Results of stability studies showed that there was no significant change in organoleptic properties, drug content, In vitro study of rosuvastatin liquisolid formulation. Thus the result showed that the formulations have good stability

KEYWARDS: Rosuvastatin, liquisolid formulation, solubility, polyethylene glycol 600

I. INTRODUCTION:

Because of its ease, high patient compliance, and low medication production costs, the oral route of drug administration remains the favoured route of drug administration[1]. A pharmaceutical must be dissolved in the stomach juices in order to be absorbed into the systemic circulation after oral delivery. Thus, one of the major challenges to drug development today is poor solubility, as an estimated 40% of all newly developed drugs are poorly soluble or insoluble in water. In addition, up to 50% of orally administered drug compounds suffer from formulation problems related to their low solubility and high lipophilicity. The solubility and dissolution rate of low water soluble hydrophobic medicines (class II in the Biopharmaceutics classification system) restrict their bioavailability[2,3].

By reducing particle size, lowering crystallinity, and/or increasing surface area, the dissolving rate of these drugs can be enhanced. Several studies have been carried out to increase the0 dissolution rate of drugs by decreasing the particle size, by creating nanoparticles and micro particles. However, due to van der Waals attraction or hydrophobicity, tiny drug particles have a strong tendency to agglomerate, resulting in a reduction in surface area over time. Adsorption of the drug onto a high-surface-area carrier is another technique to speed up dissolution. The API is first dissolved in an organic solvent, then the solution is soaked in a high-surface-area carrier such as silica. Because the drug binds to the carrier, agglomeration of the drug particles is avoided. Toxic solvents, on the other hand, are inconvenient toutilize because of the remaining solvent in the pharmaceutical formulation. To overcome the problem, the technique of 'liquisolid compacts' is a promising approach towards dissolution enhancement. Liquisolid compacts have good flowability and compressibility.[2]

In this study Rosuvastatin was selected as model drug, since it is sparingly soluble in water. Based on the Biopharmaceutics Classification System (BCS), it is classified as a Class II drug. Class II drugs have a high permeability but a low solubility in watery environments, preventing the entire dosage from being dissolved in the gastrointestinal system. As a result, dissolution is the rate-determining stage in absorption for these compounds.[4]

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The dissolution rate of Rosuvastatin, a poorly water soluble drug, may be improved by formulating it into liquisolid compacts. Since, the liquisolid capsules contain a solution of the drug in suitable solvent; the drug surface available for dissolution is increased. Liquisolid compacts of water-insoluble compounds may be predicted to have improved drug release characteristics due to considerably increased wetting qualities and surface area of drug accessible for disintegration and, consequently, improved oral bioavailability. Even though the drug is in a solid dosage form, it is kept in solution or in a solubilized, virtually molecularly distributed condition inside the powder substrate, contributing to improved drug dissolving characteristics.[1,5]

The aim of this study was envisaged to "FORMULATION DEVELOPMENT AND EVALUATION OF DOSAGE FORM OF POORLY WATER SOLUBLE DRUG". Prepare the formulation which can enhance the solubility of a poorly soluble drug. It was hypothesized that combination of drug and polymer in liquisolid compact will enhance its solubility which in turn may help in enhancing the absorption through gastro-intestinal tract and ultimately the bioavailability.

II. MATERIAL AND METHODS

Rosuvastatin was purchase sample from Pharmaguide, Mumbai. Avicel pH 102,Aerosil 200, Colloidal silicone dioxide, Tween 80, Hydrochloric acid, Methanol and sodium Tween 20, PEG 600 and PEG400 were obtained from Lobachemie Pvt. Ltd. and Ethyl cellulose obtained from Research lab fine chem industries. All the other chemical substances were of analytical grade.

INFRARED SPECTROSCOPY[6,7]:
An Infrared spectrum of Rosuvastatin was obtained by using BRUKER ALPHA-E. The spectrum was scanned over a frequency range 4000– 400 cm-1.This study was carried out at Dr. BabasahebAmbedkarMarathwada University,Aurangabad.

Differential scanning calorimetry[8–10]:
DSC was performed using HITACHI DSC7020 in order to assess the thermotropic properties and the thermal behaviors of the drug Rosuvastatin was prepared. This study was carried out at Dr. BabasahebAmbedkarMarathwada University,Aurangabad.

X-RAY POWDER DIFFRACTION[11,12]:
Crystallinity study was carried out by comparing XRD spectrum of drug with formulation to check peak of drug. Study was carried out on Smartlab Cu 1.5 KV, Rigaku, at Diya lab, Mumbai.

SCANNING ELECTRON MICROSCOPY:[6]
Morphological evaluation of Rosuvastatin was studies with the help of photograph taken on Scanning Electron Microscope. Study was carried out on Supra 55, Carl Zeiss, at Diya lab, Mumbai.

SATURATED SOLUBILITY STUDIES:[13]
To select the best nonvolatile solvent for preparation of liquid medication, saturated solubility studies were carried out in five different nonvolatile solvents, i.e. Water, PEG 400, PEG 600, polysorbate 80 and Tween 20 by preparing saturated solutions of the Rosuvastatin drug in these solvents and carried out for each sample to calculate the solubility of Rosuvastatin.

PREFORMULATION STUDIES:
Preparation of standard calibration curve of rosuvastatin using uv spectroscopy method:

PREPARATION OF STALK SOLUTION OF ROSUVASTATIN IN METHANOL:
Accurately weighed 100mg of the drug was dissolved in 100 ml of solvent i.e. methanol. 2.5ml of the aliquot from the above solution was withdrawn and added to 25 ml of volumetric flask the volume was adjusted to 25 ml to prepare final stock solution having concentration of 100 µg/ml.

Scanning of rosuvastatin in methanol:
The standard solution of the drug was scanned through 200-800nm region on Shimadzu UV spectrophotometer. The λ_{max} was determined.

PROCEDURE:
From the standard solution aliquots of 0.1, 0.2, 0.3, 0.4, 0.5, 0.6 ml were transferred to 10 ml volumetric flasks and final volume was made to 10 ml with methanol to prepare solution in the concentration in the range of 10-100 µg/ml. The absorbance values of these solutions were measured at λ_{max} of 241 nm using double beam UV spectrophotometer against a blank of methanol.

PREPARATION OF STALK SOLUTION OF ROSUVASTATIN IN 0.1N HCL ACID:
Accurately weighed 100mg of the drug was dissolved in 100 ml of solvent i.e. hydrochloric

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acid. 1ml of the aliquot from the above solution was withdrawn. And added to 50 ml of volumetric flask the volume was adjusted to 50 ml to prepare final stock solution having concentration of 20 µg/ml.

SCANNING OF ROSUVASTATIN IN 0.1N HYDROCHLORIC ACID:

The standard solution of the drug was scanned through 200-400nm regions on Shimadzu UV spectrophotometer. The λ_{max} was determined.

PROCEDURE:

From the standard solution aliquots of 0.2, 0.4, 0.6, 0.8, 1.0, 1.2 ml were transferred to 10 ml volumetric flasks and final volume was made to 10 ml with 0.1N hydrochloric acid to prepare solution in the concentration in the range of 0.1-5.0 µg/ml. The absorbance values of these solutions were measured at λ_{max} of 241 nm using double beam UV spectrophotometer against a blank of 0.1N hydrochloric acid.

Drug-excipient compatibility study:

INFRARED SPECTROSCOPY:

The interaction studies were carried out to ensure that there is no interaction occurred between drug and polymer. To analyze the compatibility of drug and polymer infrared spectrums of Rosuvastatin and combination of Rosuvastatin + PEG600 + Microcrystalline cellulose + colloidal silicon dioxide were recorded by using Fourier Infrared Spectroscopy. The spectrum was scanned over a frequency range 4000– 400 cm-1.This study was carried out at Dr. BabasahebAmbedkarMarathwada University,Aurangabad.

Differential scanning calorimetry (dsc):

DSC was performed using HITACHI DSC7020 , in order to assess the thermotropic properties and the thermal behaviors of the drug Rosuvastatin and combination of Rosuvastatin + PEG600 + Microcrystalline cellulose + colloidal silicon dioxide physical mixture were prepared. This study was carried out at Dr. BabasahebAmbedkarMarathwada University,Aurangabad.

X-RAY POWDER DIFFRACTION:

Crystallinity study was carried out by comparing XRD spectrum of drug with formulation to check peak of drug and in the formulation. Study was carried out on Smartlab Cu 1.5 KV, Rigaku, at Diya lab, Mumbai.

SCANNING ELECTRON MICROSCOPY:

Morphological evaluation of Rosuvastatin and physical mixture of liquisolid compact was studies with the help of photograph taken on Scanning Electron Microscope. Study was carried out on Supra 55, Carl Zeiss, at Diya lab, Mumbai.

FORMULATION AND DEVELOPMENT[14]:

MATHEMATICAL MODEL:

It is defined as the ratio of liquid medication (w) to the weight of coating material (q). It is determined by dissolving or dispersing the drug in nonvolatile solvent and to this carrier coating material admixture is added and blended. The amount of carrier-coating admixture is used to convert free flow powder and is determined by using the following formula.

$L_f = W/Q$

Where, W = Weight of liquid medication,

Q = Weight of carrier material, the Φ value is for calculating excipients quantities. Equation is,

$L_f = \Phi+\Phi\ (1/R)$

Where, Φ and Φ are values of carrier and coating material respectively. It is used to calculate the amount of carrier and coating material in each formulation. The excipients ratio R of powders is defined as the ratio of carrier and coating material present in the formulation. R is suitably selected for successful formulation.

Where,

R= Q/q

Q = weight of carrier, q = coating material.

CALCULATION OF LOAD FACTOR [15,16]

In a liquisolid system, the amount of liquid retained by the carrier and coating materials depends on the excipients ratio (R) while maintaining acceptable flow and compression properties. The excipient ratio R (R=Q/q) of powder is defined as a ration between the weights of the carrier (Q) and coating (q) present in the formulation. Preparation of a liquisolid system with an acceptable flow rate and compressibility is possible when a maximum amount of retained liquid of the carrier material is not exceeded. This characteristic amount of liquid is termed as liquid load factor (L_f).The liquid load factor (L_f) is defined as the weight ratio of liquid medication (W) and carrier powder (Q) in the system (i.e., L_f=W/Q). To calculate the loading factor, non-volatile solvent (liquid medication without drug) was added to 10 g carrier material and blended for

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1 min. The above procedure was repeated until a powder with acceptable flow rate was obtained.

Formulation of liquisolid system:[17]

Several liquisolid compacts were prepared as follows. The desired quantities of the previously weighed of the solid drug and the liquid vehicle (PEG 600) were mixed. The solution was then sonicated for 15 min until a homogeneous drug solution was obtained. Next, the calculated weight (W) of the resulting liquid medications (equivalent to 5 mg drug) were incorporated into the calculated quantities of the carrier material (Avicel PH102) (Q) and mixed thoroughly. The resulting wet mixture was then blended with the calculated amount of the coating material (colloidal silicon dioxide) (q) using a standard mixing process to form simple admixture. Several factors were varied like carrier:coat ratios (different R values) and Different liquid load factors (L_f) were employed. These compact were store in sealed bags for evaluation.

Table 7: Composition of different Rosuvastatin liquisolid compacts (Formula for one capsule)

Liquisolid system	Drug (mg)	PEG 600	Liquid load factor (L_f)	Powder Excipient ratio (R)	MCC (mg)	Ethyl Cellulose	colloidal silicon dioxide (mg)	Capsule weight
LS-1	5	30	0.2	5	150	-	30	215
LS-2	5	30	0.150	10	200	-	20	255
LS-3	5	30	0.2	5	-	150	30	215
LS-4	5	30	0.150	10	-	200	20	255
LS-5	5	20	0.133	5	150	-	30	205
LS-6	5	20	0.1	10	200	-	20	245
LS-7	5	20	0.133	5	-	150	30	205
LS-8	5	20	0.1	10	-	200	20	245

Table 8: Composition of Rosuvastatin liquisolid compacts with PG and PEG 200 (Formula for one capsule)

Liquisolid System	DRUG (mg)	MCC (mg)	colloidal silicon dioxide(mg)	PG (mg)	PEG 200 (mg)	LF	R	Capsule weight
LS with PG	5	200	10	30	-	0.15	20	245
LS with PEG 200	5	200	10	-	30	0.15	20	245

EVALUATION LIQUISOLID COMPACT:[18]

Determination of angle of repose, Carr's index and Hausner's ratio were used to characterize flow properties of the liquisolid powder systems. The flowability of a powder is of critical importance in the production of pharmaceutical dosage forms in order to get a uniform feed.

ANGLE OF REPOSE:[19,20]

Angle of repose has been used as indirect methods of quantifying powder flowability. Angle of repose is a characteristics related to intraparticulate friction or resistance to movement. Angle of repose for blend of each formulation was determined by fixed funnel method. The funnel is secured with its tip with height h, above a plane of paper kept on a flat horizontal surface. The

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powders were carefully poured through the funnel until the apex of the conical pile so formed just reaches the tip of funnel. Angle of repose was determined by substituting the values of the base radius 'r' and height of the pile 'h' in the given eq. given below,

Tan θ = h/r

(7)

Table 9: Angle of repose as an indication of powder flow properties

Sr. .No.	**Angle of repose** (degrees)	**Type of flow**
1	25-30	Excellent
2	31-35	Good
3	36-40	Fair-aid not needed
4	41-45	Passable-may hang up
5	46-55	Poor-must agitated
6	56-65	Very poor
7	>66	Very very poor

BULK DENSITY:[20]

Bulk density or apparent density is defined as the ratio of mass of a powder to the bulk volume. The bulk density of a powder depends primarily on particle size distribution, particle shape and the tendency of the particles to adhere to one another.

PROCEDURE:

Approximately 50 gm of test sample was accurately weighed and sifted through 18# sieve and transferred in a 100 ml graduated cylinder. The level was observed without compacting and noted as apparent volume (V_0). The bulk density was calculated by the formula as given below:

Bulk density=M/ V_0

(8)

Where, M=Mass of powder taken. V_0= Apparent untapped volume.

TAPPED DENSITY[20]**:**

The tapped density is the limited density attained after "tapping down" usually in a device that lifts and drops a volumetric measuring cylinder containing the powder from a fixed distance.

PROCEDURE:

Approximately 50 gm of test sample was accurately weighed and sifted through 18# sieve and transferred in 100 mL graduated cylinder with the help of funnel and tapped for 100 times. The powder is observed for measurement in measuring cylinder and the tapped volume (V_2) nearest to graduated units was noted.

The tapped density was calculated by the formula as given below:

Tapped density= M/ V_2

(9)

Where, M= Weight of powder;V_2= Tapped volume (after 100 taps).

CARR'S INDEX[21]

It is used to evaluate flowability of powder by comparing the bulk density and tapped density of a powder. The percentage compressibility of a powder is direct measure of the potential of powder arch or bridge strength is calculated according to the equationgiven below.

$$\% \textbf{ Compressibility} = \frac{\text{TAPPED DENSITY} - \text{BULK DENSITY}}{\text{TAPPED DENSITY}} \textbf{ X 100}$$

(10)

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Table 10: Carr's index as an indication of powder flow

Sr .No.	Carr's index (%)	Type of flow
1	<10	Excellent
2	11-15	Good
3	16-20	Fair
4	21-25	Passable
5	26-31	Poor
6	32-37	Very poor
7	>38	Very very poor

HAUSNER'S RATIO:[21]

Hausner found that the ratio tapped density/bulk density was related to inter particle friction as such, could be used to predict powder flow properties. He showed that the powder with low inter particle friction had ratio of approximately 1.2, whereas more cohesive less free flowing powders have Hausener's ratio greater than 1.6. Hausner's ratio less than 1.25 indicate good flow.

$$\textbf{Hausner's ratio} = \frac{\textbf{Tapped density}}{\textbf{Bulk density}} \quad \textbf{(11)}$$

Table 11: Hausner's ratio as an indication of powder flow

Hausner's Ratio	Flow character
1.0-1.111	Excellent
1.12-1.18	Good
1.19-1.25	Fair
1.26-1.34	Passable
1.35-1.45	Poor
1.46-1.59	Very Poor
>1.60	Very very Poor

FORMULATION AND DEVELOPMENT OF LIQUISOLID CAPSULES:

Liquisolid capsules formulations were prepared by using non-volatile solvent like PEG-600,and mcc,, ethyl cellulose and colloidal silicon dioxide as carrier and coating material respectively as mention in table 7 and 8.

EVALUATION OF LIQUISOLID CAPSULES

Prepared capsules were subjected to evaluation of different properties including drug content uniformity, weight variation, and in vitro drug release.

UNIFORMITY OF WEIGHT:[22]

Weigh an intact capsule. Open the capsule without losing any part of shell and remove the contents as completely as possible. Weigh the shell. The weight of contents is the difference between the weighing's. Repeat the procedure with a further 19 capsules. Determine the average weight. Not more than two of the individual weights deviate from the average weight by more than percentage deviation shown in table 12 and none deviates by more than twice that percentage.

Table 12: IPstandards for uniformity of weight

Sr. No.	Average weight of capsule contents	Percentage deviation
1	Less than 300mg	10
2	300 mg or more	7.5

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DRUG CONTENT UNIFORMITY[23]:
Drug content uniformity was determined as per USP using following procedure.

PROCEDURE:
20 capsules were weighed and powered. Quantity of powder equivalent to 50 mg of drug was weighed and transferred to 200 ml volumetric flask containing 60 ml of methanol. The flask was shaken to dissolve the drug; and adjusted to volume with methanol. 5 ml of this solution was diluted to 100 ml with methanol and absorbance of resulting solution was measured atλ_{max} of 241 nm.

IN VITRO DRUG RELEASE[11,24]:
The USP basket apparatus I was used for all the in vitro dissolution studies. 500 ml 0.1N hydrochloric acid was used as dissolution media, at 50 rpm and 37 ± 0.5^{o}C. Appropriate aliquots were withdrawn at suitable time interval (0, 10, 20, 30, 40, 50, 60min.) Sink conditions were maintained throughout the study. The samples were then analyzed at λ_{max} of 241nm by shimadzu UV spectrophotometer. The study was carried out in triplicate.

STABILITY STUDIES[10, 25]:
In any rationale design and evaluation of dosage forms for drugs, the stability of the active component must be major criteria in determining their acceptance or rejection.. However the studies will take a longer time and hence it would be convenient to carry out the accelerated stability studies where the product is stored under extreme conditions of temperature for short period of time. To assess the drug and formulation stability, stability studies were done according to ICH and WHO guidelines.

PROCEDURE
The Rosuvastatin physical mixture and formulations were filled in 10 ml glass vials were plugged and sealed. The vials were kept at different temperature conditions such as room temperature using desiccator containing calcium chloride, for a period of 1 month. At definite time intervals, the samples were visually examined for any physicals change. The drug content and dissolution rate was estimated after one month. At the end of studies, samples were analyzed for the drug content, in vitro release profile and other physicochemical parameters.

III. RESULTS AND DISCUSSION

INFRARED SPECTROSCOPTY
The FTIR spectrum of drug sample was shown identical peaks as reported in references sample of rosuvastatin. The results were illustrated in figure 14

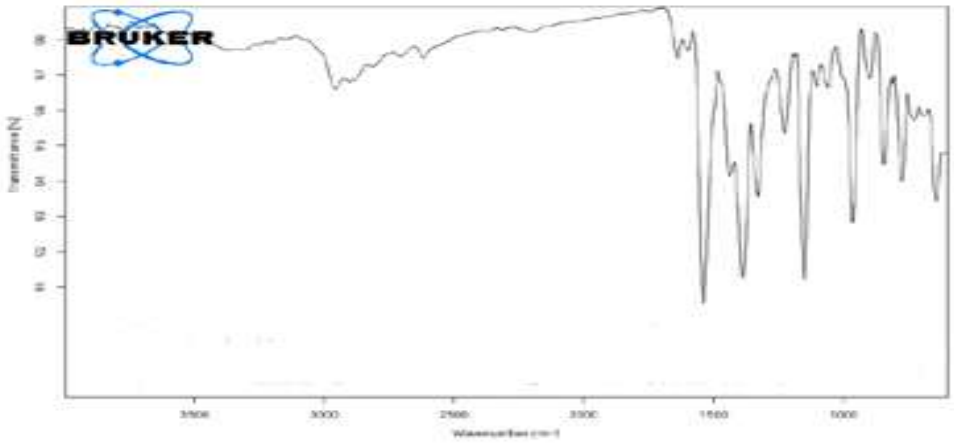

FIGURE 14: FTIR spectra of rosuvastatin

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Table 14: FTIR analysis of drug sample

Sr. No.	Wave number (cm^{-1})	Assignment
1	3364	O-H stretching
2	3320	RCO-OH Stretching
3	1338	S=O Asymmetric
4	1863	C=N C=O Stretching
5	1380	C-N Stretching
6	2935	AR- CH

DSC THERMOGRAM OF ROSUVASTATIN:

The results were illustrated in figure 15.

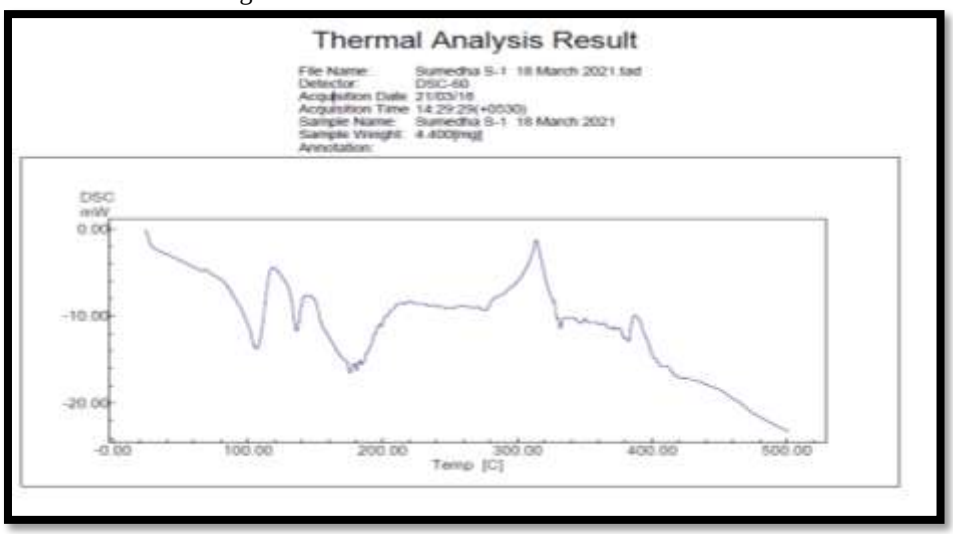

Figure 15: DSCthermogram of Rosuvastatin

The DSC thermogram of the drug depicts a sharp exothermic peak followed by an endothermic peak at 114°C corresponding to the melting transition temperature of and decomposition Rosuvastatin. Such sharp endothermic peak signifies that Rosuvastatin used was in pure crystalline state.

X-RAY POWDER DIFFRACTION (XRD:

It has been shown that polymorphic changes of the drug are important factors, which may affect the dissolution rate and bioavailability.The results were illustrated in fig.no.16

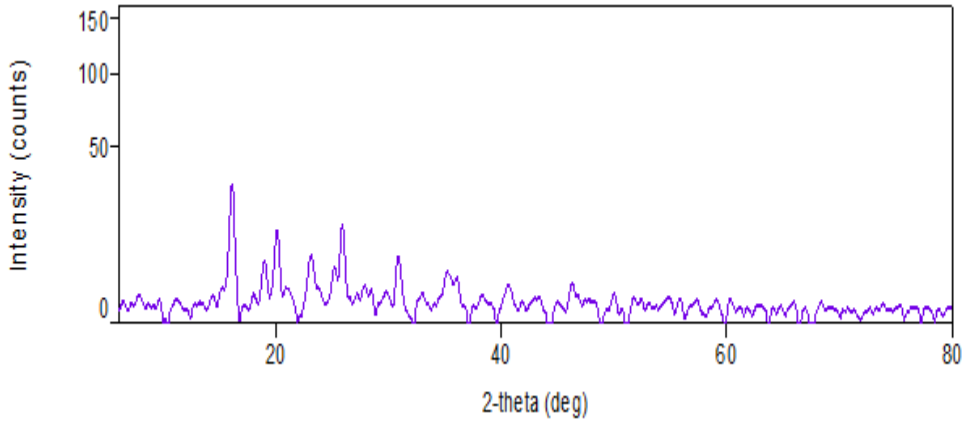

Figure no 16: X-ray diffractogramof Rosuvastatin

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SCANNING ELECTRON MICROSCOPY:

The result illustrated in the figure no. 17. The scanning electron microscopy micrograph of pure Rosuvastatin drug, the crystalline particle of Rosuvastatin were clearly observed, as proved by the DSC and XRD

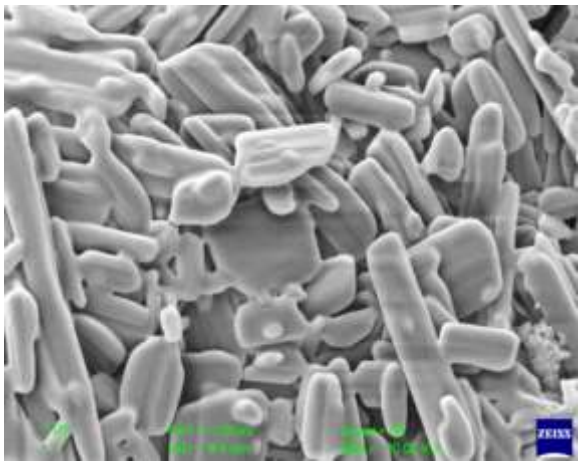

Figure 17: Scanning electron microscopy of pure Rosuvastatin drug

SATURATED SOLUBILITY STUDIES:

The solubility of Rosuvastatin in Water, Tween 80, Tween 20, PEG 400 and PEG 600 is given in the table 17. Table shows that, Rosuvastatin has lowest solubility in water. Solubility was found to be increased when semi polar solvents such as polyethylene Glycol 600 were used. Solubility of Rosuvastatin was considerably increased in presence of PG. The solubility of the drug strongly depends on the solvent used, thus on the intermolecular forces between Rosuvastatin and the solvent. The variation of solubility of the drug in different solvents may be due to dipole and hydrogen-bonding interactions. PG is semi polar in nature. PG contains small non polar hydrocarbon region and polar hydroxyl groups. The solubility of the drug is higher in PG due to polarity of the drug and hydrogen-bonding contribution. Therefore PG was selected as a nonvolatile solvent in preparation of liquisolid compacts.

Table 15: Solubility of Rosuvastatin in various solvents

Sr. No.	Solvent	Solubility mg/ml
1	Water	0.44
2	Tween 80	8.2
3	peg 600	17.3
4	TWEEN 20	4
5	PEG 400	14

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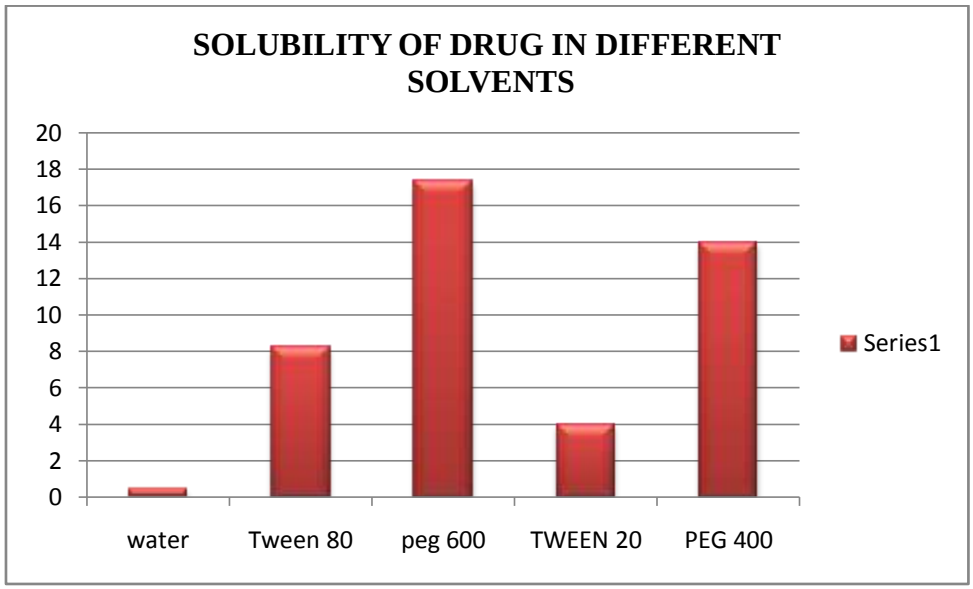

Figure18: Solubility of drug in different solvents

PREFORMULATION STUDIES:
PREPARATION OF STANDARD CALIBRATION CURVE OF ROSUVASTATIN USING UV SPECTROSCOPY METHOD:
CALIBRATION CURVE OF ROSUVATATIN IN METHANOL-

Table 16: Absorption data of Rosuvastatin In methanol

S. No	Concentration (ug/ml)	Absorbance at 241			Mean
		1	2	3	
1	1	0.202	0.204	0.2	0.202
2	2	0.3	0.299	0.304	0.301
3	3	0.375	0.36	0.37	0.3683
4	4	0.477	0.452	0.461	0.4633
5	5	0.538	0.533	0.54	0.537
6	6	0.666	0.65	0.67	0.662

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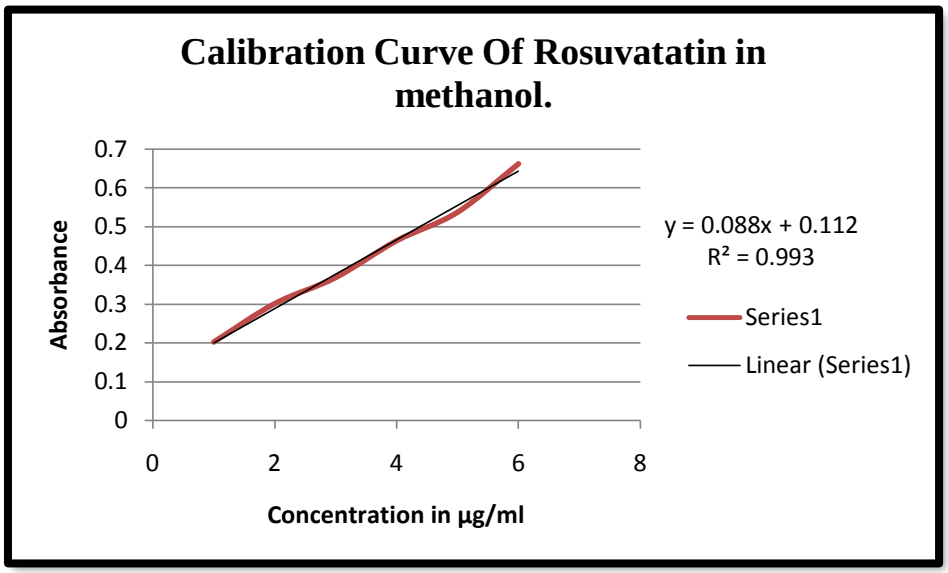

Figure 19: Calibration Curve OfRosuvatatin in methanol.

CALIBRATION CURVE OF ROSUVATATIN IN 0.1N HYDROCHLORIC ACID:

Table 17: Absorption data of Rosuvastatin In 0.1N HCL

Sr. No.	Concentration	Absorbance at 241			Mean
	(ug/ml)	**1**	**2**	**3**	
1	0.4	0.423	0.44	0.433	0.432
2	0.8	0.492	0.505	0.485	0.494
3	1.2	0.521	0.533	0.533	0.529
4	1.6	0.571	0.582	0.589	0.580666667
5	2	0.599	0.582	0.604	0.595
6	2.4	0.688	0.655	0.671	0.671333333

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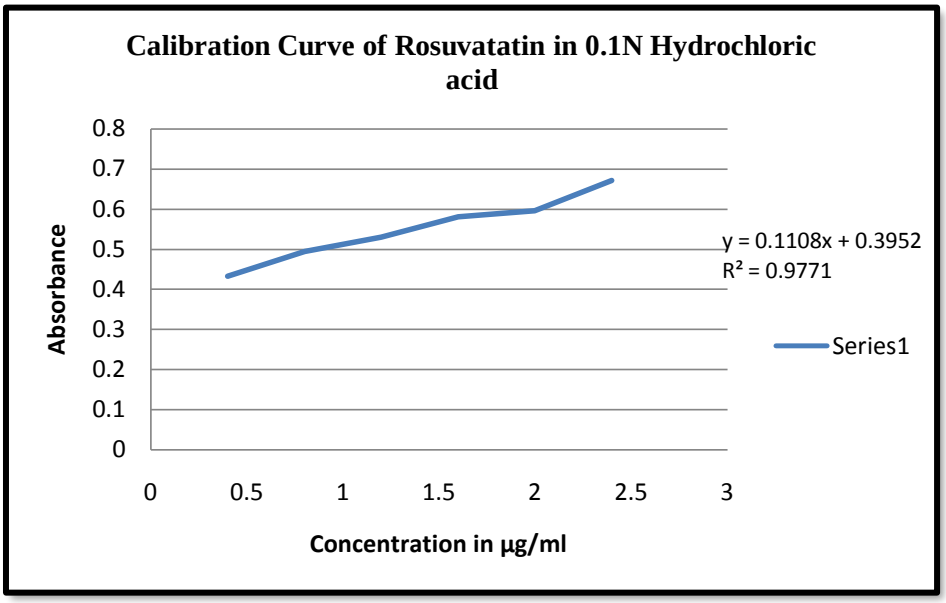

Figure 20: Calibration Curve of Rosuvatatin in 0.1N Hydrochloric acid

INFERENCE:

The procured sample of Rosuvastatin was characterized by organoleptic properties, melting point, UV, FTIR, XRD, and DSC studies. All the observed data were as same as reported in official books and literature and matched with standards.Hence, it was inference that the procured drug sample was of pure Rosuvastatin and hence used for further studies.

DRUG-EXCIPIENT COMPATIBILITY STUDY:

STABILITY STUDY OF DRUG AND EXCIPIENT:

The stability of drug and excipient shows at there is no any change in color and appearance. The results were illustrated in fig.no.18

Table 18: Drug excipient compatibility studies

Drug excipients ratio	Observation at different storage conditions				Remarks
	25 °C				
	Duration (weeks)				
	1	**2**	**3**	**4**	
Drug+ PEG 600+ MCC+ Colloidal silicon dioxide (1:1:1:1)	N	N	N	N	Accepted
Drug+ PEG 600+ EC+ Colloidal silicon dioxide (1:1:1:1)	N	N	N	N	Accepted

INFRARED SPECTROSCOPY:

The results were illustrated in fig.no.21

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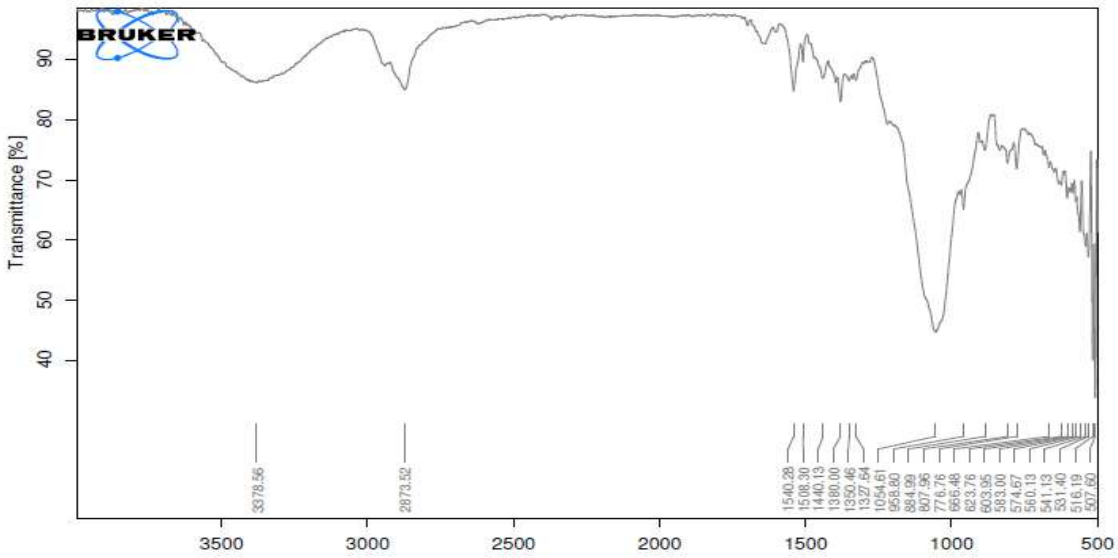

Figure 21:IR spectra of liquisolid compact LS 1

The FTIR spectral analysis showed that there is change in percent transmittance which may be due to change in crystallinity and there is no appearance or disappearance of any characteristics peaks of pure drug Rosuvastatin and in the physical mixture of drug to polymer, which confirms the absence of chemical interaction between drug and polymers

DSC THERMOGRAM OF ROSUVASTATIN:

One of the most classic applications of DSC analysis is the determination of the possible interactions between a drug entity and the excipients in its formulation.

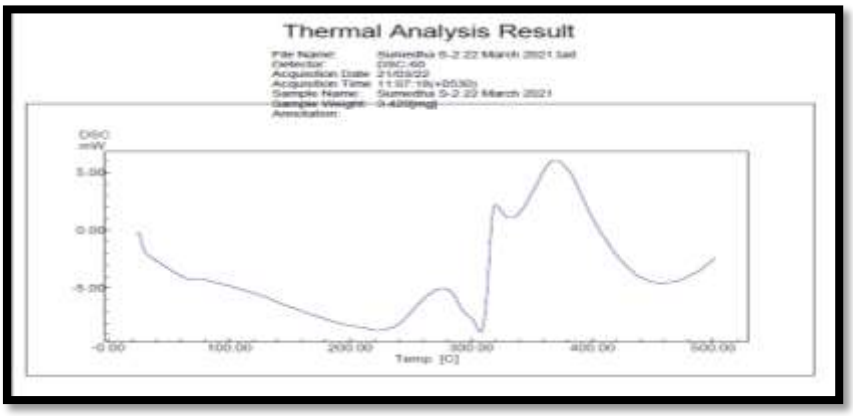

Figure 22: DSC thermogram of liquisolid compact LS 1

On the other hand, the liquisolid system thermogram in Figure 22 displayed complete disappearance of characteristic peaks of Rosuvastatin; a fact that agrees with the formation of drug solution in the liquisolid powdered system, i.e., the drug was molecularly dispersed within the liquisolid matrix. Such disappearance of the drug peaks upon formulation of the liquisolid system was in agreement with McCauley and Brittainwho declared that the complete suppression of all drug

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thermal features, undoubtedly indicate the formation of an amorphous solid solution.

X-RAY POWDER DIFFRACTION (XRD):

It has been shown that polymorphic changes of the drug are important factors, which may affect the dissolution rate and bioavailability. It is therefore important to study the polymorphic changes of the drug.

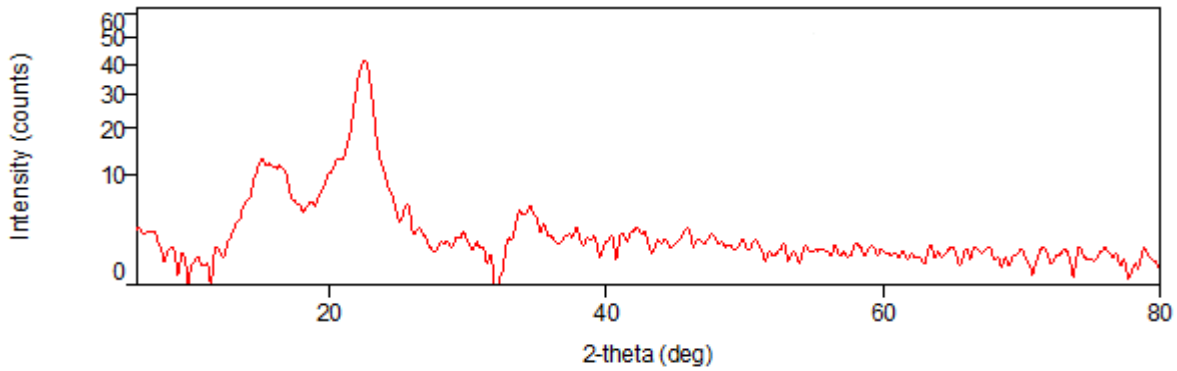
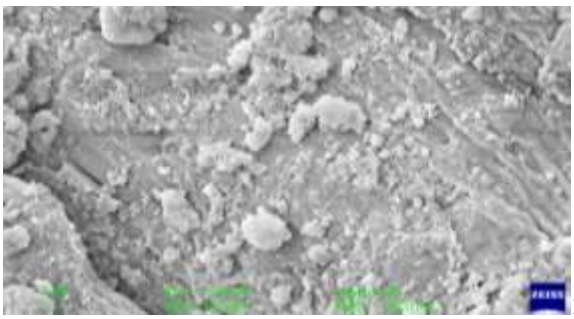


Figure 23: X-ray diffractogram of liquisolid compact LS 1

Rosuvastatin characteristic peaks were observed in the Figure 23, demonstrating that its crystalline structure remained changed in the liquisolid compact, and that the loss of crystallinity was due to liquisolid system formation.

SCANNING ELECTRON MICROSCOPY:

The result illustrated in the figure no.24 The scanning electron microscopy micrograph of pure Rosuvastatin drug The crystalline particle of Rosuvastatin were clearly observed, as proved by the DSC and XRD



1

Figure 24: Scanning electron microscopy of liquisolid compact LS 1

The microcrystalline cellulose powder composed of porous particles also is partially depolymerized cellulose. Colloidal silicon dioxide is an amorphous colloidal silicon dioxide powder. The inability to differentiate Rosuvastatin crystals in the developed liquisolid system suggested the complete drug solubilization and/or dispersion in almost molecularly dispersed state.

EVALUATION OF LIQUISOLID COMPACT

Powder flow is a complicated matter and is influenced by so many interrelated factors; the factors list is long and includes physical, mechanical as well as environmental factors. Therefore; determination of angle of repose, Carr's index, Hausener's ratio is important before formulation because it influence compressibility and dissolution. The effect of liquid load factor (L_f), which is a ratio of mass of liquid (PEG 600) added to the mass of microcrystalline cellulose on flowability and compressibility of the final admixture of the powder is shown in table 19. This is evident from the increase in the angle of repose. With increase in L_f value flow property was found to be reduced. As a general guide angle of repose greater than 45^o has unsatisfactory flow properties whereas minimum angle close to 35^o correspond to very good flow property. Powders showing Carr's

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index up to 25 are considered of acceptable flow property.

Table 19:Flowability parameters of Rosuvastatin liquisolid powder system

Liquisolid powder	Angle of repose	Density		Hausener's Ratio	Carr's index
		Bulk density	**Tapped density**		
LS-1	27.56	0.307	0.349	1.136	12.03
LS-2	31.98	0.345	0.384	1.113	10.15
LS-3	29.79	0.208	0.232	1.115	10.34
LS-4	33.12	0.31	0.36	1.161	13.88
LS-5	28.25	0.313	0.352	1.124	11.07
LS-6	30.99	0.395	0.461	1.167	14.31
LS-7	29.95	0.267	0.312	1.168	14.42
LS-8	33.53	0.289	0.332	1.148	12.95
LS with PG	25.62	0.316	0.353	1.117	10.48
LS with PEG 200	26.35	0.208	0.234	1.125	11.11

SOLUBILITY OF LIQUISOLID COMPACT IN WATER:
The liquisolid compact containing MCC shows higher solubility than the liquisolid compact containing ethyl cellulose. The liquisolid compact 1 i.e. (LS-1) shows the higher solubility on water.

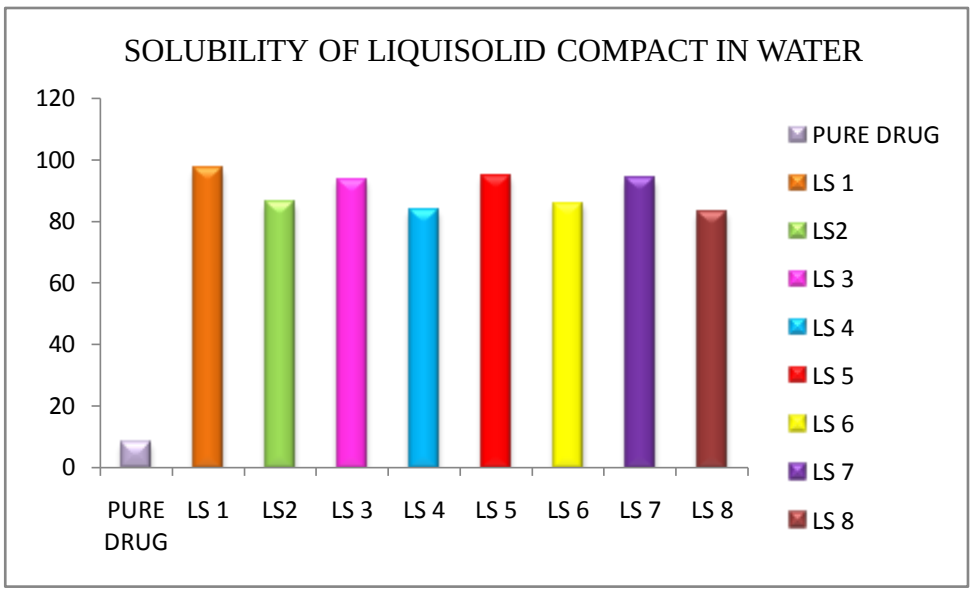

Figure 25: Solubility of liquisolid compact in water

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EVALUATION OF LIQUISOLID CAPSULES

WEIGHT VARIATION TEST

Weight variation test revealed that the capsules were within the range of Pharmacopoeial specifications. All the formulations passes weight variation test.

DRUG CONTENT:

A fundamental quality attribute for all pharmaceutical preparations is the requirement for a constant dose of drug between individual capsules. Uniform drug content was observed for all the formulations (94.30 to 96.64%), which is as per the USP specification (90%-110%). The result illustrated in table no 20.

Table 20: Evaluation of liquisolid capsules

Formulation No.	Weight Variation (g)	Drug Content(%)
LS-1	0.213±0.05	95.50
LS-2	0.254±0.05	94.70
LS-3	0.215±0.05	95.33
LS-4	0.253±0.05	95.70
LS-5	0.204±0.05	96.10
LS-6	0.243±0.05	94.30
LS-7	0.202±0.05	95.60
LS-8	0.212±0.05	95.40
LS with PG	0.245±0.05	96.02
LS with PEG 200	0.244±0.05	96.64

IN VITRO DRUG RELEASE:

The results of in vitro percentage amount of drug released at different time intervals plotted against time to obtain the release profiles.

All the liquisolid compacts showed higher drug release than the pure drug. The enhanced dissolution rates of liquisolid compacts compared to pure drug may be attributed to the fact that, the drug is already in solution in PEG 600, while at the same time, it is carried by the powder particles. Thus, its release is accelerated due to its markedly increased wettability and surface availability to the dissolution medium. The wettability of the compacts by the dissolution media is one of the proposed mechanisms for explaining the enhanced dissolution rate from the liquisolid compacts. PEG 600 facilitates wetting of drug particles by decreasing interfacial tension between dissolution medium. The dissolution profiles of the liquisolid capsule formulations together with the dissolute profile of pure Rosuvastatin are presented in Figure 21

Table 21: Percent drug release kinetics

TIME	Pure drug	LS 1	LS2	LS3	LS4	LS5	LS6	LS7	LS8
0	0	0	0	0	0	0	0	0	0
10	4.67	25.61	13.91	22.45	18.01	32.86	32.51	28.3	25.26

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20	6.05	37.35	26.12	26.53	31.35	43.23	46.15	46.65	38.98
30	8.63	47.33	47.34	47.52	47.64	52.03	53.37	51.43	52.97
40	10.08	68.95	57.63	65.29	56.3	72.34	59.79	68.33	60.67
50	11.57	88.07	67.76	84.22	61.71	80.17	69.94	78.54	64.53
60	15.53	93.27	85.9	92.74	83.47	91.06	85.88	91.73	83.18

Table 22: Percent drug release kinetics of LS of PG and peg 200

TIME	marketed formulation	LS of PG	LS of PEG 200
0	0	0	0
10	30.41	30.06	25.96
20	45.75	46.68	40.87
30	59.71	58.6	53.96
40	71.67	72.72	68.93
50	83.23	80.09	76.46
60	94.87	96.93	95.34

COMPARATIVE RELEASE PATTERN OF DIFFERENT LIQUISOLID FORMULATIONS AND DRUG:

The comparison of different liquisolid formulation shows the much more higher dissolution rate than the pure drug. The results were illustrated in figure 26.

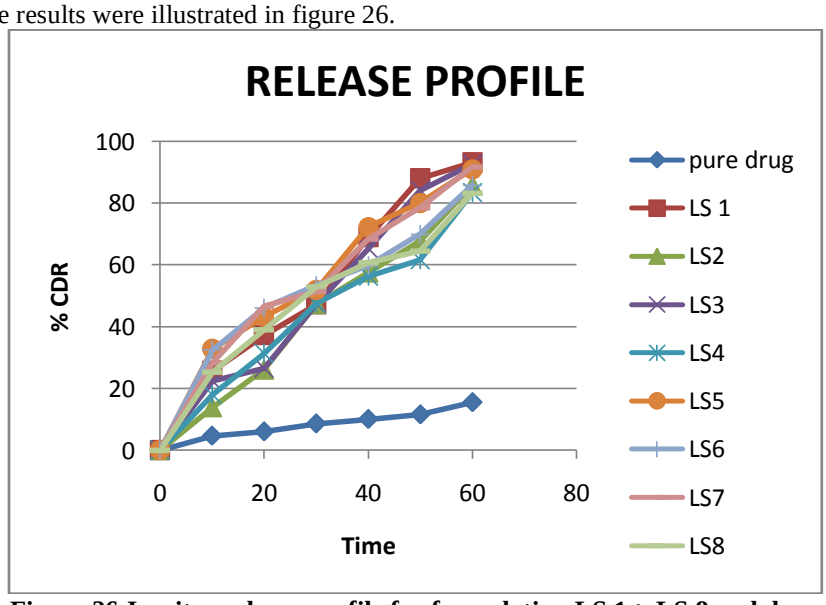

Figure 26:In-vitro release profile for formulation LS 1 toLS 8 and drug

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COMPARATIVE RELEASE PATTERN OF DIFFERENT LS 1FORMULATIONS, MARKETED AND DRUG:

The comparison between the LS 1formulations, marketed shows almost similar dissolution rate. The results were illustrated in figure 27.

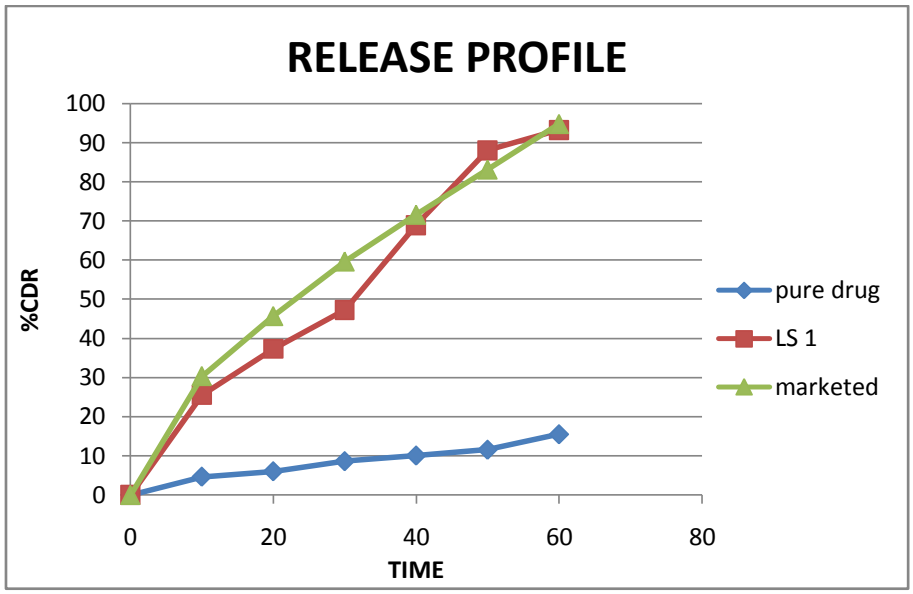

Figure 27:In-vitro release profile for formulation LS 1, marketed and pure drug

COMPARATIVE RELEASE PATTERN OF PURE DRUG, FORMULATION OF LS 1, LS OF PG AND LS OF PEG 200:

The comparison between the, formulation of LS 1, LS OF PG and LS of peg 200shows almost similar dissolution rate. The results were illustrated in figure 28.

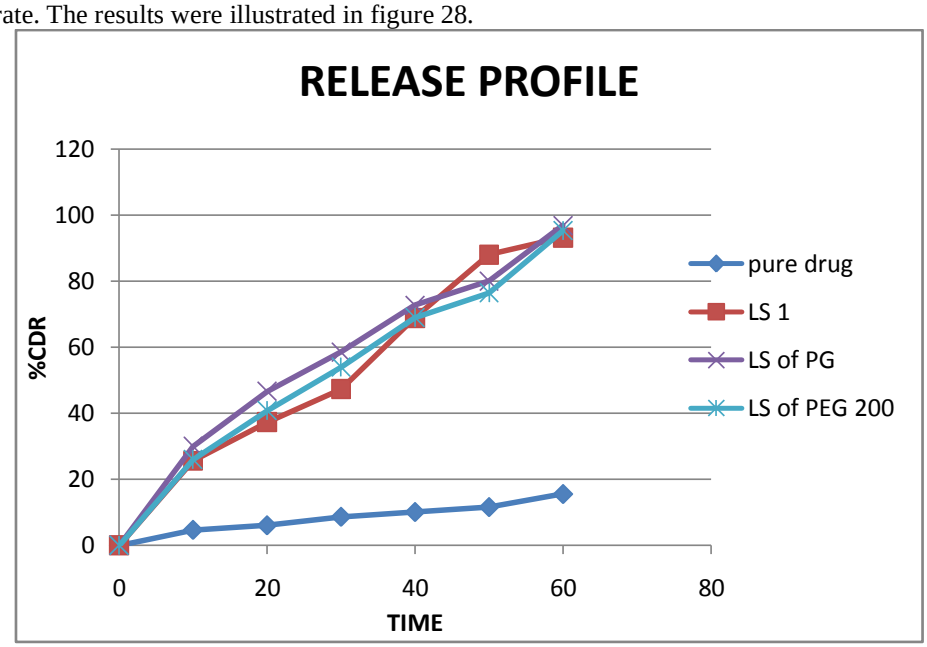

Figure 28:In-vitro release profile for Pure drug, formulation of LS 1, LS OF PG and LS of peg 200

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STABILITY STUDY:

The formulation LS 1 showed the good dissolution properties and hence this final formulation kept for stability study for 1 month at accelerated condition. The Formulation LS-1 was subjected to stability studied for a period of four week. Samples were analyzed for color changes, drug content and release characteristics. The results are given in Table 23 and 24. From the result it was observed that there was no significant change in physiochemical properties as well as in drug release profile. It may be inferred that there was no degradation and change in the liquisolid system

Table 23: Evaluation of formulation LS-1 kept for stability study

Parameter	0 week	1 week	2 week	3 week	4 week
Color	white	white	White	white	white
Drug Content (%)	95.77	95.77	95.60	95.47	95.17

Table 24:In-vitro drug release study of formulation (LS-1) kept for stability study

Time (MIN)	**Cumulative % drug released**				
	0 week	**1 week**	**2 week**	**3 week**	**4 week**
60	93.27	93.20	93.03	92.88	92.47

The final Liquisolid compact 1 (LS 1) containing Formulation shows the good release of Rosuvastatin. The formulation of rosuvastatin shown in the figure 29.

Figure 29: LS1 containing Formulation

IV. CONCLUSION

Solubility of a drug is an important property that mainly influences the extent of oral bioavailability. An enhancement of oral bioavailability of poorly water soluble drugs is the most challenging aspects of drug development. It is very important to find appropriate formulation approaches to improve the aqueous solubility and bioavailability of poorly aqueous soluble drugs.

Rosuvastatin is BCS Class II drug, having poor aqueous solubility. Due to this rosuvastatin have very poor dissolution rate and hence very low bioavailability. To enhance the aqueous solubility, liquisolid techniques are came forward & appeared as most effective method.

The PEG 600 and microcrystalline cellulose can be used to prepare liquisolid compact. The solubility study of pure drug liquisolid compact was found to be increased. The dissolution study of liquisolid compact was also found to be higher than pure drug.The changes in the FT-IR, DSC and XRD pattern when compared to pure

drug and liquisolid compact, this clearly indicates that change in the crystallinity of drug to amorphous form. This change leads to enhanced solubility of liquisolid compact than pure drug. Enhancement of solubility of rosuvastatin liquisolid compact was 93.27 % at 60 min. increase in its dissolution rate. The liquisolid compact contain a solution of the drug in PEG 600 which facilitates the wetting of the drug by decreasing interfacial tension, like PG and PEG 200.The formulation remained stable when examined effect of storage condition through stability study.Hence we can conclude that formulation of that, the f rosuvastatin liquisolid compact containing MCC, colloidal silicon dioxide and PEG 600 is successful liquisolid technique and also a very much effective technique for solubility enhancement.

This method is simple and effective and can be used on an industrial scale. The production of the Liquisolid system does not involve the application of any specialized types of equipment; hence it is an economical, yet very effective tool for enhancement of dissolution rate of poorly soluble drugs. It is a successful and simple method to prepare Liquisolid capsule to enhance its aqueous solubility and dissolution rate

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