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FORMULATION AND EVALUATION OF LOVASTATIN SOLID DISPERSIONS WITH PREGELATINISED STARCH AS NEWER SUPERDISINTEGRANT

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ABSTRACT
Solid dispersions of lovastatin were formulated using pregelatinised starch (PGS) as super disintegrant and were further compressed into tablets by using various diluents such as lactose, dicalcium phosphate (DCP) and microcrystalline cellulose (MCC) to enhance the bioavailability. The solid dispersions were prepared by physical mixing, solvent evaporation and kneading methods. The solid dispersions were found to release the drug faster than the pure drug in dissolution media. The rapid release of poorly soluble lovastatin from solid dispersions was influenced by the proportion of polymer and the method employed for its preparation. Among the three methods employed solvent evaporation and kneading methods were found to be suitable for improving the dissolution rate of lovastatin. The release data was fitted to various kinetic models. The release was found to follow first order kinetics. Some of the dispersions prepared by the solvent evaporation method and kneading method were formulated into tablets with various diluents. The tablet preparations containing different diluents were found to release the drug in the order of DCP>MCC>Lactose. The dissolution rate of tablet formulations prepared with lovastatin solid dispersions (FK1, FS4) were found to release the drug at a faster rate than that of tablets prepared with plain drug.

Keywords: *Lovastatin; Pregelatinised starch; Solid dispersions.*

INTRODUCTION

Oral drug delivery is the simplest and easiest way of administering drugs [1,2]. Because of the greater stability, smaller bulk, accurate dosage and easy production solid oral dosage forms have many advantages over other types of dosage forms. Therefore, most of the new chemical entities (NCE) under development these days are intended to be used as a solid dosage form that produces an effective and reproducible *in vivo* plasma concentration after oral administration [3]. In fact, most NCEs are poorly water soluble drugs, not well-absorbed after oral administration [4], which can detract from the drugs inherent efficacy [5-7]. Moreover, most promising NCEs, despite their high permeability, are generally only absorbed in the upper small intestine, absorption being reduced significantly after the ileum, showing that there is a small absorption window [8, 9]. Consequently, if these drugs are not completely released in the gastro intestinal area, they may have a low bioavailability. Therefore, one of the major current challenges in the pharmaceutical industry is related to strategies that improve the water solubility of drugs [10, 11]. Drug release is a crucial and limiting step for oral drug bioavailability, particularly for drugs with low gastrointestinal solubility and high permeability. By improving the release profile of these drugs, it is possible to enhance the bioavailability of such poorly soluble drugs. [12-14]

Solid dispersions are one of the most successful strategies to improve the drug release of poorly soluble drugs. In solid dispersions the particle size of the drug is reduced at molecular level which leads to increased surface area and hence the increased solubility of the drug. When a mixture consisting of a slightly soluble drug and an inert, highly water soluble carrier is dissolved in an aqueous medium, the carrier will dissolve rapidly, releasing very fine crystals of the drug. The large surface area of the resulting suspension should result in an enhanced dissolution rate and thereby improved bioavailability. The advantage of solid dispersions over other approaches is that many of the carriers that can be applied are already extensively used in the pharmaceutical industry as excipients, so additional toxicity studies above and beyond what is required for the drug itself should not be required. The possibility of combining several carriers to produce an optimized product further extends the range of possibilities for formulation. Lovastatin is an anti-hyperlipidemic drug mainly used in treatment of lowering the lipid profiles particularly in the diseased conditions such as congenital heart disease, lipoidal

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oedema, diabetes etc. Lovastatin is rapidly absorbed by the liver after oral administration. It undergoes extensive first pass metabolism in the liver. It is practically insoluble in water and other aqueous media. The very poor aqueous solubility and wettability of lovastatin give rise to difficulty in the design of pharmaceutical formulations and lead to variable oral bioavailability. A few reports are available on the enhancement of solubility, dissolution rate of lovastatin [15]. Rate of absorption and/or extent of bioavailability for such insoluble drug are controlled by rate of dissolution in gastrointestinal fluid. The peak plasma concentration (C_{max}) and the (t_{max}) depend upon extent and rate of dissolution of drug respectively. Hence the present investigation was aimed to increase the rate of dissolution of lovastatin.

MATERIALS AND METHODS

Materials

Lovastatin was a gift sample from Matrix Pharma Ltd., Hyderabad, pregelatinized starch, microcrystalline cellulose, dicalcium phosphate, lactose were gift samples obtained from Pellets Pharma Ltd., Hyderabad. Methanol, sodium hydroxide, hydrochloric acid, potassium hydrogen phosphate was procured from S.D.Fine chemicals, Mumbai. All other materials used were of analytical grade and procured commercially.

Saturated solubility studies

100mg of lovastatin was weighed and transferred in conical flasks containing 100ml of different dissolution media. These flasks were hermatically sealed and incubated at 37°C in a incubator shaker operated at 50rpm for 24hrs. Then the samples were filtered and subsequently diluted with same media. The corresponding absorbance values were measured at 238nm. The solubility of lovastatin in various mediums is shown in Table-1.

Table 1: *Solubility studies on lovastatin in different media*

S.No.	Media(100 ml)	O.D Values	Concentration (µg/ml)
1.	Distilled water	0.072	153.5
2.	7.2 P^H +Distilled water	0.145	309.5
3.	Methanol +water	0.326	495
4.	1.2 p^H +Distilled water	0.056	119.5
5.	6.4 p^H+ Distilled water	0.154	328.5
6.	Distilled water +0.5% SLS	0.220	469.5
7.	Distilled water +1% SLS	0.629	490
8.	Distilled water +1.5% SLS	0.698	390
9.	Distilled water +2% SLS	0.668	426
10.	6.4 p^H + 0.5%SLS	0.127	271
11.	6.4 p^H +1%SLS	0.211	450.4
12.	6.4 p^H +1.5%SLS	0.226	482
13.	7.2 p^H +0.5%SLS	0.219	467.5
14.	7.2 p^H +1%SLS	0.102	217.7
15.	7.2 p^H +1.5%SLS	0.419	595

Preparation of solid dispersions

Lovastatin solid dispersions with PGS were prepared by employing three methods such as:

1. Physical mixing
2. Solvent evaporation
3. Co-grinding (kneading method)

Physical mixing method

Known quantity of drug (20mg) lovastatin and pregelatinized starch were weighed separately and passed through sieve no. 80. The materials passed through sieve no. 80 were collected and transferred into a clean and dry glass mortar, and were triturated together for 5min. Then the blended mixture was passed through sieve no. 80 and it was collected and packed in wide mouthed amber colored glass containers and were hermetically sealed -[16].

Solvent evaporation method

Lovastatin was taken in a china dish and dissolved in few ml of methanol. To the methanolic solution, specified amount of pregelatinized starch was added and the mixture was heated to 50°C on a mantle with continuous stirring until the solvent was evaporated. Then the mixture was collected and packed in amber colored glass container, hermetically sealed. The mixture was stored at ambient conditions [17].

Kneading method

Lovastatin and pregelatinized starch were taken in a glass mortar and few ml of water was added and triturated vigorously until the damp granular mass was obtained. The mixture was then dried in a hot air oven to form dry powdered dispersion. Then the mixture was taken and passed through sieve no. 80 and the obtained powdered dispersion was collected and packed in wide mouthed amber colored glass container and hermetically sealed for storage[18]. The compositions of solid dispersions are shown in Table-2.

Table 2: *Composition of various solid dispersions of lovastatin*

S.No.	Composition	Ratio
	Physical mixtures	**Drug : Polymer**
1.	LOV+PGS(LVP-1)	1:0.5
2.	LOV+PGS(LVP-2)	1:1
3.	LOV+PGS(LVP-3)	1:1.5
4.	LOV+PGS(LVP-4)	1:2
	Solvent evaporation	
5.	LOV+PGS(LVS-1)	1:1
6.	LOV+PGS(LVS-2)	1:1.5
7.	LOV+PGS(LVS-3)	1:2
	Kneading method	
8.	LOV+PGS(LVK-1)	1:1
9.	LOV+PGS(LVK-2)	1:1.5
10.	LOV+PGS(LVK-3)	1:2

**One part is equal to 20mg*

Characterization and evaluation of solid dispersions

The solid dispersions prepared by various methods were characterized by particle size determination, and flow properties such as angle of repose and Carr's index [19]. Flow properties of solid dispersions were shown in Table-3.

Table 3: *Flow properties and drug content of lovastatin solid dispersions*

S. No.	Solid Dispersions	Angle of Repose(°)	Carr's Index (%)	Avg. Particle Size(μ)	Drug Content (%)
1.	LVP-1	25.5	20.2	179	99.3±0.5
2.	LVP-2	26.1	16.8	174	98.7±0.6
3.	LVP-3	25.5	17.2	172	99.6±0.5
4.	LVP-4	26.1	23.8	164	99.2±0.4
5.	LVK-1	34.3	18.7	172	99.3±0.5
6.	LVK-2	32.5	19.6	178	98.4±0.7
7.	LVK-3	31.3	22.5	171	99.2±0.5
8.	LVS-1	27.2	23.5	173	99.7±0.5
9.	LVS-2	28.4	24.6	179	99.4±0.5
10.	LVS-3	25.3	21.8	168	98.7±0.7

Estimation of lovastatin in solid dispersions

20mg of solid dispersion was dissolved in methanol by vigorous shaking in the solvent. The solutions were filtered and filtrate was diluted suitably with 6.4 pH phosphate buffer containing 0.5% sodium lauryl sulphate (SLS). Drug content of samples were determined by measuring absorbance at 238nm. Drug content of solid dispersions was shown in Table-3.

Dissolution rate studies

Dissolution rate studies of pure lovastatin and solid dispersions were performed in 8 stage Toshiba dissolution test apparatus with rotating paddle method at 50rpm using 900ml of 6.4pH buffer containing 0.5% SLS. The temperature of the bath was maintained at 37±0.5°C throughout the experiment. 5ml of samples were withdrawn at various time intervals and were further diluted with 6.4pH buffer containing 0.5% SLS medium. The absorbance of the samples was measured at 238nm for determining the amount of drug released at various time intervals. Each time the same volume of buffer was added to the dissolution media for maintaining the sink conditions. The dissolution studies were carried out in triplicate. Based upon the data obtained from the dissolution studies various parameters such as T_{50}, T_{90}, DE_{30}%, zero order and first order release rate constants were estimated. The dissolution parameters such as T_{50} and T_{90} were measured directly from the dissolution profile curves and DE_{30}% was estimated by employing trapezoidal rule to the dissolution profiles. The zero order constant (K value) was obtained by calculating the slope value from the percentage drug released versus time profile curve. The first order constant was calculated by multiplying the slope value obtained from log percent drug un dissolved versus time plot with 2.303. The dissolution parameters of lovastatin solid dispersions is presented in Table 4 and dissolution profiles are presented in Fig 1-3.

Table 4: *Dissolution parameters of lovastatin solid dispersions*

S.No.	Solid Dispersion	% drug released at 90 mins	T_{50} (mins)	T_{90} (mins)	DE_{30} %	Zero order Constant K	R^2	First order Constant K (min^{-1})	R^2
1.	LOV PURE DRUG	59.0	51	>90	23.3	0.8017	0.5135	0.0115	0.946
2.	LVP1	77.43	14	>90	28.6	0.4761	0.6517	0.0133	0.980
3.	LVP2	81.85	13	>90	29.6	0.4685	0.6536	0.0216	0.989
4.	LVP3	88.54	12	>90	32.5	0.5328	0.6579	0.0147	0.981
5.	LVP4	88.94	10	>90	32.6	0.5166	0.6344	0.0149	0.858
6.	LVK1	89.60	13	>90	32.5	0.5756	0.7084	0.0212	0.888
7.	LVK2	94.46	10	74.86	36.7	0.6231	0.7333	0.0268	0.918
8.	LVK3	99.82	9	58.96	42.5	0.6346	0.7200	0.0326	0.992
9.	LVS1	97.76	13	>90	32.6	0.5733	0.7028	0.0202	0.982
10.	LVS2	99.49	11	79.65	39.4	0.6134	0.7314	0.0293	0.989
11.	LVS3	99.89	9	60.93	42.8	0.6884	0.7036	0.0327	0.983

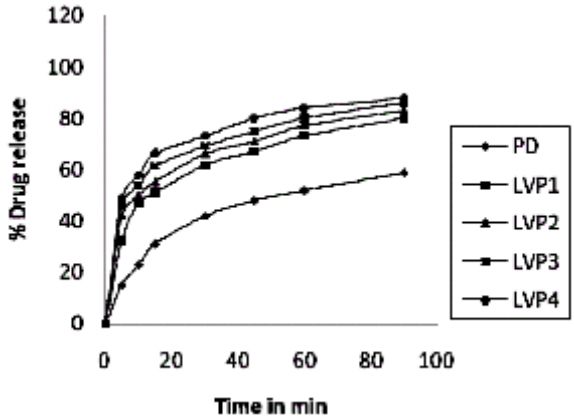

Fig. 1: *Dissolution profiles of lovastatin solid dispersions by physical mixing method.*

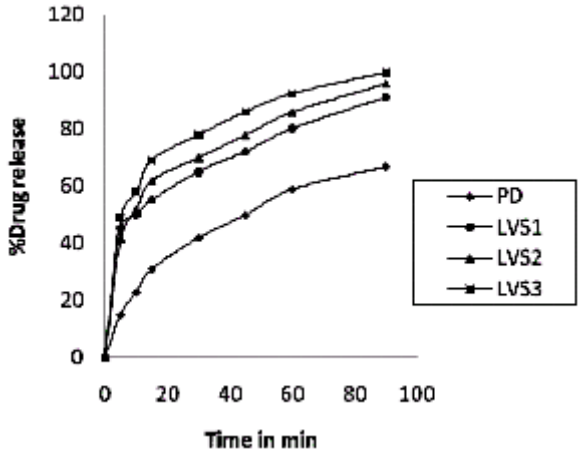

Fig. 2: *Dissolution profiles of lovastatin solid dispersions by solvent evaporation method.*

Preparation of lovastatin tablets with solid dispersions

Among the solid dispersions prepared and based upon the dissolution studies performed, two optimized dispersions were selected for preparation of tablets. The selected solid dispersions were blended with

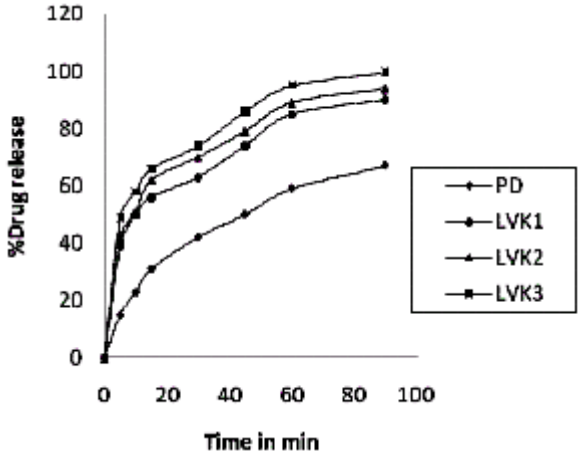

Fig. 3: Dissolution profiles of lovastatin solid dispersions by kneading method.

diluents like lactose, DCP, MCC and 0.5% of lubricant and then directly compressed by using 16 station rotary punching machine with 6mm flat surface punches with a compression force of 3-5kg/cm^2. The compositions of various tablet formulations were given in Table-5.

Table 5: Composition of lovastatin solid dispersions containing tablets

S.No	Ingradients (mg/tablet)	Formulations with LVK 3			Formulations with LVS 3		
		FK_1	FK_2	FK_3	FS_4	FS_5	FS_6
1.	Solid dispersion mixture	20	20	20	30	30	30
2.	DCP	179.5	-	-	169.5	-	-
3.	MCC	-	179.5	-	-	169.5	-
4.	Lactose	-	-	179.5	-	-	169.5
5.	Magnesium stearate	0.5	0.5	0.5	0.5	0.5	0.5
6.	TOTAL	200	200	200	200	200	200

Evaluation of physical parameters for lovastatin tablets

The physical parameters such as weight uniformity, hardness, friability, and drug content and disintegration time were evaluated for the prepared tablets as per I.P standards [21]. The physical parameters of various tablet formulations were given in Table-6.

Table 6: Physical parameters of lovastatin tablet formulations

S.NO	Solid dispersion tablet	Weight Uniformity (mg)	Friability (%loss)	Hardness (kg/cm^2)	Disintegration time (Min)	Drug content (%)
1.	MF	198±4	0.45	3.5	14.6	99.5±4
2.	FK_1	197±4	0.23	3.5	4.4	99.5±4
3.	FK_2	198±4	0.25	3.3	6.6	99.4±7
4.	FK_3	200±2	0.24	3	6.9	99.2±2
5.	FS_4	198±4	0.24	3	4.6	99.2±2
6.	FS_5	197±5	0.28	4	6.8	97.8±4
7.	FS_6	198±4	0.23	3.5	7.1	98.05±7

Dissolution rate studies of lovastatin tablet

Dissolution rate studies of lovastatin tablets were performed in 8 stage Toshiba dissolution test apparatus as per the procedure described earlier. The dissolution parameters of tablet formulations prepared with lovastatin solid dispersions is presented in Table-7 and dissolution profiles in Fig 4& 5.

Table 7: Dissolution parameters of lovastatin tablet formulations

S.No	Solid Dispersion	% drug released at 90mins	T_{50} (mins)	T_{90} (mins)	DE_{30} %	Zero order Constant K	R^2	First order Constant K (min^{-1})	R^2
1.	FK_1	99.94	1.3	58.78	38.17	0.7125	0.7977	0.0289	0.973
2.	FK_2	98.29	1.4	60.10	35.97	0.7055	0.7016	0.0271	0.962
3.	FK_3	97.79	1.4	65.32	33.34	0.7129	0.7696	0.0272	0.968
4.	FS_4	99.12	1.3	58.78	38.16	0.7351	0.8014	0.0293	0.986
5.	FS_5	98.94	1.3	60.10	35.91	0.7500	0.8019	0.0305	0.973
6.	FS_6	97.69	1.5	70.24	33.36	0.7577	0.8082	0.0253	0.962
7.	Marketed tablet	80.26	1.9	>9.0	28.00	0.6056	0.7468	0.0128	0.979

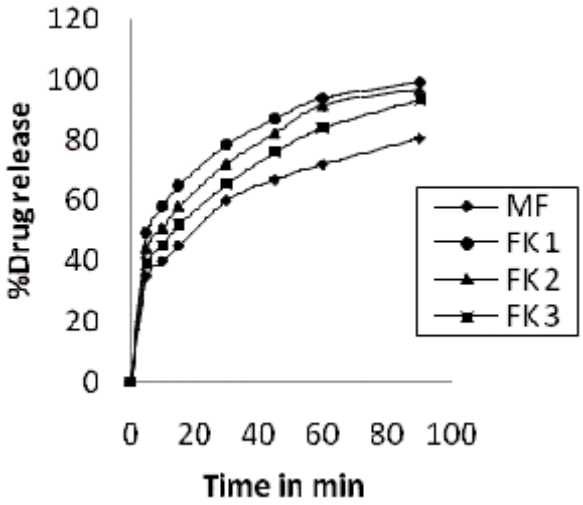

Fig. 4: Dissolution profiles of lovastatin marketed formulation and tablet formulations prepared by kneading method.

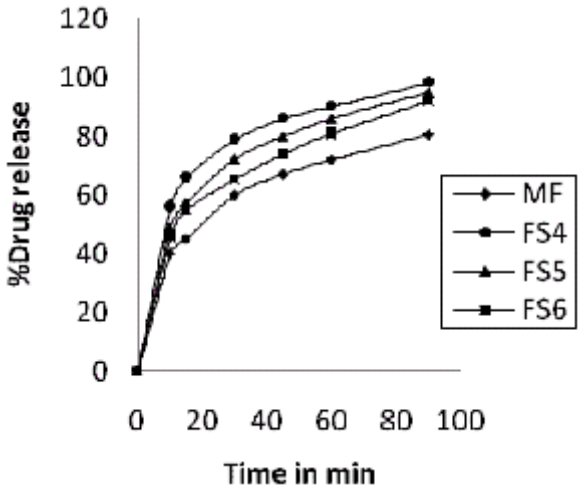

Fig. 5: Dissolution profiles of lovastatin marketed formulation and tablet formulations prepared by solvent evaporation method.

RESULTS AND DISCUSSION

Solubility studies revealed that lovastatin exhibit maximum solubility in pH 6.4 phosphate buffer containing 0.5% SLS as medium among the different media used. Hence pH6.4 phosphate buffer containing 0.5% SLS was used as dissolution medium for further studies. The solubility of lovastatin in various mediums was shown in Table-1. The drug concentration was measured at an absorption maximum of 238nm using UV spectrophotometer for all the dissolution media. The solid dispersions were prepared with a novel super disintegrant such as pregelatinized starch by physical mixing, solvent evaporation and kneading methods. The compositions of solid dispersions are shown in Table-2.

All the dispersions were prepared under similar conditions to avoid batch to batch variations. The dispersions were found to be uniform in their characteristics. All the solid dispersions were in the size range of 178±10µm. The angle of repose and Carr's index values of all the dispersions prepared indicated the good and free flowing characteristics Flow properties of solid dispersions were shown in Table-3. The drug content estimated in all the solid dispersions were highly uniform and in the size range of 98±2%, indicated the uniformity. Drug content of solid dispersions was shown in Table-3. The dissolution studies of lovastatin as pure drug and its solid dispersions prepared was performed in 6.4pH phosphate buffer containing 0.5% SLS as medium by using paddle method. The dissolution rate of all the solid dispersions were found to be rapid than compared to its pure drug lovastatin. The T_{50}, T_{90} and DE_{30}% values of the dispersions indicated their rapid drug dissolution than their respective counterpart lovastatin pure drug. The kinetics of drug release from all the dispersions followed first order. The R^2 values obtained for all the dispersions were linear for the first order plots. The dissolution parameters of lovastatin solid dispersions were shown in Table-4 and dissolution profiles are shown in Fig 1-3. Among the solid dispersions prepared, solvent evaporation and kneading methods were found to be suitable in increasing the dissolution rates of poorly soluble lovastatin. It was observed that as the concentration of pregelatinized starch increases the rate of dissolution of the drug was also increased. Solid dispersions prepared by solvent evaporation and kneading methods at a drug to super disintegrant ratio of 1:2 were found to undergo rapid dissolution. Hence solid dispersion, LVS3 AND LVK3 was further directly compressed as tablets by using lactose, MCC and DCP as diluents. The compositions of various tablet formulations were given in Table-5.

All the tablets were compressed under identical conditions to avoid processing variables. The physical parameters such as weight uniformity, hardness, friability, drug content and disintegration time were evaluated for the prepared tablets. The physical parameters evaluated were highly uniform and all the tablets were found to be within the I.P limits. The physical parameters of various tablet formulations were given in Table-6. The dissolution studies on the lovastatin marketed tablet and all the tablet formulations were performed in 6.4pH phosphate buffer containing 0.5% SLS medium using paddle method. The rate of dissolution of tablet formulations was rapid when compared to the marketed tablet of lovastatin. The rate of drug release from all the tablets followed first order kinetics. The dissolution parameters of tablet formulations prepared with lovastatin solid dispersions is shown in Table-7 and dissolution profiles in Fig 4 & 5. Among the tablets prepared with the lactose, MCC and DCP as diluents, tablets with DCP tend to exhibit rapid dissolution. The rate of rapid release is in the order of DCP>MCC>lactose in the tablet formulations. The disintegration time for the DCP containing tablets were found to be much faster than its respective counter parts. The rapid disintegration may be due to increased uptake of water by both diluents and superdisintegrant which lead to faster dissolution of the tablets gave improved dissolution profiles of poorly soluble lovastatin.

CONCLUSION

The present study has shown that it is possible to increase the dissolution rate of poorly soluble drug lovastatin by preparing solid dispersions with superdisintegrant like pregelatinized starch. The solid dispersions exhibit faster dissolution characteristics as compared to plain drug. This was due to solubilising effect of carrier or crystallization of drug entrapped in molecular state by the carrier. A higher dissolution rate was obtained with solid dispersions prepared by solvent evaporation method and kneading method in the ratio of 1:2 for the drug and polymer. Based on the study it may be concluded that lovastatin tablets prepared by solid dispersions with DCP as a diluents was found to be rapid disintegration and for improving the dissolution rate and bioavailability.

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