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Evaluation of dissolution enhancement of lovaststin by solid dispersion technique

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Abstract

The areas of current interest which have a significant impact on clinical therapy are enhancement of dissolution rate and bioavailability of insoluble and poorly soluble drugs. Lovastatin is an antihyperlipidimic drug, which inhibits the production of cholesterol in liver is poorly water soluble drug. Due to poor solubility of drug, its bioavailability rate is limited by drug dissolution. In the present study, an attempt has been made to increase the solubility and dissolution of Lovaststin by solid dispersion technique using hot melt, solvent evaporation and kneading method with Poloxamer F-68. Effects of various parameters such as type of carrier system used, drug: carrier ratio were studied. The evaluation of solid dispersion was done by solubility and dissolution studies. Improvement in dissolution of drug was observed in all the solid dispersions as compared to pure drug. The dissolution rate of Lovaststin was directly proportional to increment in proportion of the carrier. Pure Lovaststin showed only 61% drug release in 1 hour where as the Solid dispersion prepared by solvent evaporation method using Poloxamer F-68 showed faster in vitro drug release incomparision to pure drug (plain tablet) and marketed formulation.

Key-Words: Lovastatin, Solid dispersion, Hot-melt, Solvent evaporation, Kneading, Poloxamer

Introduction

Poorly water soluble compounds have solubility and dissolution related bioavailability problems. The dissolution rate is directly proportional to solubility of drug. Drugs with low aqueous solubility have low dissolution rates and hence suffer from poor oral bioavailability. The solid dispersion approach has been widely used to improve the solubility, dissolution rate, and consequently the bioavailability of poorly water soluble drugs[1-3]. Solid dispersion is defined as dispersion of one or more active ingredients in an inert carrier or matrix at solid state prepared by melting, solvent, or melting solvent method. The release mechanism of drug from variety of solid dispersions depends upon the physical properties of carriers as well as drug substance and preparation method used

There are number of carriers used in the preparation of solid dispersion like acids, sugars, polymeric materials, surfactants[4].Lovastatin is an Antihyperlipidimic drug, which inhibits the production of cholesterol in liver.

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It is an inactive lactone, and hydrolyzed to the corresponding β-hydroxy acid form, which are a principal metabolite and an inhibitor of 3-hydroxy-3-methylglutaryl-Coenzyme A (HMG-CoA) reductase. Chemically identified as [1*S*-[1a(*R**), 3a, 7b; 8b(2*S**, 4S*), 8ab]] -1,2,3,7,8,8a- hexahydro-3, 7-dimethyl-8 -[2- (tetrahydro-4 -hydroxy-6-oxo-2*H*-pyran-2-yl ethyl]-1-naphthalenyl 2-methylbutanoate[6]. The present investigation was an attempt to improve the dissolution rate of Lovaststin by solid dispersion using PoloxamerF-68 as carriers. Solid dispersion of Lovaststin was prepared by solvent evaporation, and hot melt and kneading method using proportions of drug: carrier. All the solid dispersions and physical mixtures were characterized for solubility study and dissolution study.

Material and Methods

Experimental

Lovaststin was obtained as gift sample from M/S Biochem LTD, and Poloxamer F-68, Methanol, Ethanol, Acetone Qualigens Mumbai (India).

Preparation of solid dispersion[8]

In solvent evaporation method, Poloxamer F- 68 was dissolved completely in ethanol in different ratio in a beaker. Lovaststin was dispersed in the solution in

drug: polymer ratio of 1:1, 1:3, 1:5. The resulting solution was kept on the thermostatically controlled water bath (at 60 ± 0.5ºC) to remove the solvent from resulting mixture. The obtained mass was dried in the desiccator for 24hrs. The resultant mass was pulverized using a glass mortar and pestle. The pulverized mass was sifted through # 60, weighed and transferred to the glass vials.

In hot melt method, Poloxamer F- 68 was heated at a temperature of 55 ± 0.5ºC using a thermostatically controlled water bath. Lovaststin in a 1:1, 1:3 and 1:5 drug: carrier ratio was dispersed in the melted polymer. The resultant mixture was immediately cooled using ice-water bath and was maintained for a specific period of 2 hrs. The solidified mass was then removed from the ice water bath and allowed attaining, the room temperature for 24 hrs and then pulverized using a glass mortar and pestle. The pulverized mass was sifted through # 60, weighed and transferred to the glass vials.

In kneading method, Poloxamer F- 68 was mixed thoroughly with Lovastatin in a 1:1, 1:3 and 1:5 drugs: carrier ratio in a glass mortar and pestle. The pulverized mass was sifted through # 60, weighed and transferred to the glass vials.

Formulation of tablets using polymer carrier

Each 300 mg Tablets containing 20 mg of Lovastatin were formulated employing solid dispersion mixture along with MCC ph 102, DCL 11, sodium starch glycolate and magnesium sterate. Drug Excipients like MCC, DCL 11 and SSG after passing through # 40;mixed thoroughly with Solid dispersion mixture in a Blender for 10 min. extra granular magnesium sterate was passed through mesh # 60 and mixed with blend in the blender for 5 min. Tablets were prepared by conventional direct compression method as per formula.

Formulation of plain tablets

In this Batch, the tablets were formulated without any polymer. Drug Excipients like MCC, DCL 11 and SSG after passing through # 40; mixed thoroughly with mixture in a blender for 10 min. extra granular Magnesium Sterate was passed through mesh # 60 and mixed with blend in the blender for 5 min. Tablets were prepared by conventional direct compression method as per formula.

Evaluation of tablets

The tablets prepared were evaluated for hardness, friability, and disintegration time and dissolution rate (Table 3) as per IP.

Drug content estimation

The percentage drug content in Solid dispersion was estimated by dissolving quantities of Solid dispersion equivalent to 50 mg. of Lovaststin was weighed accurately and dissolved in suitable quantity of ethanol. The solutions were filtered through nylon disc filter. The drug content was determined at 238 nm using UV double beam spectrophotometer (Shimadzu Japan) after suitable dilution. The percentage yields were also calculated for each formulation.

Solubility studies[9]

Solubility studies were performed according to method reported by Higuchi and Koners. Excess of solid dispersion were added to 25 ml of distilled water taken in a stoppered conical flask and mixture were shaken for 24 hrs in rotatory shaker. After shaking to achieve equilibrium, 2 ml aliquots were withdrawn at 1 hr interval and filtered through Whattman filter paper no. 41.The filtrate was analyzed spectrophotometrically (Shimadzu Japan) at 238 nm. Shaking was continued until three consecutive readings were same (Table 1).

***In Vitro* dissolution studies**[10]

In vitro dissolution studies of pure drug, solid dispersion were carried out for 120 minutes. Drug, solid Dispersion equivalent to 20mg of Lovastatin was used for the dissolution Studies. The study was performed using USP type II apparatus at 37±0.5ºC at 50 rpm, using Monobasic Sodium orthophosphate pH - 7 using 1% SLS. A 10-ml amount of aliquot was withdrawn at an interval of 10, 20, 30, 45 and 60 min. An equal amount of the fresh dissolution medium was replaced immediately after withdrawal of test sample. Test samples were filtered through a 0.45µm nylon filter and suitably diluted. The absorbance of each diluted sample was measured at 238 nm using UV-Visible spectrophotometer (Shimadzu Japan) (Fig. 2, 3 and 4).

Results and Conclusion

Solubility of Lovaststin was found to be 0.00004gm/100 ml, while improvement in solubility was observed in all physical mixture and solid dispersions. Maximum solubility enhancement was found in 1:5 ratio of drug: Poloxamer. Solid dispersion prepared by solvent evaporation method. (Table 1) enhancement in saturation solubility was found to be in order Poloxamer 1:1 > Poloxamer 1:3 > Poloxamer 1; 5. All the solid dispersion system prepared were fine, free flowing and white in color. The low standard deviation values in case of % drug content showed that the drug distribution was uniform in all the solid dispersions. (Table 1)

Time for 50% drug dissolution (T_{50}), Time for 70% drug dissolution (T_{70}) and Time for 90% drug dissolution (T_{90}) calculated from the percent cumulative release versus time plot. As the amount of carriers increased in the formulations, T_{50} (time for

50% dissolution of drug), T_{70} (time for 70% drug dissolution) and T_{90} (time for 90% drug dissolution) values decreased. T_{50} values, T_{70} values, T_{90} values indicated that there was enhancement in dissolution rate of Lovaststin (Table 1). The dissolution studies showed faster release of drug from solid dispersion. The dissolution rate was found to increase with increase in carrier proportions in case of Poloxamer F-68 Solid dispersion system. Among the polymer ratios the decreasing order of dissolution is given as 1:5 < 1:3 < 1:1. It has been found that among the three methods of solid dispersion preparation, solid dispersion prepared by solvent evaporation method had comparatively better in vitro drug release. The distribution of drug in this solid dispersion prepared by Solvent evaporation method is more uniform than the solid dispersion prepared by other method. The increased dissolution rate in the system was probably the result of increased wettability and dispensability of Lovaststin that may be due to surface lowering effect to medium resulting in wetting of hydrophobic. Thus it can be concluded from the present investigation that Poloxamer can be used as hydrophilic carriers to enhance the in vitro dissolution of Lovaststin.

Acknowledgement

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Table 1: Data obtained from evaluation of solid dispersion of lovaststin

System	% Drug Content*	Solubility gm/100ml	T_{50} (Min)	T_{70} (Min)	T_{90} (Min)
Pure Drug	99.24±0.24	0.00004	25	> 60	> 60
SD1 (1:1)	90.24±0.36	0.00224	17	27	47
SD2 (1:3)	93.72±0.42	0.00324	9.5	25	33
SD 3 (1:5)	96.60±0.28	0.00448	5.5	08	12
SD 4 (1:1)	92.87±1.00	0.00442	18	32	46
SD 5 (1:3)	94.41±1.00	0.00518	07	09	42
SD 6 (1:5)	95.12±1.84	0.00553	07	10	33
SD 7 (1:1)	85.24±0.04	0.00172	26	36	> 60
SD 8 (1:3)	88.24±0.36	0.00196	11	19	59
SD 9 (1:5)	90.24±0.44	0.00242	09	17	42

*** indicates mean of three readings, SD – Solid dispersion, SD 1 to SD 3 corresponds Solid dispersion prepared by Hot melt method, Solid dispersion, SD 4 to SD 5 corresponds Solid dispersion prepared by Solvent evaporation method, Solid dispersion, SD 7 to SD 9 corresponds Solid dispersion prepared by Kneading method**

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Table: 2 Formulation of solid dispersion in tablet dosage form

Batch No	Drug + Excipients (mg.)					
→	Lovastatin	Poloxamer	MCC ph102	DCL 11	SSG	Mg. Sterate
Pure Drug	20	-	202	60	9	9
SD1 (1:1)	20	20	182	60	9	9
SD2 (1:3)	20	60	142	60	9	9
SD 3 (1:5)	20	100	102	60	9	9
SD 4 (1:1)	20	20	182	60	9	9
SD 5 (1:3)	20	60	142	60	9	9
SD 6 (1:5)	20	100	102	60	9	9
SD 7 (1:1)	20	20	182	60	9	9
SD 8 (1:3)	20	60	142	60	9	9
SD 9 (1:5)	20	100	102	60	9	9

Table: 3 Compression parameter of different lovastatin batches

Batch	Weight	Thickness	Hardness	Friability	DT	Drug: Polymer
SD1 (1:1)	300mg	3.41mm	4-5 kg/cm^2	0.07 %	15sec	1 : 1
SD2 (1:3)	300mg	3.36mm	4-5 kg/cm^2	0.06%	45sec	1 : 3
SD 3 (1:5)	300mg	3.21mm	4-5 kg/cm^2	0.11%	2-3min	1 : 5
SD 4 (1:1)	300mg	3.41mm	4-5 kg/cm^2	0.09%	20-25sec	1 : 1
SD 5 (1:3)	300mg	3.25mm	4-5 kg/cm^2	0.08%	1-2 min	1 : 3
SD 6 (1:5)	300mg	3.20mm	4-5 kg/cm^2	0.11%	3-4min	1 : 5
SD 7 (1:1)	300mg	3.40mm	4-5 kg/cm^2	0.06%	20-25sec	1 : 1
SD 8 (1:3)	300mg	3.25mm	4-5 kg/cm^2	0.08%	2 – 3 min	1 : 3
SD 9 (1:5)	300mg.	3.41 mm	4-5 kg/cm^2	0.06%	2 – 3 min	1: 5

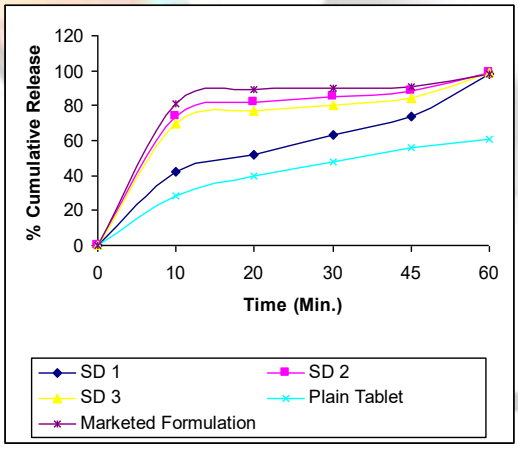

Fig. 1

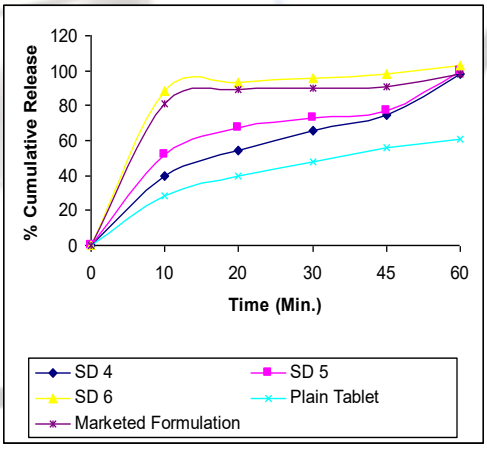

Fig. 2

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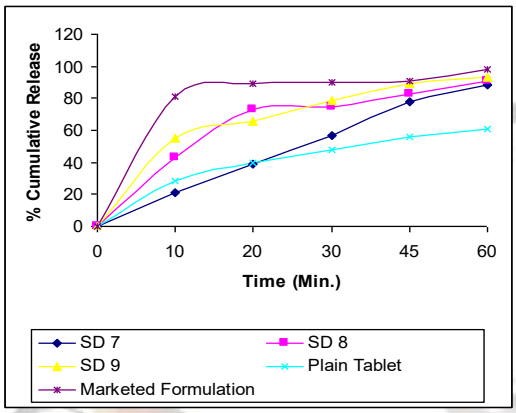

Fig. 3

Fig.1:Comparative Dissolution profile of Lovaststin from Solid dispersions prepared by Hot Melt method using Poloxamer F-68 using USP type II apparatus (Veego, Mumbai) at 37 ± 0.5ºC at 100 rpm, using Monobasic Sodium orthophosphate pH -7

Fig.2:Comparative Dissolution profile of Lovaststin from Solid dispersions prepared by Solvent evaporation method using PoloxamerF-68using USP type II apparatus (Veego, Mumbai) at 37 ± 0.5ºC at 100 rpm, using Monobasic Sodium orthophosphate pH -7

Fig.3:Comparative Dissolution profile of Lovaststin from Solid dispersions prepared by Kneading method using Poloxamer F-68 using USP type II apparatus (Veego, Mumbai) at 37 ± 0.5ºC at 100 rpm, using Monobasic Sodium orthophosphate pH -7