Tablet Formulation Development and Solubility/Dissolution Enhancement of Simvastatin by using different Combination of Polymers with Solid Dispersion Method

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Abstract

Hyperlipidemia or hyper lipoproteinemia or dyslipidemia is the presence of elevated or abnormal levels of lipids or lipoproteins in the blood. Lipid and lipoprotein abnormalities are extremely common in general population and are regarded as a highly modifiable risk factor for cardiovascular diseases due to influence of cholesterol and its more common in elderly patients.

The objective of the present study was to formulate Solid dispersion of simvastatin formulated with combination of HPMC and Methyl Cellulose for the beneficial of cholesterol patients, to provide sustained release effects.

Simvastatin is a selective competitive inhibitor of HMG CoA reductase. Simvastatin belongs to BCS class 2 having low solubility & therefore low oral bioavailability (5%). Solid Dispersions were prepared by Kneading technique to enhance solubility of Simvastatin using carriers at different drug carrier ratio (HPMC and MC).

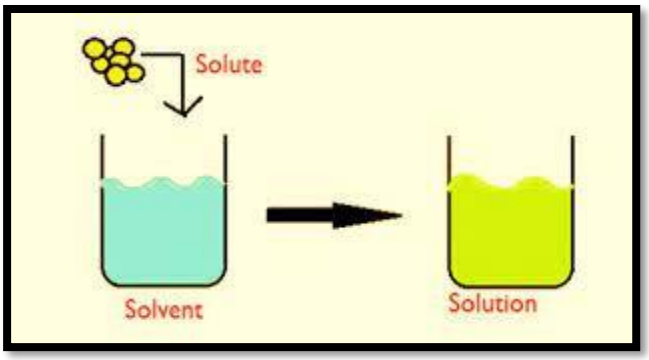
***Keywords**:* Solid dispersions; Simvastatin; MC (Methyl Cellulose); HPMC (Hydroxy propyl methyl cellulose) Hyperlipidemia; Kneading Method; hyper lipoproteinemia, Tablet dosage form , Carriers

1. INTRODUCTION:

Recent advancement in the pharmaceutical sciences aims to produce the simples dosage form which is convenient to the patient, have good solubility, proper bioavailability and ultimately of proper therapeutic effect. The important phenomenon in pharmaceutical formulation is “solubility” and “dissolution” which plays very vital and significant role in the formulation of various dosage forms.

1.1 SOLUBILITY (13, 21, 1-2)

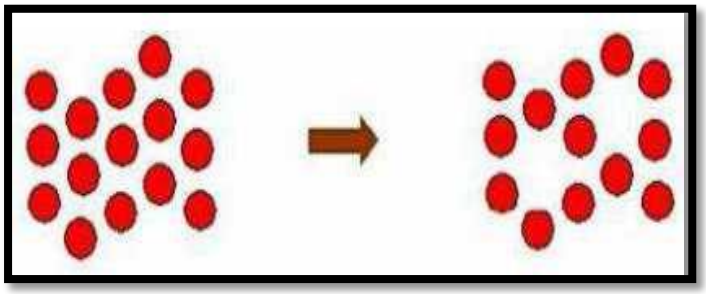
In chemistry, solubility is ability of a substance, the solute, to form a solution with another substance, the solvent. Insolubility is the opposite property, the inability of the solute to form such a solution. Solubility of a compound in a particular solvent is defined as the “concentration of a solute in a saturated solution at a certain temperature”. Solubility is very important parameter in any pharmaceutical dosage form because it is solubility which determines the amount of compound that will dissolve and therefore the amount of drug which is available for absorption. To understand the solubility of the drug, firstly understand the factor which influences the solubility of the drug.



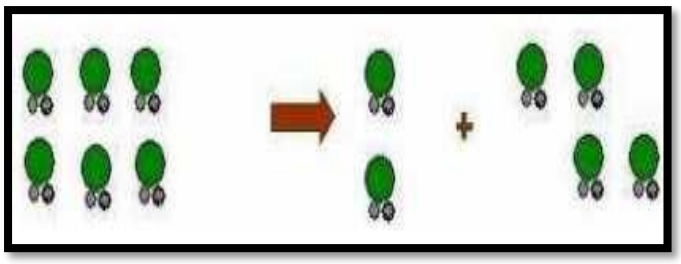
1.1.2 PROCEES OF SOLUBLIZATION

The process of solubilization involves the breaking of intermolecular or inter-ionic bonds in the solute, the separation of the molecules of the solvent to provide space in the solvent for the solute, interaction between the solvent and the solute molecule or ion.

Step 1: Holes opens in the solvent



Step2: Molecules of the solid breaks away from the bulk



Step 3: The freed solid molecule is integrated into the hole in the solvent

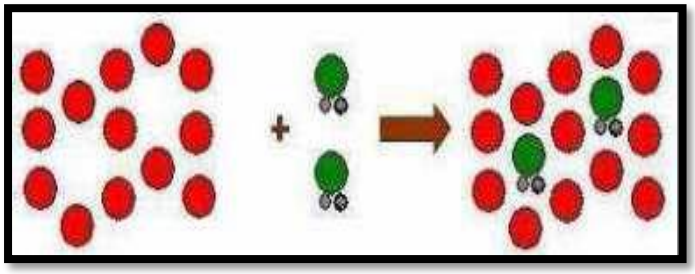


Figure : Schematic Presentation of Process of Solubilization

1.1.3 VARIOUS SOLUBILITY ENHANCEMENT TECHNIQUES [10-11]

PHYSICAL MODIFICATION

Particle Size Reduction

By reducing the particle size, the increased surface area improves the dissolution properties of the drug. Various methods are applied to reduce the particle size

For example, Micronzation, Nano-suspension, Sonocrystalisation.

CHEMICAL MODIFICATION

Salt Formation

For increasing the aqueous solubility of poorly water soluble drugs, change in pH of a system is the simplest and most effective method. The drug which is to be efficiently solubilized should be a weak base with a high pKa value or weak acid with a low pKa value. Salt formation of both acidic and basic drug is a promising method to increase the solubility. It is performed on weak acid and weak basic drugs because of simple chemical manipulation which may alter the physiochemical formulation and therapeutic properties.

1.2 DISSOLUTION [5, 12, 20]

For greater understanding of dosage form the dissolution behaviors of drugs with low aqueous solubility are required to successfully formulate them into bioavaliable drug products. Theoretically Dissolution is defined as “the process by which a solid substance enters in solvent to yield a solution”. In 1897, Noyes and Whitney suggested that the rate of

dissolution of solid substances is determined by the rate of diffusion of a very thin layer of saturated solution that forms instantaneously around the solid particle. They developed the mathematical relationship that correlates the dissolution rate to the solubility gradient of the solid.

$$dc/dt=k\ (Cs-Ct)$$

dc/dt is the dissolution rate of the drug,

k is the proportionality constant

Cs is the saturation concentration (maximum solubility)

Ct is the concentration at time t

(Cs- Ct) is the concentration gradient.

Nernst and Brunner incorpated Fick's first law of diffusion and modified the Noyes and Whitney equation to:

$$dc/dt=DAK_{w/o}(C_s-C_b)/Vh$$

where,

D = diffusion coefficient of the drug

A = surface area of the dissolvig drug

$K_{w/o}$ = water/oil partition coefficient of the drug considering the fact that dissolution body fluids are aqueous.

V = volume of the dissolution medium.

H = thickness of the stagnant layer

(C_s-C_b) = concentration gradient for diffusion of drug.

1.3 BIOPHARMACEUTICAL CLASSIFICATION SYSTEM [3, 20]

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

2. EXPERIMENTAL WORK
Materials and Methods

MATERIAL USED AS IDEAL CARRIER FOR SOLID DISPERSION

While selecting a carrier for solid dispersion of drug several factors need to be considered. Most important factors are the nature of carrier, drug to carrier ratio, method of preparation, polymer chain length/molecular weight, and synergistic effect of two carriers.

Table : Common examples of carriers used in solid dispersions

S.No.	Nature	Carrier
1.	Acid	Citric acid, tartaric acid, succinic acid
2.	Sugar	Dextrose, Mannitol, Sorbitol, Sucrose
3.	Polymeric Materials	Polyvinylpyrrolidone, PEG-4000
4.	Surfactants	Polyoxyethylene stearate, Poloxamer, Tween
5.	Hydrotropes	Sodium acetate, Sodium- o-hydroxy benzoate,
6.	Others	Urea, Urethane, Silica gel

GENERAL TYPES OF CARRIER USED IN SOLID DISPERSION [22]

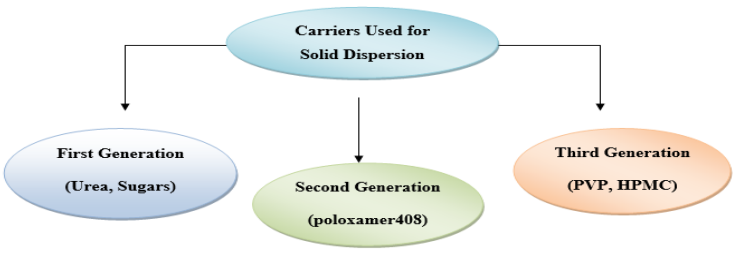
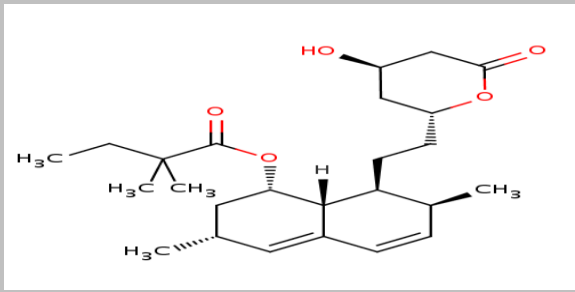


Figure : Types of Carriers used in Solid Dispersion

DRUG REVIEW

Simvastatin

Drug	Simvastatin
Synonyms	Synvinolin, Velastatin
Appearance	White colored
State	Solid
Chemical name	(1S,3R,7S,8S,8aR)-8-{2-[(2R,4R)-4-hydroxy-6-oxooxan-2-yl]ethyl}-3,7-dimethyl-1,2,3,7,8,8a-hexahydronaphthalen-1-yl 2,2-dimethylbutanoate
Chemical structure	
Molecular formula	$C_{25}H_{38}O_5$
Molecular weight	418.5662
Categories	Anticholesteremic Agents Hydroxymethylglutaryl-CoA Reductase Inhibitors Hypolipidemic Agents
BCS Class	Class II
Melting point	135-138 °C
Solubility	Methanol and ethanol
Bioavailability	5%.

POLYMER REVIEW

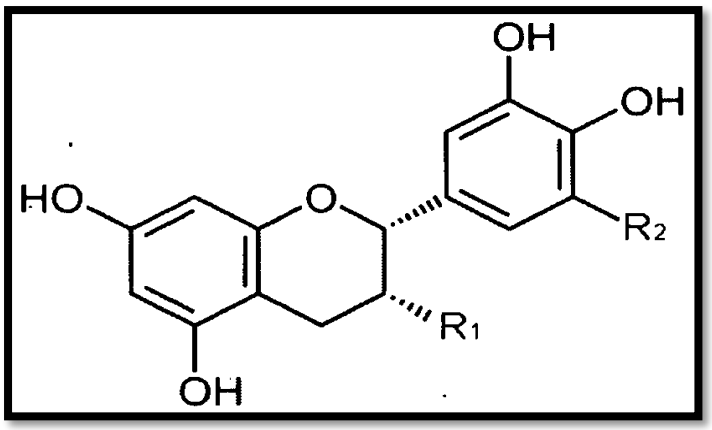
Hydroxypropyl Methyl Cellulose (HPMC)

Synonyms

- In BP- Hypromellose
- In USP-Hydroxy propyl methyl cellulose

Chemical Name

- Cellulose ,2-hydroxy propyl methyl ether
- **Chemical Structure**



General Characterization

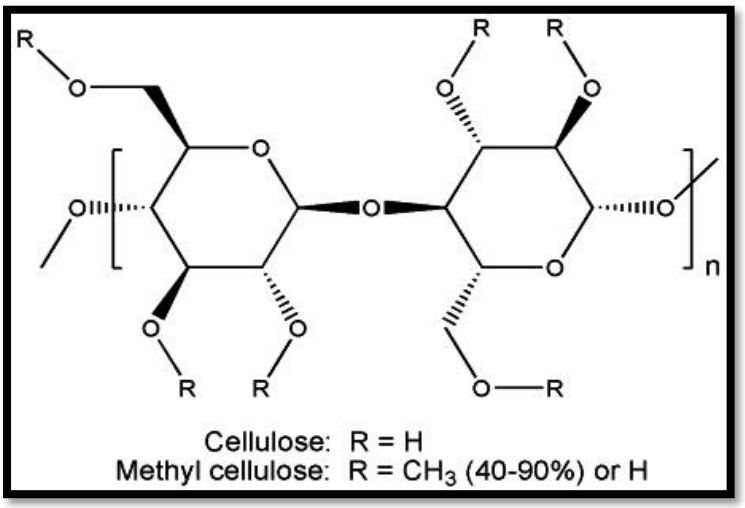
Solubility	**Soluble in water** **Ethanol :water** **Propanol :water**
Apparent Density	0.25~0.70g/cm 3 (Typical:0.5g/cm 3)
Molecular Weight	10 000 to 1500 000
Surface tension	42-56mN/m
pH Value	5.0-8.0
Melting point	190 -200^{0}C (At browns) 225-230^{0}C(At chars)
Density	0.5-0.7gm/cm^3

Methyl Cellulose

Synonyms

- In USP-Cellulose Methyl Ether
- In BP- Benecel
- **Chemical Name**
- Methyl Ether of Cellulose

Chemical Formula $[C_6H_7O_2(OH)_x(OCH_3)_Y]_n$



General Characterization

Solubility	**Soluble in water, glacial acetic acid** **Insoluble in ether, ethanol**
pH Value	5.5-8.0(for 1% solution)
Surface tension	53-59mN/m
Melting point	190^0C -200^0C

MATERIALS AND EQUIPMENTS

Table : List of Materials Used in the Research Work

S.No	Name	Manufacturer
1.	Simvastatin	Merck and co., USA
2.	Hydroxy Propyl Methyl Cellulose	S.D Fine Chemicals., Mumbai
3.	Methyl cellulose	S.D Fine Chemicals., Mumbai
4.	Ethanol	Balaji Drugs,Changshiu Yangyuan, China
5.	Methanol	S.D Fine Chemicals., Mumbai
6.	Lactose	S.D Fine Chemicals., Mumbai
7.	Talc	S.D Fine Chemicals., Mumbai
8.	Magnesium Stearate	National Chemicals., Mumbai
9.	Alluminium Foil	Hindalco Industries Ltd., Silvasa

Table : List of Instruments Used in the Research Work

S.NO	NAME	MANUFACTURER/MODEL
1.	Melting Point Apparatus	Remi's Equipment Pvt. Ltd.
2.	Digital Weighing Balance	Shimadzu, Japan
3.	UV Spectrophotometer	Shimadzu-1700 spectrophotometer
4.	Infra Red Spectrophotometer	Perkin Elmer 1600
5.	Tablet Punching Machine	Cadmach, Ahmedabad
6.	pH Meter	Control dynamic pH meter
7.	Micrometer	Mityato, Japan
8.	Hardness Tester	Scientific Engineering Co. Ltd., Delhi
9.	Friabilator	Campbell Electronics, Mumbai
10.	Tablet Disintegration Apparatus	Campbell Electronics, Mumbai
11.	Hot-Air Oven	Narang Scientific Works NSW-129
12.	Dissolution Rate Test Apparatus	Campbell Electronics, Mumbai
13.	High Precision Water Bath	Narang Scientific Works NSW-129

METHODS

5.2.1 Physical Appearance: Physical appearance of drug was examined by its various organoleptic properties like color, state, odour and taste.

5.2.2 Melting Point Determination: The melting point of the drug (Rosuvastatin Calcium) was determined by capillary fusion method. A capillary sealed at one end was filled with small amount of drug and the capillary was kept inverted i.e. sealed end down words into the melting point apparatus. The temp at which the solid drug converts into liquid was noted down with the thermometer provided.

5.23 Infrared Spectral Assignment: The IR analysis of sample was carried out for qualitative compound identification. The infrared spectra of Rosuvastatin calcium was performed on fourier transformed infrared spectrophotometer. The pellet of approximately 01mm diameter of drug was prepared grinding 3-5mg of sample with 100-150mg of potassium bromide in pressure comparison machine. The sample pellet was mounted in IR compartment and scanned at wavelength $4000cm^{-1}$-$500cm^{-1}$.

5.2.4 Determination of Absorption Maxima(λ max) A UV absorption maxima of the drug was determined by scanning (10µg/ml) solution of drug in methanol between 200-400nm

5.2.5 Preparation of Calibration Curve in Phosphate Buffer(pH 6.8)

a)Preparation of phosphate Buffer(pH 6.8) : Take 28.80gm of disodium hydrogen phosphate and 11.45 gm of Potassium dihydrogen phosphate in sufficient water to produce 1000ml.

b)Preparatrion of calibration curve: 50mg of drug dissolved in small amount of methanol and dilute to 100ml with phosphate buffer pH 6.8,50ml of this solution was taken and dilute to 100ml with phosphate buffer pH 6.8 to prepare stock solution of 250 µg/ml.From this solution take 0.1,0.2,0.3,0.4,0.6 and 0.8ml and transferred it into 10 ml volumetric flask and volume make upto 10 ml with phosphate buffer and take absorbance at 238 nm using phosphate buffer as blank.

5.2.6 Preparation of Calibration Curve in Methanol

50mg of drug dissolved in 100ml of methanol,50ml of this solution was taken and dilute to 100ml with methanol to prepare stock solution of 250 µg/ml.From this solution take 0.1,0.2,0.3,0.4,0.6 and 0.8ml and transferred it into 10 ml volumetric flask and volume make upto 10 ml with methanol and take absorbance at 238 nm using methanol as blank.

5.2.7 Preparation of Calibration Curve in Water

50mg of drug dissolved in 100ml of methanol,50ml of this solution was taken and dilute to 100ml with methanol to prepare stock solution of 250 µg/ml.From this solution take 0.1,0.2,0.3,0.4,0.6 and 0.8ml and transferred it into 10 ml volumetric flask and volume make upto 10 ml with water and take absorbance at 238 nm using water as blank

RESULTS AND DISCUSSION:

Infrared spectroscopy

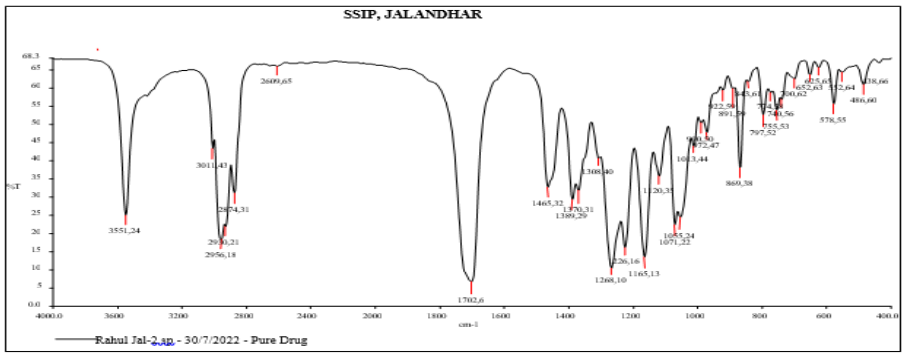


Figure : IR Spectra of Simvastatin Determined Practically

Table : Observed Peaks of Simvastatin

Functional groups	Peaks(cm^{-1})
O-H	3551.48cm^{-1}
C-H	2969.57 cm^{-1},2956.15 cm^{-1}
C=O	1698.38cm^{1}
C-H	1467.24 cm^{1},1390.97 cm^{1}
C-O	1268.32 cm^{1}
Ester -C-O-C- bend	1165.13

Absorption Maxima (λ max) of Drug

Absorptionmaxima (λ max) of simvastatin were observed in different solvents.

Table : Absorption maxima (λmax) of the Simvastatin in different solvent

Solvent	(λmax)nm
Phosphate buffer	239nm
Water	238nm
0.1N HCL	238nm
Methanol	239nm

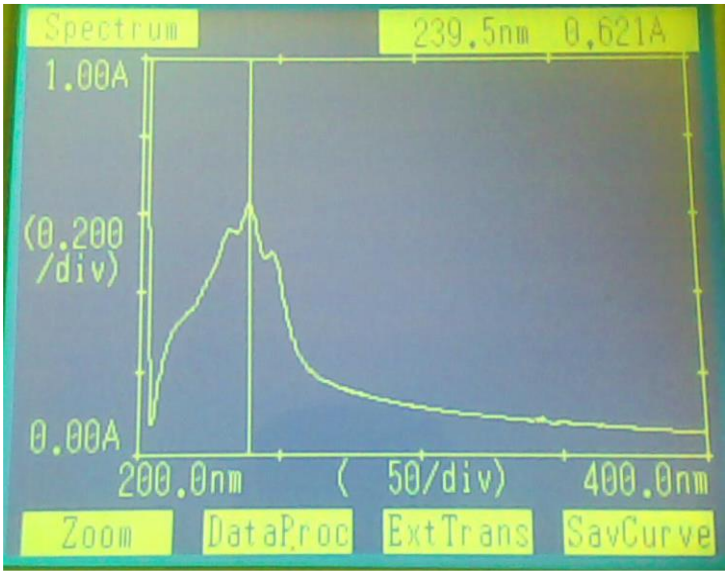


Figure : Scan graph of Simvastatin in phosphate buffer pH 6.8

Solubility

Solubility of Simvastatin in different solvents

Solvent	Solubility
Phosphate buffer	4.036±0.548
Water	1.686±0.356
0.1N HCL	2.166±0.622
Methanol	2.516±0.164

Data Expressed as mean ± S.D (n=3)

Solubility of the Simvastatin found to be higher in phosphate buffer as compared to 0.1N HCL and also confirms the weekly acidic nature of the drug.

Drug Excipient Compatibility Studies

Physical mixtures of both simvastatin and excipients HPMC and Methyl Cellulose are prepared and put in to stability chamber for one month. No major changes were observed in the drug like there was no discoloration of the drug, No liquefaction between drug and polymer, No odour changes in the pure form of the drug was noticed which confirms the compatibility between the drug and excipients. The FTIR spectra of simvastatin and HPMC /MC physical

mixtures are shown below which indicate that simvastatin compatible with the HPMC and Methyl Cellulose

Table : Drug Excipient compatibility study between SIM/HPMC

	Week 1	**Week 2**	**Week3**	**Week 4**
Drug				3553cm^{-1},3011cm^{-1},1267 cm^{-1} 1166cm^{-1},2872cm^{-1}
Drug +polymer				3464cm^{-1},2932cm^{-1},1719 cm^{-1} 1646cm1461cm^{-1}

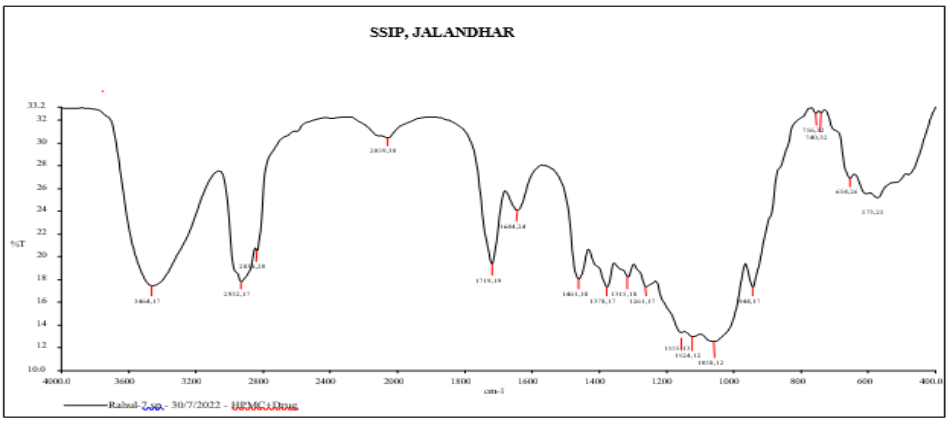


Figure : IR Spectra of Mixture of Drug & HPMC

Table : Drug Excipient compatibility study between SIM/MC

	Week 1	**Week 2**	**Week3**	**Week 4**
Drug				3553cm^{-1},3011cm^{-1} 1267 cm^{-1}1166cm^{-}2872cm^{-1}
Drug +polymer				3839cm^{-1},3447cm^{-1}, 2931cm^{-1},2057cm^{-1}

Standard curves

The standard curve of Simvastatin was found to be linear at 237nm in phosphate buffer (pH6.8) in the concentration range of 2-12(µg/ml), which obeys Lambert Beer Law. The absorbance at different concentrations is shown in tables and graph is represented in figure respectively.

Table : Standard Curve of Simvastatin in Phosphate Buffer (pH6.8)

S No.	Concentration(µg/ml)	Absorbance
1	2	0.134±0.022
2	4	0.236±0.006
3	6	0.345±0.012
4	8	0.465±0.033
5	10	0.558±0.036
6	12	0.662±0.036

Data Expressed as mean ± S.D (n=3)

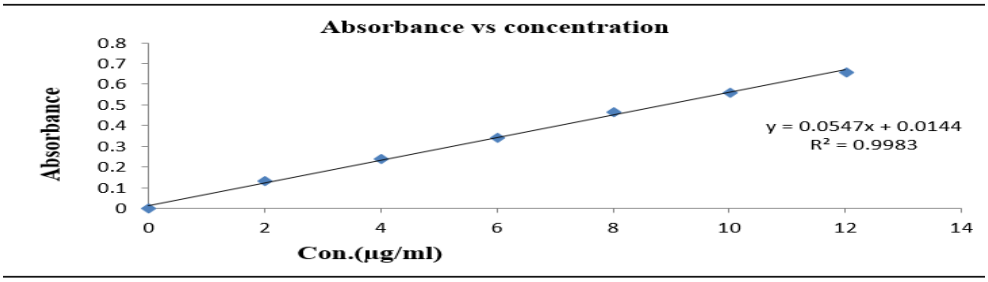


Fig.: Standard Curve of Simvastatin in Phosphate Buffer (pH6.8)

Table : Standard Curve of Simvastatin in distilled water

S No.	Concentration(µg/ml)	Absorbance
1	2	0.148±0.028
2	4	0.248±0.032

3	6	0.364±0.036
4	8	0.469±0.018
5	10	0.556±0.036
6	12	0.678±0.024

Data Expressed as mean ± S.D (n=3)

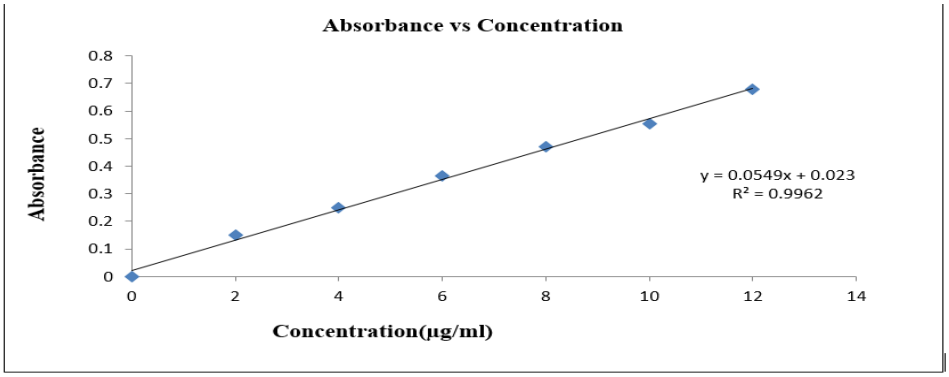


Fig.: Standard Curve of Simvastatin in Distilled water

Table : Standard Curve of Simvastatin in Methanol

S No.	Concentration(µg/ml)	Absorbance
1	2	0.128±0.018
2	4	0.242±0.018
3	6	0.348±0.018
4	8	0.432±0.018
5	10	0.538±0.022
6	12	0.642±0.028

Data Expressed as mean ± S.D (n=3)

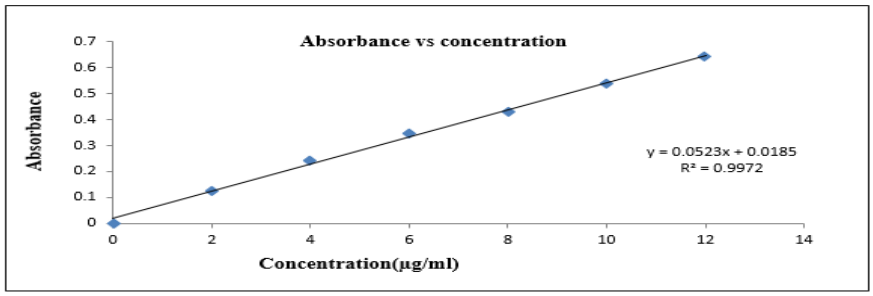


Fig.: Standard Curve of Simvastatin in Methanol

Percent yield and drug content

The percent yield and drug content of pure drug and different solid dispersions which are prepared with polymers were determined. The % yields decreased at the higher concentrations due to the difficulty in sieving at higher polymer and surfactants concentration

Table :Percent yield or drug content of solid dispersions Sim/HPMC

Formulation Code	Percentage yield	Drug content
SIH1:1	95.54±0.806	84.44±0.022
SIH1:3	94.82±0.636	91.74±0.008
SIH1:5	90.28±0.246	95.96±0.008

Data Expressed as mean ± S.D (n=3)

Table : Percent yield or drug content of solid dispersions Sim/MC

Formulation Code	Percentage yield	Drug content
SM1:1	90.15±0.758	77.68±0.016
SM1:3	89.64±0.516	87.88±0.004
SM1:5	89.28±0.866	84.24±0.018

Data Expressed as mean ± S.D (n=3)

Table :Percentage yield and drug content of solid dispersion Simvastatin MC: HPMC

Formulation Code	Percentage yield	Drug content
SHM1:1	92.28±0.936	85.78±0.016
SHM1:3	91.99±0.406	89.62±0.015
SHM1:5	92.56±0.404	92.12±0.006

Data Expressed as mean ± S.D (n=3)

Solubility studies

Solubility data of pure drug and different solid dispersions as shown in given Tables respectively. Solubility of drug increased with increased in the ratio of polymer.

Table: Solubility of Pure Drug Simvastatin and HPMC

Formulation Code	Solubility
Pure drug	4.038±0.544
SIH 1	6.158±0.646
SIH2	7.044±0.424
SIH3	8.272±0.152

Data Expressed as mean ± S.D (n=3)

Table: Solubility of Pure Drug Simvastatin and MC

Formulation Code	Solubility
Pure drug	4.038±0.546
SM1	5.358±0.286
SM2	6.068±0.352
SM3	7.676±0.444

Data Expressed as mean ± S.D (n=3)

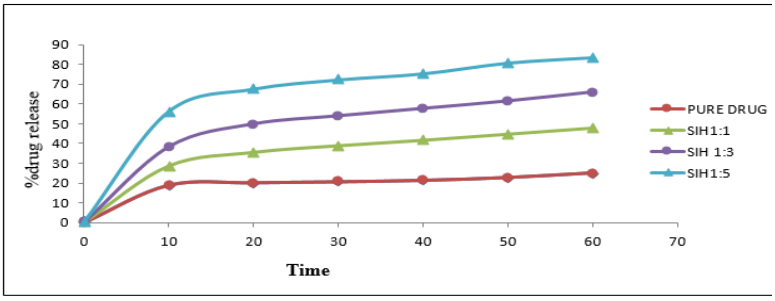
Dissolution studies

The In vitro release of pure drug and different solid dispersions were determined and plotted the graph between % drug released vs time.

Table: Dissolution profile of pure drug and solid dispersions Sim/HPMC

Mean Percentage Drug Release ± Standard deviation				
Time (min)	**Pure drug**	**SH1:1**	**SH1:3**	**SH1:5**
10	8.418± 2.646	28.56±0.406	38.16±0.054	56.08±0.456
20	20.08±2.605	35.52±0.208	49.76±0.016	67.52±0.416
30	20.58±0.014	38.84±0.208	53.84±0.578	72.12±0.578
40	21.36±0.026	40.52±0.054	57.56±0.616	75.26±0.564
50	22.74±0.274	45.06 ± 0.038	61.34±0.548	80.66±0.682
60	25.06±0.144	46.26 ± 0.064	65.84±0.158	83.46±0.328

Data Expressed as mean ± S.D (n=3)



Formulation code	D.E(%DE_{60})
Pure drug	19.96±0.008
SIH 1:1	35.66±0.998
SIH 1:3	50.18±1.956
SIH 1:5	65.48±1.908

Optimized formulation

On the basis of dissolution data optimized formulation is detected and formula was prepared which was shown below the table.

Table: Dissolution efficiency and yield of optimized formulations

Optimized formulation	$\%DE_{60}$	% Yield
100:500	65.46	90.28
100:500	53.42	89.28
100:250:250	60.92	92.56

Table: Evaluation parameters of optimized solid dispersion (HPMC) after stability

Time period (in days)	0	7	14	21	30
Color appearance	No change in color	No change in color	No change in color	No change in color	No change in color
Drug release	-	-	-	-	95.47

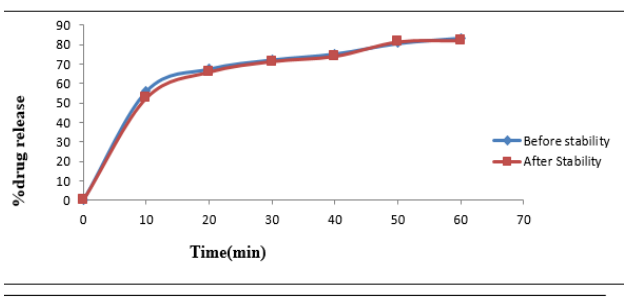


Fig.: Drug Release Data of Before and After Storage (Sim/HPMC)

Table: Evaluation parameters of optimized solid dispersion (MC) after stability

Time period (in days)	0	7	14	21	30
Color appearance	No change in color	No change in color	No change in color	No change in color	No change in color
Drug release	-	-	-	-	91.17

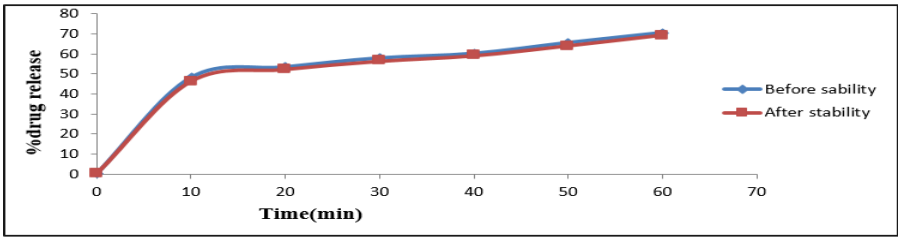


Fig.: Drug Release Data of Before and After Storage (Sim/MC)

Identification tests for tablet dosage form:

Table : Characterization of Tablet Dosage form

S.no	Hardness (kg/cm)	Wt. Variation (mg)	Disintegration Time (min)	Drug Content (%)	Percent Yield (%)
1	4.5±0.096	101.2±1.124	6.23	99.14±0.166	76.26±0.264
2	4.1±0.049	100.2±1.066	6.01	98.64±0.266	78.26±0.168
3	4.3±0.169	100.8±1.266	7 .46	99.33±0.146	81.66±0.258
4	4.2±1.026	99.2±2.568	7.01	97.14±0.208	75.66±0.306
5	4.4±0.059	100.8±1.544	6 .32	95.28±0.118	79.56±0.336
6	4.7±0.076	100.8±2.056	6. 52	98.76±0.206	80.99±0.288

7	4.6±0.088	101.8±1.358	7.18	99.66±0.118	81.46±0.178
8	4.5±0.156	100.4±2.086	6.02	98.06±0.148	79.84±0.168
9	4.2±0.169	101.8±1.448	7.18	99.84±0.258	76.46±0.248
10	3.8±0.094	102.4±2.008	6.01	97.36±0.326	82.12±0.208

Data Expressed as mean ± S.D (n=3)

Dissolution Profile

Table: Dissolution profile of Tablet Dosage Form

Mean Percentage Drug Release ± Standard deviation		
Time (min)	**Pure drug**	**Tablets**
10	6.28± 1.676	82.58±0.316
20	9.12±1.152	83.94±0.418
30	12.56±1.256	85.72±0.524
40	15.49±0.418	87.28±0.418
50	19.16±1.572	88.33±0.208
60	25.02±0.732	89.91±0.106

Data Expressed as mean ± S.D (n=3)

STABILITY TESTING:

Dissolution profile After Stability

Table : Dissolution profile of Tablet Dosage Form After Stability

Mean Percentage Drug Release ± Standard deviation		
Time (min)	**Pure drug**	**Tablets(After Stability)**
10	6.28± 1.676	81.12±0.316
20	9.12±1.152	82.58±0.106
30	12.56±1.258	84.36±0.208
40	15.48±0.418	85.31±0.106
50	19.16±1.572	86.36±0.316
60	25.02±0.734	87.82±0.316

Data Expressed as mean ± S.D (n=3)

CONCLUSION

In now days, Low oral bioavailability and low dissolution rate of poorly water-soluble drugs poses a great challenge during drug development. This study is based upon to increase the solubility of poorly water soluble drug with different kind of carriers and prepare solid dispersions to increase the solubility. For this purpose, a poor water soluble drug should be taken as a model drug. Simvastatin (lipid lowering agent) was selected as a model drug due to its poor water solubility and low dissolution rate (BCS class II), so this is necessary to increase the water solubility of the drug. First step is to prepare the solid dispersion of Simvastatin by using different carriers. Both hydroxy propyl methyl cellulose (HPMC) and methyl cellulose (MC) were used to prepare solid dispersions. First both polymers used separately to prepare solid dispersion and then both the polymers used in combination by melt method. Solid dispersion of both HPMC and Methyl cellulose shows better solubility and with their combination along with Simvastatin shows sharp increase in solubility. Which further characterized for percent yields drug content, solubility, and *in vitro* drug release. From above parameters it was concluded that solid dispersion of HPMC/Methyl cellulose shows better

dissolution rate as compared to solid dispersion of individual HPMC and Methyl cellulose along with drug. A particular drug to polymer ratio, were optimized which was having highest %DE60 and percent yield. The optimized solid dispersions were prepared and for FTIR, x-ray diffraction studies and *in vitro* dissolution studies.

Finally it was concluded that there was a large difference in the range of bioavailability of pure drug and in the form of solid dispersions along with polymers. The bioavailability of Simvastatin shows sharp increase in bioavailability when both polymers are used in combination as compared to used separately. Dissolution rate and Dissolution Efficiency (DE_{60}) of Solid Dispersion is very much high as compared to pure drug Simvastatin and shoes no remarkable changes are noticed after stability studies.

FUTURE IMPLICATIONS

- The principle of solid dispersions system can be used to improve the dissolution rate of the poorly water soluble drug
- This work can be extended to the further pharmaceutical dosage form like tablet capsule etc.

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