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Formulation and Evaluation of Simvastatin Solid Dispersion Tablets

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Abstract: ***The purpose of the study is to improve the dissolution & stabilization of simvastatin, a poorly water soluble drug by solid dispersion. Simvastatin belongs to BCS class 2 having low solubility & therefore low oral bioavailability (5%) 3.the solid dispersions is prepared by kneading method us using carriers at different drug carriers ratio (pvp-k30). The characterization of solid state properties of pure simvastatin is done by using FTIR. The formulation of simvastatin is done by direct compression method. The evaluation of formulated simvastatin is done by using physiochemical parameters such as hardness, friability, weight variation, uniformity of drug content &In vitro dissolution time.***

Keywords: Formulation, Evaluation, Simvastatin, Dispersion

1. Introduction

The term solid dispersion refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug. The matrix can be either crystalline or amorphous. The drug can be dispersed molecularly, in amorphous particles or in crystalline particles. Oral bioavailability of a drug depends on solubility and /or dissolution rate, therefore efforts to increase dissolution of drug with limited water solubility is often needed. Improvement in the dissolution rate of the poorly soluble drudges after oral administration is one of the most crucial challenges in modern pharmaceutics. Many methods are available to improve these characteristics including salt formation, micronization and addition of solvent or surface active agents. Solid dispersion has traditionally been used as an effective method to improve the dissolution properties and bioavailability of poorly water soluble drug. In solid dispersion system, a drug may exist as an amorphous form in polymeric carriers and this may result in improved solubility's and dissolution rate as compared with crystalline material. Drugs mole curly dispersed in polymeric carriers may achieve the highest levels of size reduction and surface area enhancement**,** which result in improved dissolution rate. Furthermore no energy required breaking up the crystal lattice of a drug dissolution process and drug solubility and wet ability may be surrounding hydrophilic carriers.

2. Need of Work

The purpose of the present study was to investigate the possibility of improving the dissolution and stabilization of simvastatin, a poorly water –soluble drug by solid dispersion. The dissolution rate of solid drug affect their bioavailability through a dissolution rate which dependent on surface area solubility, disintegration time**,**an wet ability of the powder particle, In addition the solubilisation of water insoluble drug is an important factor when making high quality pharmaceutical Simvastin shoes poor water solubility and this can give rise to low and erratic bioavailability and poor proportionality. The necessity to improve the dissolution properties of simvastatin been suggested, Particles size reduction, decrees in drug crystalline till amorphization or formation of met stable polymorphic modification are possible factor responsible for the apparent increase in dissolution rate. Simvastatin belongs to BCS class 2 having low solubility and therefore low oral bioavailability (5%). Simvastatin has the disadvantage of low bioavailability due to not being soluble in water and its intestinal metabolism by Cyp3 enzyme .poor aqueous solubility present great challenge to further development of these agents. Hence it is important to enhance the aqueous solubilise dissolution rate, and bioavailability of drug from its oral solid dosage form in the present study, solid dispersions were prepared by a kneading method using carriers at different drug carrier ratio (PVP-K30) and evaluated for different parameters like drug content in vitro drug release studies further simvastatin solid dispersion tablet were prepared and evaluated.

3. Objectives

1) To prepare solid dispersion of simvastatin for enhancement of dissolution.
2) To characterize solid state properties of pure simvastatin and solid dispersion using FTIR.
3) To formulate oral disintegrate simvastatin tablet to achieve better solubility of simvastatin
4) To characterize the prepared tablet by physicochemical parameters such as hardness, Friability, weight variation, uniformality of drug, in vitro dissolution time.

4. Plan of Work

- Literature survey
- Selection of drug and excipient
- Characterization of drug

1) Appearance
2) Melting point
3) Calibration curve

- Preparation of solid dispersion
  Method: Kneading method
- Characterization of solid dispersion

1)Flow Properties of solid dispersion
   a) Bulk Density
   b) Tapped density
   c) Angle of repose

d) d)Carr's Compressibility ratio
e) f) Hausners ratio

2) Determination of percent yield
3) Quality control test :% Drug content
4) Physical method –FTIR
5) In- Vitro Drug release dissolution Testing

- Formation of tablet by direct compression method
- Evaluation of tablet
  a) Thickness test
  b) Weight variation
  c) Drug Content
  d) Hardness
  e) Friability
  f) In-Vitro Disintegration Time
  g) In-Vitro Dissolution study

5. Materials, Methods and Equipments

5.1 Materials

Table 1:

Sr .No	Name of Ingredient	Name of supplier
1	Simvastatin	Cipla Pvt .ltd.Pataganga, Mumbai
2	PVPK-30	Loba chemic Mumbai
3	Microcrystalline cellulose	Loba chemic Mumbai
4	Sodium starch Glyconate	Loba chemic Mumbai
5	Talc	Loba chemic Mumbai
6	Crosspovidone	Loba chemic Mumbai

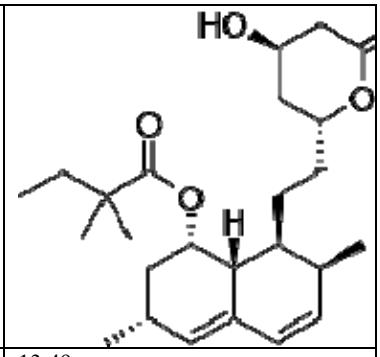
5.2 List of Equipments

Table 2:

Sr. No	Name of Equipment
1	Electronic balance
2	USP Dissolution apparatus -2
3	KBR Punch machine
4	Hardness Tester
5	Friability Tester
6	UV Visible spectrometer
7	Vernier calliper
8	FTIR

5.3 Drug Profile: SIMVASTATIN

Table 3: Physicochemical properties

1)Name	Simvastatin
2)Synonym	Simvastatin, Simvastatinum
3)Appearance	White colored
4)Molecular weight	418.6
5)Melting point	127-132
6)Molecular formula	$C_{25}H_{38}O_5$
7)Chemical IUPAC name	(1*S*,3*R*,7*S*,8*S*,8a*R*)-8-{2-[(2*R*,4*R*)-4-hydroxy-6-oxotetrahydro-2*H*-pyran-2-yl]ethyl}-3,7-dimethyl-1,2,3,7,8,8a-hexahydronaphthalen-1-yl 2,2-dimethylbutanoate
8)chemical structure	
9)Pka	13.49
10)Half LIFE	3 hr
11)Dose	40 mg
12)Drug category	Anticholestremic , Hydroxymethlglutaryl-CoA Redctase Inhibitores, Hypolipodemic
13)Solubility	Ethanol
14)BCS Class	Class 2
15)Plasma protein binding	Both simvastain and its β-hydroxyacid metabolite are highly bound to human plasma proteins.

Pharmacological data:

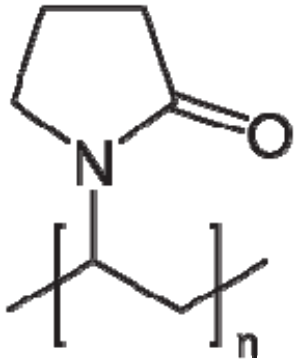
Metabolism	All statins act by inhibiting 3-hydroxy -3-methyglutaryl coenzyme A HMG-CoA reductase the rate limitingenzyme of the HMG-CoA reductase pathway responsible for the endogenous production of cholesterol
Elimination	Following an oral dose of 14c –labeled simvastatin in man 13%of the dose was excreted in urine and 60% in feces
Mechanism of action	Simvastatin is a pro drug in which the 6-membered lactone ring of simvastatin is hydrolyzed in vivo to generate the beta, delta-dihydroxy acid, an active metabolite structurally similar to HMG-CoA. Once hydrolyzed ,simvastatin competes with HMG-CoA for reductose hepatic microsomal enzyme . Interference with the activity of enzyme reduces the quantity of mevalonic acid ,a precursor of cholesterol

Pharmokinetics:-

Absorption	Absorption of simvastain , estimated relative to an intravenous reference dose ,in each of two animal specis tested ,averaged about 85% of an oral dose. In animal studies after oral dosing simvastatin achived substantially higher concentration in the liver than in non-target tissue .however because simvastatin undergoes extensive first pass metabolism ,the availability of the in the systemic is low .Peak plasma concentration occurs 1.3-2.4 hr after administration
Therapeutic Uses	The primary uses of simvastain are the treatment of dyslipidemia and the prevention of cardiovascular daises. it is recommended to be used only after other measure such as diet ,exercise ,and weight reduction have not improved cholesterol levels sufficiently
Adverce effect	Abdominal pain , diarrhea , indigestion and a general feeling of weakness .rare side effects include joint pain ,memory loss and muscle cramps cholestatic hepatitis

Polymer Profile:
PVPK-30

Table 4

SR NO	*Criteria*	*Remark*
1	Structure	
2	Chemical name	1-Ethenyl-2-pyrrolidon homopolyme
3	Empirical formula	$(C_6H_9NO)_n$
4	Mol weight	50000
5	Category	Dsintegrant ; dissolution enhancer ,suspending agent ; tablet binder
6	Solubility	Water and ethanol
7	Melting point	150–180 °C
8	Storage	It may be stored under ordinary condition without undergoing decomposition or degradation**,** since the powder is hygroscopic is should be stored in an airtight container in a cool, dry place.
9	Stability	It is stable cycle of heat exposure around 110-130°C and darkens extent on heating at 150°C with a reduction in aqueous solubility
10	Pharmaceutical application	It is primarily used in solid –dosage forms, binders in wet granulation process, solubilizer in oral and paranteral formulation**,** as coating agents, suspending agents, stabilization viscosity increasing agent in a topical and oral suspension**.**

6. Method

Preparation of solid dispersion by kneading method:

In this method, weighed quantity of drug and polymer placed in a mortar and then the mixture was Kneaded with 1.5 times the amount of either ethanol 70% v/v or water for 20 min. the kneaded mixtures were dried in oven at 40°c until it reached uniform weight and then pulverized and screened through 100-mesh sieve.

Table 5

Formulation code	*Carrier*	*Drug: carrier ratio*
PS1	PVPK30	1:1
PS2	PVPK30	1:2
PS3	PVPK30	1:3

7. Characterisation of Drug

1) Appearance

Determination of colour, odour, test and nature of powder

2) Melting point

Fill a melting point capillary tube with the sample. In order to work the plug of solid material down to the sealed end of the capillary, tap the sealed end on the table. Place the thermometer in the apparatus so that the mercury container is in level with the mouth of the circular tube. Place the capillary in the melting point apparatus through one of the side tubes so that the sealed end of the capillary is touching the front of the mercury reservoir and began to heat the apparatus with a micro burner. Place the burner under the back end of the oil bath of the apparatus to ensure the circulation of the silicon oil. The melting point of the unknown should be determined at least three times separately, accepting the average of the values as a result.

3) Calibration curve

- Preparation of stock solution:
  Accurately weighed 100mg of simvastatin was transferred to the 100ml volumetric flask containing phosphate buffer solution pH 6.8 and was sonicated for 30min. from the resulting solution 10ml was pipette out and diluted to 100ml with PBS pH 6.8 giving the stock solution of 100µg/ml.
- Preparation of the working solution:
  The beers-lamberts range of simvastatin was reported to be 5-25µ/ml. from the above stock solution, aliquots of 0.5 ml, 1.0 ml, 1.5 ml, 2.0 ml, and 2.5 ml were withdrawn and transferred to the 10ml volumetric flask containing PBS Ph 6.8 to get concentration of 5µg/ml, 10µg/ml, 15µg/ml, 20µg/ml, 25µg/ml, respectively. Finally the absorbance of prepared solutions was measured against blank (PBS Ph 6.8) at 247 nm using UV visible spectrophotometer and calibration curve was plotted for absorbance Vs concentration.

8. Evaluation of Solid Dispersion

a) Flow properties of solid dispersion:
   The powdered blend was evaluated for flow properties viz. Angle of repose, Bulk density, tapped density, Carr's compressibility index, and Hausner's ratio.
b) Determination of percent yield:
   The percent yield of simvastatin solid dispersions can be determined by using the following expression:
   Percent yield= (weight of prepared solid dispersion / weight of drug + carriers) × 100
c) Determination of percent drug content:
   Weighed amount of solid dispersions, equivalent to 20 mg of simvastatin were separately taken and added to 100 ml of phosphate buffer 6.8 in stopper conical flask. The sealed flasks were agitated on a sonicator. The solution was diluted with phosphate buffer 6.8 And was assayed by a UVVIS spectrophotometer for drug content at 247 nm using the following expression:

Percent drug content= (practical drug content in solid dispersion / theoretical drug content in solid dispersion) × 100

d) Fourier transform infrared spectroscopy (FTIR) analysis:
Drug-polymer interactions were assessed by FTIR spectroscopy. FTIR spectra of simvastatin & formulations containing PVP K-30 were recorded on IR affinity-1 (Shimadzu, Japan) using KBr discs. The instrument was operated under dry air purge & the scans were collected at scanning speed of 2 mm per sec with resolution of 4 cm -1 over the region 4000-400cm-1.

e) Dissolution study
Dissolution studies were performed in phosphate buffer (ph 6.8, 900ml) at 37 ±0.5 °c, using USP XXIV- Type 2 apparatus (Electro lab Mumbai) with a paddle rotating at 100 rpm. The samples equivalent to 40 mg, were subjected to dissolution. At time intervals of 10, 20, 30, 40, 50, 60 min samples (5ml) were withdrawn and equal amount of fresh dissolution medium was added. Withdrawn samples were filtered through 0.45µm membrane filter, and suitably diluted and spectrophotometrically analyzed for drug content at 247nm wavelengths using a UV-VIS spectrophotometer.

Preparation of Tablets For 1:1 Ratio

All the ingredients were passed through sieve, blended and disintegrate were incorporated in the powder mixture and finally talc where added as lubricant. The powder mix was weighed individually and compressed with KBR punch machine.

Ingredients	*Quantity for tablets(mg)*								
	F1	*F2*	*F3*	*F4*	*F5*	*F6*	*F7*	*F8*	*F9*
Solid dispersion (1:1 ratio)	40	40	40	40	40	40	40	40	40
Sodium starch glyconate	15	15	15	20	20	20	25	25	25
Crospovidone	30	35	40	30	35	40	30	35	40
Talc	1	1	1	1	1	1	1	1	1
Microcrystalline cellulose	120	120	120	120	120	120	120	120	120
Total	206	211	216	211	216	221	216	221	226

9. Evaluation Of Oral Dispersion Tablet

a) Thickness test
Thickness was determined using screw gauge 5 tablets from each batch were used and the average values were calculated.

b) Weight variation test
To study weight variation, 20 tablets of each formulation were weighed using an electronic balance and the test was performed according to the official method.

c) Drug content uniformity
Tablet containing 20 mg of drug is dissolved in 100ml of 6.8 ph phosphate buffer taken in volumetric flask. The drug is allowed to dissolve in the solvent. The solution was filtered, 1 ml of filtrate was of simvastatin in mg/ml was obtained by using standard calibration curve of the drug. Drug content studies were carried out in triplicate for each formulation taken in 100ml of volumetric flask and diluted up to mark with 6.8 ph phosphate buffer and analyzed spectrometric ally at 247 nm.

d) Hardness test
Hardness indicated the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablets was determined using Monsanto hardness tester. It was expressed in Kg/cm2. Three tablets were randomly picked and analyzed for hardness. The mean and standard deviation values were also calculated.

e) Friability test
The friability of tablets was determined using Roche Friabilator. The friabilator was operated at 25rpm for 4 minutes or run up to 100 revolutions. The % friability was then calculated by eq.1. f= initial weight – final weight / initial weight × 100……. (1)

f) In-vitro disintegration time
The process of breakdown of a tablet into smaller parts is called disintegration. The in-vitro disintegration time of a tablet was determined using disintegration test apparatus as per I.P specifications. Place one tablet in each of the 6 tubes of the basket. Ada disc to each tube and run the apparatus using ph 6.8 maintained at 37±20 c as the immersion liquid. The assembly should be raised and lowered between 30cycles per minute in the ph 6.8 maintained at 37±20c. The time taken up by the tablet for complete disintegration with no palpable mass remaining in the apparatus was measured and recorded.

g) In –vitro dissolution studies
Dissolution studies were performed in phosphate buffer (ph 6.8, 900ml) at 37±0.5 °c, using USP XXIV – Type 2 apparatus with a paddle rotating at 100 rpm. The samples equivalent to 40mg, were subjected to dissolution. At time intervals of 2, 4, 6,8,10,12,14,16 min. samples (5ml) were withdrawn and equal amount of fresh dissolution medium was added. Withdrawn samples were filtered through 0.45µm membrane filter, suitably diluted and spectrophotometrically assayed for the drug content at 247 nm wavelength using a UV-VIS spectrophotometer.

10. Result And Discussion

Characterization of simvastatin

1) Appearance

Simvastatin was found to be white, odourless, amorphous powder having bitter taste.

2) Melting point

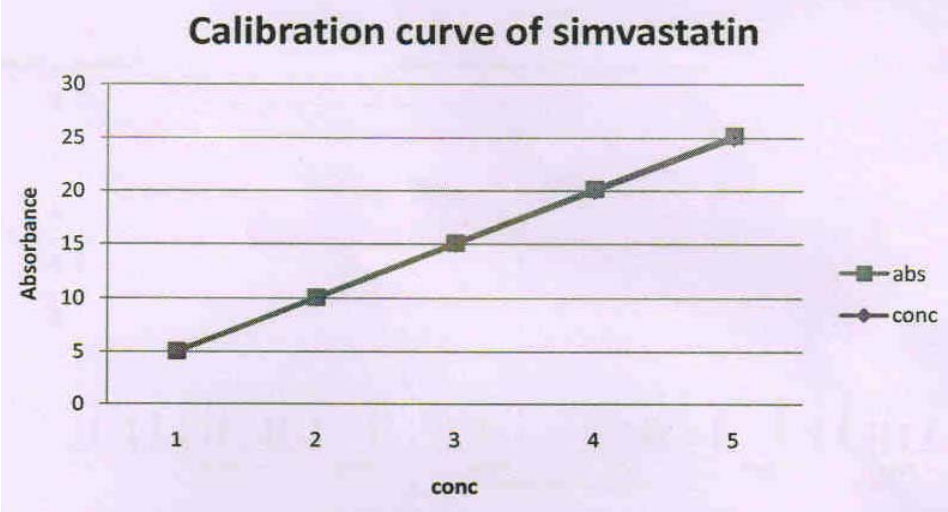
127-132°c

3) Calibration curve: Drug

Table 7

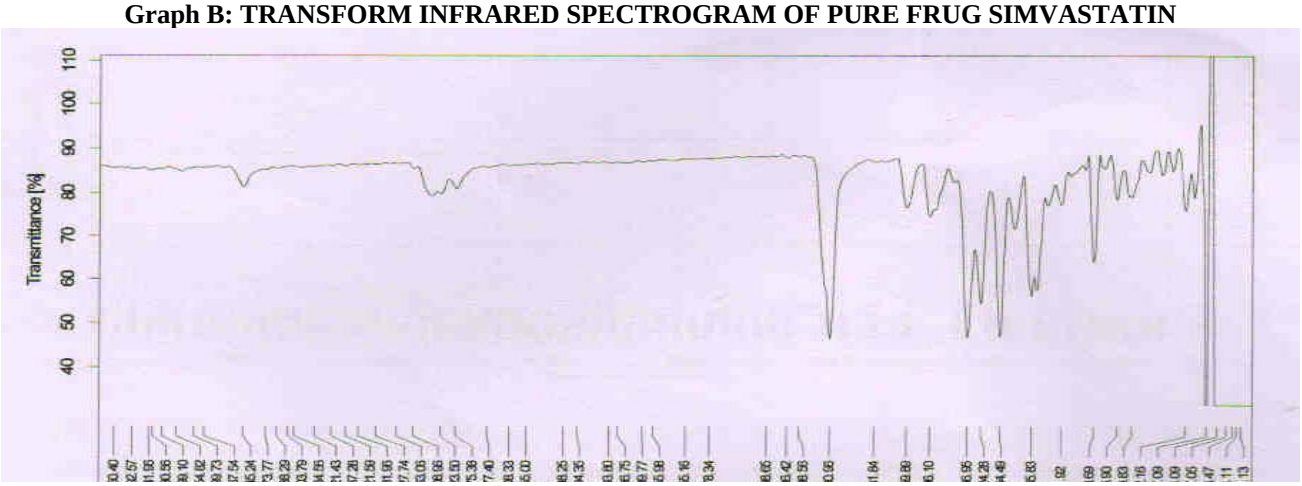
Conc.	Abs
5	0.061
10	0.087
15	0.1126
20	0.186
25	0.227
Slope	0.0086
Intercept	0.00542
R2	0.9798

Graph no. A

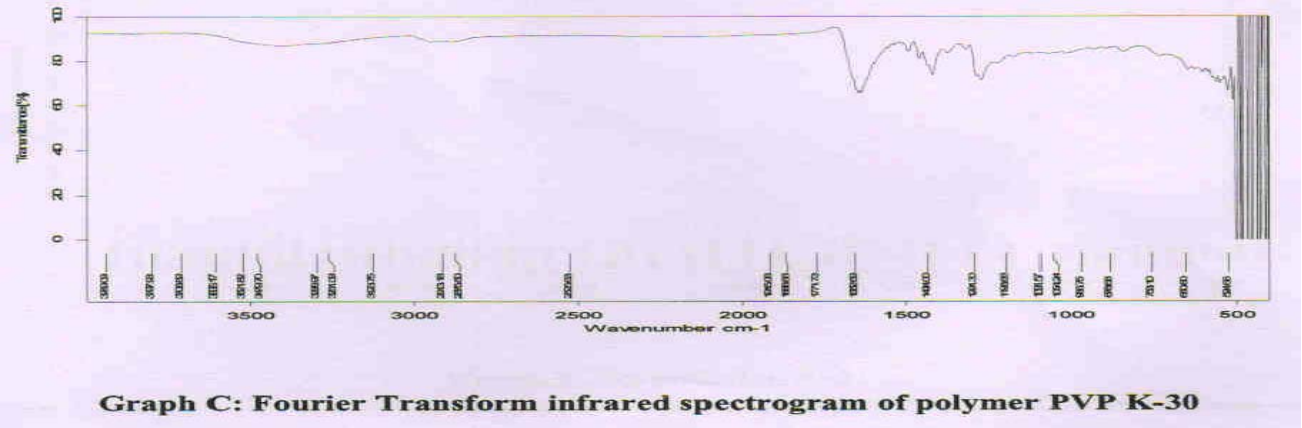


4) FTIR

Graph B: TRANSFORM INFRARED SPECTROGRAM OF PURE FRUG SIMVASTATIN

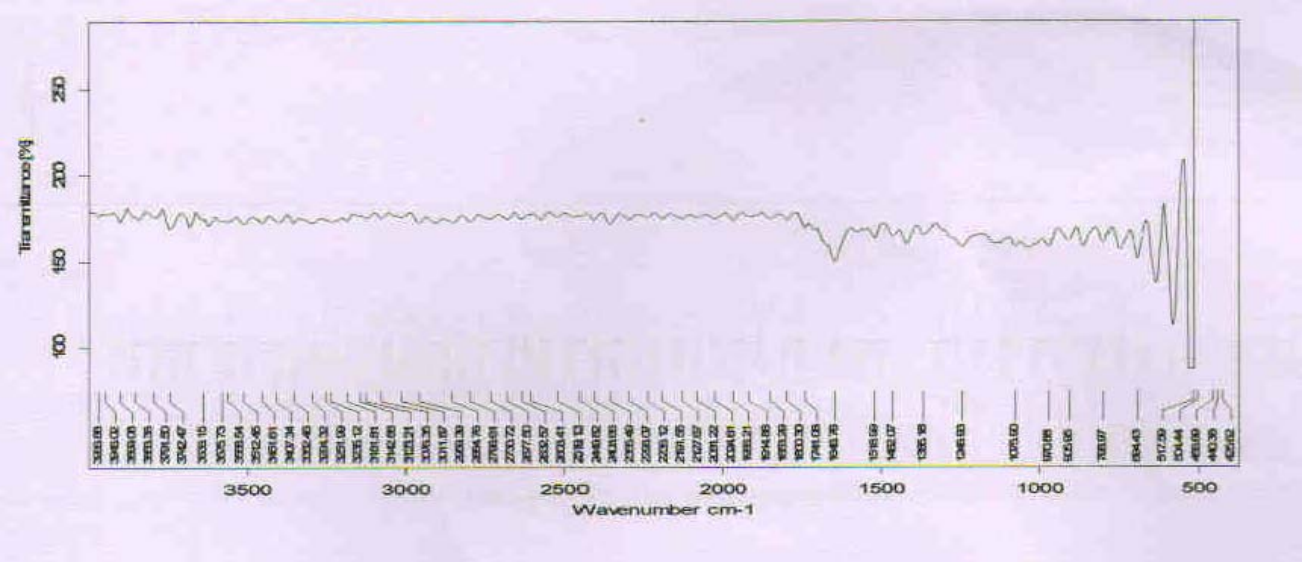


Graph C

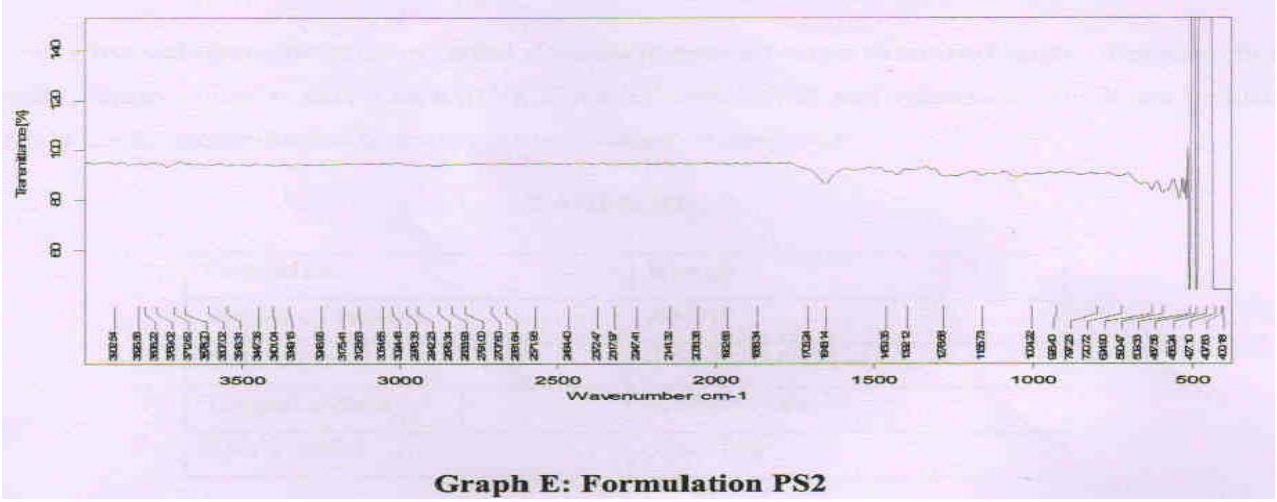


Graph C: Fourier Transform infrared spectrogram of polymer PVP K-30

Graph D: formulation PS1

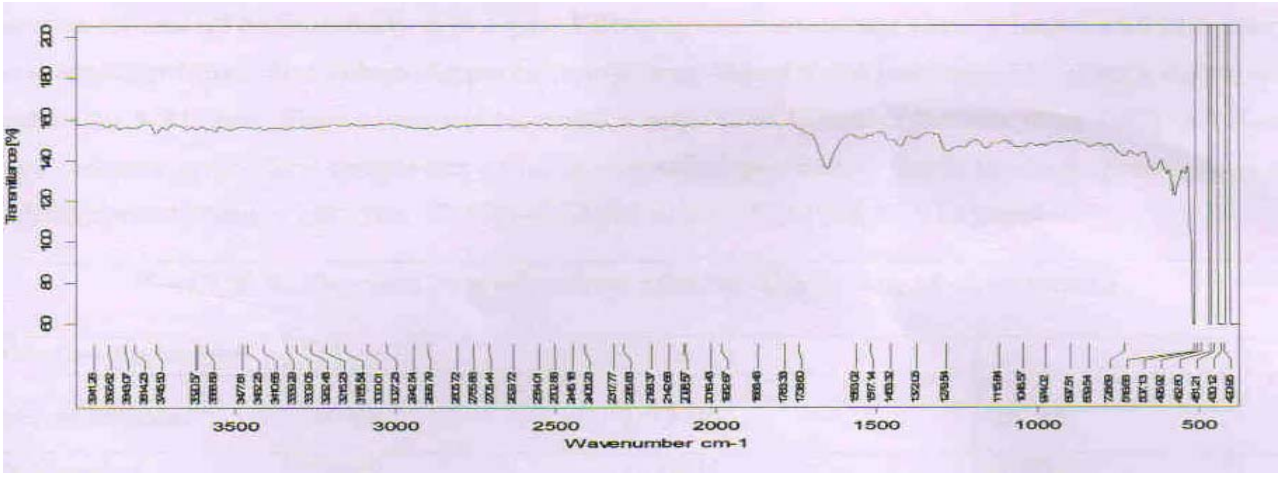


Graph E



Graph E: Formulation PS2

Graph F: Formulation PS3



Infrared spectra of simvastatin & formulations containing PVP K-30 are presented in fig.1 simvastatin shows major peaks at 1266.95, 1164.49, 2923.50 & 1796 cm-1 assigned to –OH bending alcohol, C-O stretching ketone respectively & almost the similar bands are observed & identified in the spectrum of the formulation is shown in fig (a, b). Hence the study indicates that there was no drug-polymer interaction.

5) Physical Characteristics of Solid Dispersion Powder

Physical characteristics of solid dispersion powder were examined angle of repose, bulk density, tapped density, carr's index (CI), Hausner's ratio and values for which are reported in the table no. 8

Table 8

Properties	Range
Angle of repose	20-30
Bulk density	0.5938-0.6691
Tapped density	0.708-0.784
Carr's index	5%-18%

From the values of bulk and tapped density the values of carr's index and Hausner's ratio were calculated. The values angle of repose was found to be less than 25°. Carr's index was found to be 5-21 less. The value of Hausner's ratio was found to be less than 1.27. All these values indicate good flow properties of solid dispersed powder. Also study % practical yield and drug content ranges between 77.55% - 87.65% and 27.27µg/ml – 51.81µg/ml.

Table 9

Evaluation parameters	1:1	1:2	1:3
Angle of repose	24.44	23.96	25.45
Bulk density	0.495	0.595	0.605
Tapped density	0.63	0.626	0.6808
Hausner's ratio	1.272	1.050	1.1252
Carr's index	21.428	5.271	11.252
%practical yield	77.5%	82.133%	87.65%
Drug content	51.81	31.57	27.27

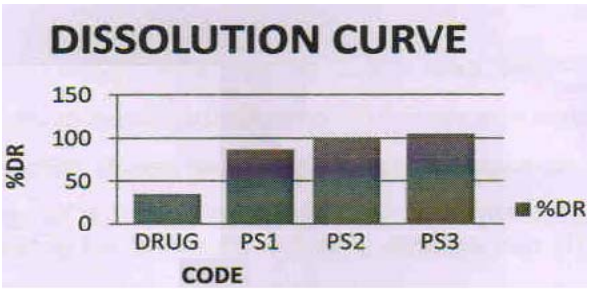
a) Dissolution Studies

The dissolution curves of simvastatin and its various binary systems with PVP K-30 in phosphate buffer 6.8

Table 10

Sr. no	Code	%DR
1	Drug	34.94
2	Ps1	86.64
3	Ps2	100.24
4	Ps3	104.37

The result of dissolution studies are shown in the table and the dissolution patterns in the graph. The results show that improvement in dissolution of solid dispersion as compares to pure simvastatin. It was observed that dissolution rate of drug polymer ratio was increased significantly compared to original drug. The increase in dissolution rate was found to be 2.5 fold greater in (1:1) ratio, while in case of (1:2) ratio dissolution pattern was found to be greater. In (1:3) ratio drug release pattern was found to be 2.6 fold greater than drug. The drug release in drug: polymer (1:1) ratio was found to be 86.64% in 16 min, in (1:2) ratio it was found to be 100.64% & in (1:) it was found to be 104.37%.



b) Evaluation of Simvastatin Tablet

Physiochemical evaluation of simvastatin tablet of different formulation were carried out, in that weight variation, hardness, friability, In-vitro disintegration time, Drug content study of tablet carried out.

Table 11: Evaluation of post-compression parameters of simvastatin oral dispersible tablet

F *code	Thickness (mm)	Hardness (kg/cm)	Friability (%)	DT* (Sec)	Weight variation (mg)	Drug content (%)
F1	7.3	3.4	1.197	35	Complies	81.23
F2	6.8	3.166	1.1	20	Complies	85.65
F3	7.3	3.7	1.3	30	Complies	56.23
F4	7.2	3.56	0.975	40	Complies	74.56
F5	7.0	3.7	1.057	45	Complies	45.56
F6	6.8	3.6	1.6	31	Complies	85.85
F7	7.1	3.7	0.9	51	Complies	69.25
F8	7.0	3.6	1.86	45	Complies	56.84
F9	7.7	3.5	1.17	35	Complies	89.54

The thickness was observed between 6.8-7.7mm respectively. Drug content of all formulations was observed between 45.56-89.54%. Whereas the weight of all formulation was complies hardness test for all formulation was carried out and observations obtained were in the range of 3.1-3.7 Kg/cm2. Test for friability was conducted for all formulations. % friability was found to be in the range of 0.9-186% in vitro disintegration time for all formulations was found to be in the range of 20-45 sec.

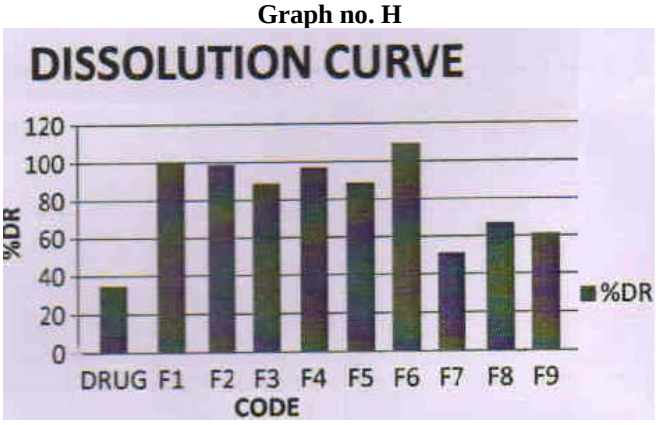
6) Dissolution Studies:

The dissolution curve of simvastatin tablet buffer 6.8

Table 12

Sr. No	Code	%DR
1	Drug	34.94
2	F1	100.74
3	F2	98.67
4	F3	88.73
5	F4	97.105
6	F5	88.88
7	F6	109.62
8	F7	51.05
9	F8	66.75
10	F9	61.10

Graph no. H



Observation showed that formulation F6 showed high drug release compared to drug and also other formulations.

11. Conclusion

Simvastatin is poorly water soluble drug hence by solid dispersion of simvastatin by Kneading method the dissolution of simvastatin is enhanced. The result showed that the dissolution rate of the drug in solid dispersed from higher than pure drug. It means solid dispersion form of simvastatin strongly improves the dissolution of simvastatin. Thus successful development of a novel simvastatin tablets fulfils the objectives of work.

12. Future Prospects

According to the present scenario of pharmaceutical industry, we can conclude that much effort must be taken for enhancing solubility of class 2 drugs to give life to the drug. Solid dispersion is one of the most promising techniques giving so many attractions from scientist due to its effects on improving solubility and dissolution rate of poorly soluble drug. Thus efforts must be taken to develop innovative for enhancement of class 2 drug.

References

[1] G.Sainath, A. Mamatha Sree, J. Subba Rao An International Journal Of Advances In Pharmaceutical Sciences Volume 4, Issue 1, January-February 2013, Pages94-104
[2] Shobhit kumar *, Satish kumar gupta, et.al Dissolution Rate enhancement of aceclofenac by solid dispersion technique ,ISSN2231-4423
[3] A.Luhadiya, S.Agrawal, P.Jain, P.K.Dubey A review on solid dispersion. int .j .Adv .Res Pharm.biol Sci., 2012,1:281-291
[4] J.Kaur, G Aggrawal, G .singh, A.C.Rana .Improvement of drug solubility using solid dispersion. Int .j. pharm .Sci .,2012,4:50
[5] R.CRowe, P.J.Shekey, ME. Quinn, Handbook of Pharmaceutical Exicpients, 6 th Edition 2009, RPS Publisher: 181,549,675.
[6] A.Rawat, S. Verma m. Kaul ,S.Saini Solid dispersion :astraegy for solubility enhancement. Int .j.pharma tech,.2011, 3:1062_1099
[7] A.Kalia, MPoddar, Sold Dispersion;an approach Towardes Enhancing Dissolution rate.Int j.Pharma, Sci., 2011,1:1-14, Etc.