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"Formulation and evaluation of fast dissolving lovastatin tablets by solid dispersion"

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ABSTRACT

The Fast Dissolving Tablets of Lovastatin by solid dispersion using Eudrgit RS100 were successfully prepared by direct compression method. The physiochemical evaluation results for the powdered blend of all trials pass the official limits in angle of repose, compressibility index. The prepared tablet for immediate release also maintained the physiochemical properties of tablets such as thickness, hardness, weight variation, friability.

The optimized formulation **F4** contains the average thickness of 2.75 mm average hardness of 5.6 kg/ cm^2, average weight variation of ± 0.5, and friability of 0.66%. The **F4** formulation of Fast Dissolving Tablets of Lovastatin showed 100% drug release within 20 mins using Eudragit RS100 as carrier whereas marketed formulation showed 100% drug release in 60 mins.

Keywords: Angle of repose, Compressibility index and Direct compression method

INTRODUCTION

The oral route is most common and preferred route for drug delivery system, it is convenient and easy ingestion. Poorly water-soluble drugs are expected to have dissolution-limited absorption. [1] Increasing the drug solubility may substantially improved drug absorption, and consequently drug bioavailability. Solid dispersion techniques have been used to enhance the dissolution and oral bioavailability of many poorly soluble drugs. Hence the researchers focused on two areas i) to enhance solubility and dissolution ii) to increase the permeability of poorly water soluble drugs. The main use of solid dispersion technique is to improve the dissolution rate and bioavailability of poorly water soluble drugs. [2] Many researches denoted that drugs are poor water solubility and high permeability for solid dispersion system (BCS) classification, this type of drugs shown dissolution rate is limited and categorized class-II drugs. Therefore for oral route of administration to increase the dissolution and bio availability by using solid dispersion systems for class-II drugs. [3]

Carrier molecules (which are inert) play the most important role in enhancing solubility of the

resultant dispersion and hence improvement in oral bioavailability. Among various approaches to improve the dissolution rate of poorly soluble drugs, the preparation of solid dispersions has often proved to be successful. [4]

Solid dispersions

Chiou and Riegelman defined the term solid dispersion as 'the dispersion of one or more active ingredients in an inert carrier matrix at solid-state prepared by the melting (fusion), solvent or melting- solvent method' While Corrigan suggested the definition as 'product formed by converting a fluid drug-carrier combination to the solid state [5]

Several insoluble drugs have been shown to improve there dissolution character when incorporated into solid dispersion. It releases the drug through different mechanisms, and the rate of release of drug to the surrounding fluid is mainly dependent on the type of solid dispersion formed. [6] Solid dispersion technique has been widely employed to improve the dissolution rate, solubility and oral adsorption of poorly water soluble drug's. [7]

AIM AND OBJECTIVE OF THE STUDY

The aim of the present study is to prepare fast dissolving tablets of Lovastatin by solid dispersion techniques and compare with marketed product. [8]

Objectives

1. To improve the solubility and dissolution rate.
2. To estimate release of drug after solid dispersions.
3. To optimize the best formulation of Lovastatin with the most suitable technique.
4. To evaluate tablets for their fast dissolving properties.
5. To compare with market formulation.

METHODOLOGY

Formulation of Solid Dispersion

An accurately weighed quantity of solid dispersion equivalent to 20 mg of Lovastatin was taken into a 100ml volumetric flask, dissolved in acetone and suitably diluted with 0.1N Hcl. The content of Lovastatin was determined spectrophotometrically at 243 nm against suitable blank using UV-visible spectrophotometer.[9]

In-vitro dissolution studies [10]

- Powdered blend of α-cyclodextrin, Chitosan, Eudragit which were prepared using kneading method, solvent evaporation method, co-precipitation method in different ratios (i.e., 1:1, 1:2, 1:3) were filled in muslin cloth, tied with thread and tied to the paddles of USP-II.
- Beakers were filled with 900ml of 0.1N Hcl with pH 1.2 at 37±0.5◦C at a speed of 50rpm.
- Aliquot of 5ml was withdrawn at predetermined time intervals (5, 10, 15, 20, 30, 45, 60) and equivalent amount (5ml) of fresh medium was replaced to maintain a constant volume after each sampling and analyzed spectrophotometrically at 243nm against suitable blank using UV-visible spectrophotometer.

Preparation of fast dissolving tablets of lovastatin solid dispersion by direct compression method [11]

Solid dispersion of Lovastatin: Eudragit (1:3) equivalent to 20 mg of drug prepared by solvent evaporation method were taken and mixed with directly compressible disintegrant, filler and glidant, in a plastic container. Powder blend were directly compressed using 8 mm, round-shaped flat punch in a tablet compression machine.

Solid Dispersion of Lovastatin with α - Cyclodextrin, Chitosan and Eudragit

Methods of Preparation of Solid Dispersion

Solid dispersions were prepared by different methods like kneading method, solvent evaporation method, co-precipitation method in 1:1, 1:2, 1:3

Where,

1:1 = 200 mg Drug + 200 mg Carrier

1:2 = 200 mg Drug + 400 mg Carrier

1:3 = 200 mg Drug + 600 mg Carrier

Formula to calculate % drug release [12]

$$\frac{Absorbance}{Slope} \times \frac{900}{1000} \times \frac{100}{lable\ claim} \times DF$$

Where,

Slope = 0.07

Lable claim = 20 mg

λ_{max} for Lovastatin = 243nm

Invitro dissolution studies using solid dispersion

Invitro dissolution studies for lovastatin: α-cyclodextrin

In vitro drug release studies were carried out using USP XXIV dissolution apparatus type II, with 900ml of dissolution medium maintained at 37±0.5°C for 1 hr, at 50 rpm, 0.1 N HCl was used as a dissolution medium. 5ml of sample was withdrawn at predetermined time intervals replacing with an equal quantity of drug free dissolution fluid. The samples withdrawn were filtered, and drug release in each sample was analyzed after suitable dilution by UV/Vis Spectrophotometer at 243nm.

Table No: 1 Dissolution Studies of Solid Dispersion Lovastatin: α-Cyclodextrin (1:1, 1:2, 1:3)

Lovastatin : α-Cyclodextrin									
	Kneading Method (1:1, 1:2, 1:3)			Solvent evaporation Method (1:1, 1:2, 1:3)			Co-precipitation Method (1:1, 1:2, 1:3)		
TIME (min)	SDC1	SDC2	SDC3	SDC4	SDC5	SDC6	SDC7	SDC8	SDC9
5	7.2	8.0	7.9	8.4	10.2	10	15.6	16.4	7.3
10	19.2	20.4	22.1	20.3	19.0	26.5	25.4	26.1	22.6
15	36.5	32.2	34.4	30.0	35.1	37.9	38.5	37.1	34.5
20	45.4	46.5	49.8	48.7	46.5	48.8	48.1	48.3	49.3
30	59.8	59.9	56.6	60.1	60.4	56.4	54.2	55.1	56.6
45	64.1	66.2	69.4	72.1	63.7	64.5	65.1	68.4	69.1
60	70.1	78.4	78.9	80.1	71.4	74.5	79.6	80.4	78.1

Invitro dissolution studies for lovastatin: chitosan

Table No: 2 Dissolution Studies Of Solid Dispersion Lovastatin: Chitosan (1:1, 1:2, 1:3)

Lovastatin : Chitosan									
	Kneading Method (1:1, 1:2, 1:3)			Solvent evaporation Method (1:1, 1:2, 1:3)			Co-precipitation Method (1:1, 1:2, 1:3)		
TIME(mins)	SDS1	SDS2	SDS3	SDS4	SDS5	SDS6	SDS7	SDS8	SDS9
5	15.4	16.4	18.7	10.2	10	15.6	8.0	7.9	18.9
10	21.4	22.8	25.6	19.0	26.5	25.4	20.4	22.1	21.4
15	36.4	35.4	39.6	35.1	37.9	38.5	32.2	34.4	38.4
20	49.5	48.7	50.9	46.5	48.8	48.1	46.5	49.8	51.4
30	56.5	66.1	79.4	60.4	56.4	54.2	59.9	56.6	78.9
45	56.5	80.4	79.4	60.4	64.5	65.1	59.9	69.4	84.5
60	56.5	90.1	79.4	60.4	74.5	79.6	59.9	78.9	92.1

Invitro dissolution studies for lovastatin: Eudragit Rs 100

Table No: 3 Dissolution Studies Of Solid Dispersion Lovastatin: Eudragit (1:1, 1:2, 1:3)

Lovastatin : Eudragit RS 100										% Drug Release of Pure Drug
	Kneading Method (1:1, 1:2, 1:3)			Solvent evaporation Method (1:1, 1:2, 1:3)			Co-precipitation Method (1:1, 1:2, 1:3)			
TIME (mins)	SDE1	SDE2	SDE3	SDE4	SDE5	SDE6	SDE7	SDE8	SDE9	
5	13.4	8.9	12.2	8.0	7.9	**21.7**	10	15.6	14.23	**7.21**
10	22.8	17.3	14.0	20.4	22.1	**38.4**	26.5	25.4	23.33	**12.21**

15	32.4	33.6	39.1	32.2	34.4	**78.9**	37.9	38.5	36.34	**27.24**
20	42.7	60.9	49.5	46.5	49.8	**84.5**	48.8	48.1	56.34	**46.98**
30	68.1	78.4	63.4	59.9	56.6	**100**	56.4	54.2	68.45	**50.18**
45	78.4	78.4	77.8	59.9	69.4	**100**	64.5	65.1	74.98	**63.28**
60	89.1	78.4	77.8	59.9	78.9	**100**	74.5	79.6	74.98	**70.8**

Dissolution graph

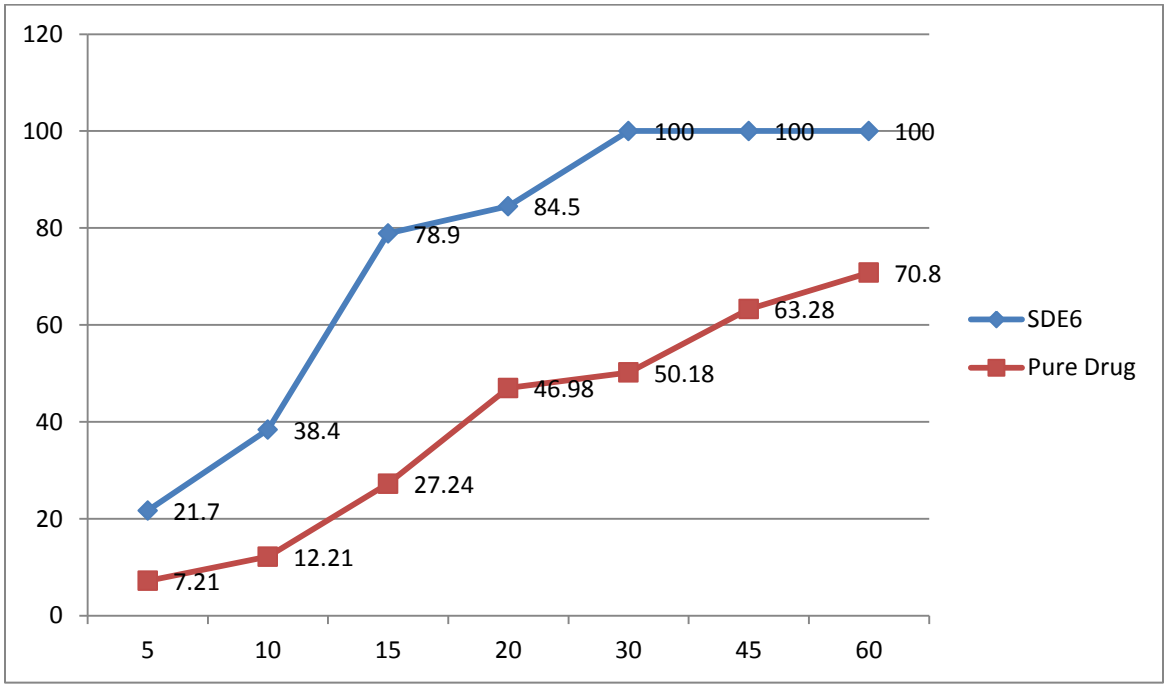

Fig No: 1 Comparison of Dissolution Studies of SDE6 Formulation and Pure Drug

DISCUSSION

Dissolution studies were carried out by different Solid Dispersion techniques (Kneading Method, Solvent Evaporation Method, Co – Precipitation Method) using different carriers (α – cyclodextrin, Chitosan, Eudragit RS100) in different ratios (1:1, 1:2, 1:3).Formulation SDE 6 (Solvent Evaporation using Eudragit RS100) in 1:3 ratio released 100% drug in 30 mins whereas pure drug released 50.18% in 30 mins. Therefore tablets were prepared using Eudragit RS100 as carrier.

Formulation development of lovastatin fast dissolving tablets

Preparation of fast dissolving tablets

Accurately weighed quantities of ingredients were blended manually. Homogeneous blend was compressed in to tablets (200 mg each) using 8mm diameter, deep concave punches. The compression force was adjusted to give tablets with approximately 2.92 kg/cm^2 on a Monsanto tablet hardness tester. [13]

Table: 4 Formulation Chart

Ingredients(mg)	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)	F7 (mg)	F8 (mg)	F9 (mg)
Lovastatin SD	40	40	40	**40**	40	40	40	40	40
SSG	10			**15**			20		
CCS		10			15			20	
CP			10			15			20
Mg.stearate	5	5	5	**5**	5	5	5	5	5

Talc	5	5	5	**5**	5	5	5	5	5
Lactose	140	140	140	**135**	135	135	130	130	130
Total weight	200	200	200	**200**	200	200	200	200	200

*** SD – Solid Dispersion**
*** SSG – Sodium Starch Glycolate**
*** CCS – Cross Carmellose Sodium**
*** CP – Cross Povidone**

Conclusion

Formula 4 **(F4)** has shown optimized results.
Optimized Formulation: F4

RESULTS AND DISCUSSION

Pre formulation studies

PARAMETER	DRUG
Organoleptic Evaluation	White, fine hygroscopic powder.
Observed Melting Point	174 °C
Solubility Analysis	Insoluble in water and partially soluble in organic solvents

PRE-COMPRESSION PARAMETERS

Evaluation of lovastatin powder

Table No 5: Evaluation Parameters For Pre-Compression Studies

Formulation code	Angle of Repose (θ)	Bulk Density (g/cm^2)	Tapped Density (g/cm^2)	%Compressibility	Hausner's ratio
F1	24.6	0.45	0.52	13.4	1.15
F2	26.9	0.44	0.52	15.3	1.18
F3	24.2	0.45	0.51	11.7	1.13
F4	29.5	0.44	0.50	12.0	1.13
F5	20.6	0.45	0.52	13.6	1.15
F6	23.1	0.44	0.52	15.3	1.18
F7	25.3	0.44	0.54	14.2	1.15
F8	24.6	0.49	0.56	15.1	1.13
F9	25.1	0.48	0.58	14.2	1.12

From the above pre-compression parameters it was clear evidence that powder has excellent flow properties.

POST COMPRESSION EVALUATION PARAMETERS

Post Compression Parameters for Immediate Release Tablets

Table No 6: Evaluation Parameters for Post-Compression Studies

Formulation code	Weight variation (%)	Hardness (kg/cm^2)	Friabilty (%)	Thickness (mm)	Content uniformity (%)
F1	+(0.5)	6.4	0.72	2.6	99.28
F2	0	6.3	0.68	2.6	97.16
F3	-(0.5)	5.8	0.69	2.7	100.1

F4	0.5	5.6	0.66	2.75	101.1
F5	1	5.7	0.68	2.6	98.19
F6	-(1)	5.9	0.65	2.62	99.41
F7	3	5.6	0.68	2.6	98.23
F8	2	5.5	0.69	2.7	96.98
F9	-(2)	5.9	0.66	2.75	99.00
Acceptance criteria	7.5	4-8	<1	-	90-110

Physical characterization of tablets

The thickness of the tablets was found to be in the range of ***2.75 – 2.6 mm***. Hardness was found to be in between ***5.5 – 6.4 Kg/cm^2***. Friability below 1% was an indication of good mechanical resistance of tablets. All the formulations showed more than 95% of drug content indicating content uniformity in the prepared batches.

COMPARISON BETWEEN OPTIMISED FORMULATION AND MARKETED FORMULATION

Table No: 7 Dissolution Values Of Optimized Formulation And Comparison With Marketed Formulation.

Time in min	F1	F2	F3	F4	F5	F6	F7	F8	F9	Marketed Formulation
5	20	22	38	**54**	46	32	38	35	45	**24**
10	30	33	43	**66**	48	57	46	46	63	**38**
15	41	41	55	**74**	57	68	68	55	70	**46**
20	53	52	63	**89**	73	74	78	70	82	**59**
30	69	77	70	**100**	87	83	78	86	90	**74**
45	72	87	89	**100**	97	83	78	96	91	**82**
60	80	97	96	**100**	97	83	78	96	91	**100**

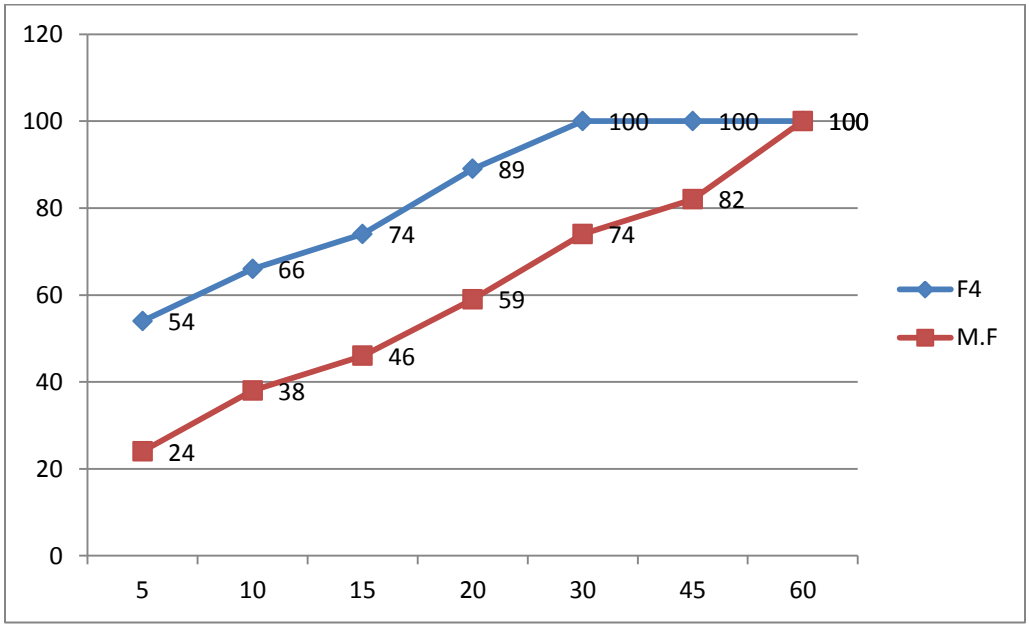

Fig No: 2 Comparison Of Dissolution Studies Of Optimized Formulation (F4) And Marketed Formulation.

DISCUSSION

The release profile of formulations F_1, F_2, F_3, F_4 F_5, F_6, F_7, F_8 and F_9 comprising various polymers like crospovidone, croscarmellose and sodium starch glycolate with different concentrations exhibits different release rates at various time intervals as shown in the table. Among all of these 9 formulations **F_4** which contains **sodium starch glycolate** shows maximum drug release at the end of 30 mins where as marketed formulation shows maximum drug release at 60 mins. Hence it was optimized and decided to develop further formulations.

STABILITY DATA OF OPTIMIZED FORMULATION

Stability studies were carried out according to ICH guidelines by exposing the formulations CSF4 in their final packing mode to the temperature 40±2°C and relative humidity 75±5 % in programmable environmental test chamber (CHM-10S, Remi Instruments Ltd., Mumbai, India). Aliquot were withdrawn at 30 and 60 days and analyzed for change in drug content and in-vitro dissolution profile.

Following conditions were used for Stability Testing

1. 21˚C/45% RH analyzed every month for period of three months.
2. 25˚C/60% RH analyzed every month for period of three months.
3. 30˚C/70% RH analyzed every month for period of three months.

1ST MONTH

	INITIAL	LONG TERM	INTERMEDIATE	ACCELERATED
Wt variation	0.5	0.5	0.5	0.49
Hardness	5.6	5.7	5.8	5.8
Friability	0.66	0.7	0.8	0.8
Thickness	2.75	2.75	2.75	2.75
Content uniformity	99.8	99.0	99.8	99.0

2ND MONTH

	INITIAL	LONG TERM	INTERMEDIATE	ACCELERATED
Wt variation	0.5	0.5	0.5	0.5
Hardness	5.75	5.82	5.84	5.84
Friability	0.66	0.7	0.8	0.8
Thickness	2.75	2.75	2.75	2.75
Content uniformity	99.4	99.8	99.0	99.2

3RD MONTH

	INITIAL	LONG TERM	INTERMEDIATE	ACCELERATED
Wt variation	0.5	0.5	0.5	0.5
Hardness	5.77	5.84	5.86	5.86

Friability	0.66	0.7	0.8	0.8
Thickness	2.75	2.75	2.75	2.75
Content uniformity	99.6	99.8	99.4	99.0

STABILITY STUDIES FOR DISSOLUTION

1ST MONTH

DISSOLUTION TIME (Mins)	INITIAL	LONG TERM	INTER MEDIATE	ACCELERATED
15	71	70.6	69.8	68.6
30	98	97.8	96.9	96.5
60	100	99.6	99.5	99.1

2ND MONTH

DISSOLUTION TIME (Mins)	INITIAL	LONG TERM	INTER MEDIATE	ACCELERATED
15	68.9	70.6	69.6	67.9
30	96.9	97.6	96.8	96.3
60	98.9	97.6	95.1	92.4

3RD MONTH

DISSOLUTION TIME (Mins)	INITIAL	LONG TERM	INTER MEDIATE	ACCELERATED
15	64.8	61.6	61.6	61.9
30	92.9	90.5	94.7	96.3
60	96.8	99.6	98.0	99.1

CONCLUSION

For preparation of Fast Dissolving Tablets of Lovastatin, dissolution studies were carried out by different Solid Dispersion techniques (Kneading Method, Solvent Evaporation Method, Co – Precipitation Method) using different carriers (α – cyclodextrin, Chitosan, Eudragit RS100) in different ratios (1:1, 1:2, 1:3). Formulation SDE 6 (Solvent Evaporation using Eudragit RS100) in 1:3 ratio released 100% drug in 30 mins whereas pure drug released 50.18% in 30 mins. Therefore tablets were prepared using Eudragit RS100 as carrier.

Formulation (F4) using Eudragit RS 100 as carrier in solid dispersion technique (solvent evaporation - 1:3) and Sodium Starch Glycolate as superdisintegrant was optimised. Results of pre compression and post compression were within acceptable limits. Of all formulations, F4 was found to be better for stability and dissolution studies when compared to marketed formulation.

Therefore solid dispersion was found to be better for drug release of poor aqueous soluble drugs belonging to class - II.

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