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FORMULATION, DESIGN AND EVALUATION OF ORALLY DISINTEGRATING TABLETS OF LOVASTATIN

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ABSTRACT

Lovastatin, is a potent competitive inhibitor of 3-hydroxy-3-methyl glutaryl coenzyme A. It is a powerful serum cholesterol-lowering drug in humans and other species. The major problem with this drug is its very low solubility in biological fluids which results in poor solubility after oral administration. Therefore Lovastatin with Poly ethylene glycol-6000 and PVP K30 in different weight ratios (1:1, 1:2, 1:3) were prepared to increase its water solubility. The solid dispersions were evaluated by solubility study, drug content, in-vitro drug release study, dissolution efficiency and characterized by FT-IR, Differential scanning calorimeter, X-ray diffraction and surface morphology by Scanning electron microscopy. It was prepared by Solvent evaparation methods by addition of superdisintigrant like Sodium starch glycolate, Crosscarmalose sodium, and Crospovidone in different concentration (1-5% w/w) and by effervescence technology by using combination of (2:3 ratio) Citric acid and sodium bicarbonate in different concentration (1-5% w/w) to enhance the patient compliance.

KEYWORDS

Lovastatin, Direct compression, Fast dissolving Tablets, Superdisintigrants, Effervescent method and Stability Study.

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INTRODUCTION

Oral route has been considered as one of the most easiest routes of drug delivery due to its ease of administration, patient compliance, and flexible design of dosage forms. To release the active principle immediately after oral administration to obtain rapid and complete systemic drug absorption Conventional oral drug products were formulated[1]. For drugs that have very poor aqueous solubility, the rate at which the drug dissolves (dissolution) is

often the slowest step and therefore exhibits a rate limiting effect on drug bioavailability[2]. The main possibilities for improving dissolution is to increase the surface area by decreasing the particle size of the solid compound and/or by optimizing the wetting characteristics of the compound to decrease the boundary layer thickness, to ensure sink conditions for dissolution and to improve the apparent solubility of the drug under physiologically relevant conditions. Food and Drug Administration defines "A solid dosage form containing medicinal substances or an active ingredient which disintegrates rapidly usually within a matter of seconds when placed upon tongue". The disintegration time for fast dissolving tablets generally ranges from several seconds to about a minute[3]. Challenges to develop fast dissolving tablet are Mechanical strength, disintegration time, Taste masking, Mouth feel, Sensitivity to environmental conditions, Amount of drug[4]. Polymers used are Polyethylene glycols, Polyvinyl pyrrolidone, Cyclodextrins, excipients used are Super disintegrants, Flavours, Sweeteners, Surface active agents such as Sodiumdoecylsulfate, sodiumlaurylsulfate, polyoxyethylenesorbitan fatty acid esters (Tweens), sorbitan fatty acid esters (Spans), polyoxyethylene stearates and Lubricants.

MATERIAL AND METHODS

Lovastatin is a gift sample from Concept Pharmaceuticals, Aurangabad, India. Polyvinylpyrollidone K-30, Ac-Di-Sol, Sodium Starch Glycolate, Crospovidone, Avicel PH 102 was supplied from M/s Healer's Lab. Pvt. Ltd. Baddi, India. Polyvinylglycol-6000, Acetone LR was procured from S.D. Fine Chem. Ltd, Mumbai, India. All other chemicals used were of analytical grade.

Preparation of orally disintegrating tablets[5]

Lovastatin solid dispersions were prepared by solvent evaporation method using carriers (i.e. PVP K-30, PEG-6000) in proportions, viz. 1:1, 1:2, 1:3 (Drug: Carrier). Methanol is selected as common solvent for solid dispersion. The respective amount of carrier was dissolved in methanol 20 ml and ketoprofen was added in parts with continuous stirring. The solvent was then removed by evaporation. The prepared solid dispersion were pulverized and shifted through sieve no. 100 and stored over a fused calcium chloride in a desiccator for further use.

Pre- compression parameters[6]

Before going to compression, the powder mixtures of different formulations were measured for bulk density, tapped density, Hausners ratio, Compressibility index, angle of repose. Angle of Repose was determined using funnel method and it was calculated using the following formula:

$\mathrm{Tan}\Theta = h/r$

In which, θ is angle of repose, h is height of cone, r is radius of cone. The compressibility index is a measure of the propensity of a powder to be compressed. It is determined from the bulk and tapped densities and it is calculated using the following formula:

$$I = \frac{\rho_t - \rho_b}{\rho_t} \times 100$$

In which, ρ_t is Tapped density and ρ_b is Bulk density

Post- compression parameters[7]

The prepared tablets were studied for Weight variation, Hardness, Friability, Disintegration Test, Wetting Time, *In-vitro* Dispersion Time, content uniformity, for estimating weight variation 20 tablets of each formulation were weighed using an Electronic weighing balance. The strength of tablet is expressed by measuring hardness (kg/cm^2) and friability. Tablet hardness of each formulation was done by using Pfizer hardness tester. Friability of the tablets was determined using Roche friabilator for 4 min at 25rpm. The thickness of the tablets was determined using screw gauge. Five tablets from each batch were used.

Determination of Drug Content[8]

Drug content was calculated by dissolving solid dispersions equivalent to 100mg Lovastatin in 10 ml of methanol, filtered using 0.45µm Whatman filter paper, suitably diluted with Sorenson's buffer (pH 6.8) and analyzed by using UV

spectrophotometer against Sorenson's buffer as blank.

Wetting Time

A piece of tissue paper (12 cm X 10.75 cm) folded twice was placed in a small Petri dish (ID = 65 cm) containing 6 ml of Sorenson's buffer having [pH 6.8]. A tablet was kept on the paper, and the wetting period was measured. Three trials were performed from each batch and the standard deviation was also estimated.

***In-vitro* Dispersion Time**

The tablet is placed in a glass cylinder where it contains 6 ml of Sorenson's buffer (pH 6.8). Whereas randomly from each formulation three tablets were selected and period was performed.

***In-vitro* dissolution studies**

In-vitro dissolution studies of formulation were carried out using USP paddle method at 50 rpm in 900 ml of Sorenson's buffer (pH 6.8) as dissolution media, maintained at 37±0.5ºC. 5ml of aliquot was withdrawn at the specified time intervals, filtered through whatmann filter paper and analysed spectorphotometrically at 260nm. An equal volume of fresh medium, which was prewar med at same condition was replaced into the dissolution media after each sampling to maintain the constant volume throughout the test.

Drug Polymer Interaction Studies[9]

The infrared absorption spectra of pure polymer and physical mixture of polymer and drug were performed for polymer drug interaction studies. DSC analysis was performed on 5mg samples. Samples were heated in an open aluminum pans at a rate of 10^0 per min^{-1} in a 30 to 300°C temperature range under a nitrogen flow of 40mL/min. The samples were recorded by using FTIR spectra. Samples were prepared in potassium bromide disks by means of a hydrostatic press. 400 to 4000 $cm^{-1}$was the scanning range and the resolution range was 4 cm^{-1}.

Stability studies[10,11]

The stability studies were done according to ICH guidelines. The procedure was divided into two parts, the sealed formulations are placed in amber colored bottles, tightly plugged with cotton and capped, stored at 25ºC /60% RH and 40ºC / 75% RH for two months and evaluated for their physical appearance and drug content.

RESULTS AND DISSCUSSION

Lovastatin prepared by solvent evaporation technique were found to be discrete and through SEM analysis. The drug entrapment efficiency of lovastatin containing drug: polymer in various ratio 1:1, 1:2, 1:3 were found to be 97.94 to 99.37. Thus there was a steady increase in the entrapment efficiency on increasing the polymer concentration in the formulation. The results of bulk density (0.553 to 0.681gm/cm^3), tapped density (0.630 to 0.783gm/cm^3), % compressibility (10.782 to 14.542) and the results of angle of repose, hausner's ratio were also found within the limits. All the developed formulations were evaluated for friability, hardness, disintegration time, wetting time, weight variation, drug content and *in vitro* drug release study. The average hardness of tablet was varied from (2.5-3.6 kg/cm^2), friability (less than 1.0%), wetting time (27.45±1.40 to 125.66±5.76), drug content of variation was found to be less than 0.5, the results were shown in Table No.1 and No.2. *In-vitro* drug release experiments were performed at 37±1ºC in eight basket dissolution apparatus. The results of dissolution profile are shown in the Figure No.3. The maximum drug release was found in formulation F15 (99.56%).

For the *In-vitro* drug release profile the kinetics of drug release is first order for all the prepared fast dissolving tablets as the plot between Log cumulative percent drug retained versus Time showed the good linearity of 'R^2' obtained was near to one. The prepared final preparation gives better in terms of release profile Figure No.1. Stability studies of the prepared fast dissolving tablets were performed at temperatures (40^0C/75RH) Figure No.2. The tablets were analyzed for weight, hardness, friability, disintegration time, and for drug content in each formulation at a time interval of one month for the period of three months.

Drug-polymer interaction study was carried out and evaluated for physical changes, change in absorption maxima and by FT-IR studies. Results were shown in Figure No.4. The FT-IR spectra of the various physical mixtures retain all the peaks of the pure drug. So there was no significant shift in the peaks corresponding to the drug were observed on storage. Both the drug and polymers were compatible with each other. The DSC curve for Lovastatin showed a sharp melting endotherm at 94.54^{o}C.

Table No.1: Physical properties of lovastatin orally disintegrating Tablets

Formulation	Thickness (mm)	Weight (mg)	Friability (%)	Hardness (Kg/cm^2)
F1	6.325±0.014	500.6667±1.527525	0.478151±0.000291	3.166667±0.057735
F2	6.342±0.026	496.6667±3.785939	0.440411±0.000269	3.133333±0.057735
F3	6.343±0.034	497.3333±0.57735	0.639744±0.000256	2.8±0.1
F4	6.325±0.004	501.3333±2.081666	0.781955±0.045364	2.8±0.1
F5	6.349±0.037	496.6667±1.527525	0.876262±0.000533	2.733333±0.152753
F6	6.342±0.029	502.6667±1.527525	0.719904±0.0006	3±0.173205
F7	6.348±0.043	500.3333±1.527525	0.519308±0.000432	3.6±0.1
F8	6.349±0.021	500.3333±2.309401	0.800108±0.00103	3±0.173205
F9	6.334±0.034	499.3333±1.527525	0.638808±0.00039	3.266667±0.057735
F10	6.325±0.008	498.6667±2.081666	0.519654±0.000523	3.533333±0.11547
F11	6.345±0.016	499.3333±3.21455	0.519792±0.000208	3.433333±0.11547
F12	6.372±0.031	498.6667±0.57735	0.719138±0.000994	3.133333±0.152753
F13	6.346±0.034	501.6667±2.081666	0.76132±0.000466	3.166667±0.152753
F14	6.335±0.031	499.3333±1.527525	0.519662±0.002573	3.066667±0.208167
F15	6.348±0.031	501.3333±1.527525	0.478151±0.000396	3.3±0.2
F16	6.344±0.034	498.6667±0.57735	0.760102±0.000978	2.666667±0.152753
F17	6.363±0.035	498.6667±1.527525	0.67991±0.000415	2.8±0.173205
F18	6.343±0.016	499.3333±2.081666	0.840785±0.000514	2.566667±0.208167
F19	6.366±0.041	498.6667±3.05505	0.919755±0.000212	2.5±0.173205
F20	6.321±0.339	500.6667±1.527525	0.958467±0.000383	2.7s±0.264575

Table No.2: Physical properties of lovastatin orally disintegrating Tablets

Formulation	Disintegration time (Sec)	Wetting time (Sec)	Dispersion time (Sec)
F1	95.53333±1.507459	87.37±1.770339	114.3467±3.381262
F2	86.50333±2.360452	80.13667±3.928897	101.4433±2.408513
F3	70.25667±3.769726	65.34333±3.674647	84.76±4.26522
F4	60.65±1.85696	55.04±3.125972	71.81±3.404453
F5	51.94667±3.34403	49.22333±3.511885	64.70667±4.265024
F6	134.2233±5.162183	125.6633±5.760046	142.7133±4.83864
F7	119.93±4.994207	110.2733±3.544014	124.9033±4.639874
F8	59.48±1.509073	80.09333±4.400231	86.23333±2.717174
F9	45.11333±2.155327	62.69±2.507349	69.72333±1.804476
F10	35.60667±1.471915	48.98333±3.493799	55.07333±3.127944
F11	47.48333±1.878546	60.04333±3.823354	67.46667±2.541679
F12	36.01333±1.651676	42.94±3.040049	54.35±2.626385
F13	29.02333±1.708489	31.83667±2.848233	42.83667±1.180777
F14	27.71±1.141753	29.67±1.477329	33.69667±2.080993
F15	25.68±1.411063	27.44667±1.404754	30.91±1.681547
F16	68.31333±2.26809	59.38333±1.8037	69.56±1.915385
F17	51.65667±2.110126	49.47333±2.941451	56.48±3.137276
F18	39.41±2.201704	43.66333±2.033749	49.44667±3.786322
F19	31.52667±3.023183	36.40667±1.420047	42.74333±2.555902
F20	29.16±1.746396	31.11667±2.146214	34.19±1.93

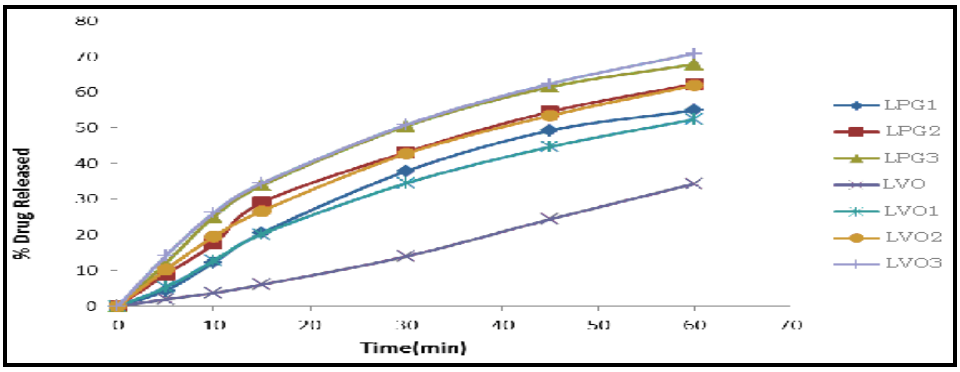

Figure No.1: %Cumulative drug Release of Lovastatin tablets

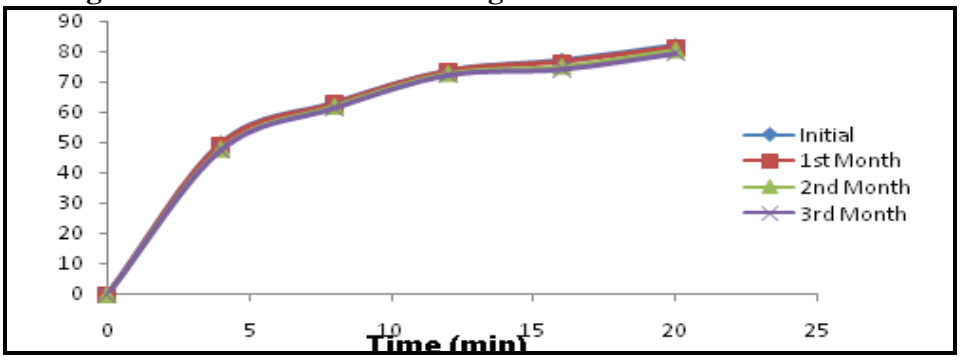

Figure No.2: *In-vitro* release profile of F18 during Stability studies at (40°C/75% RH)

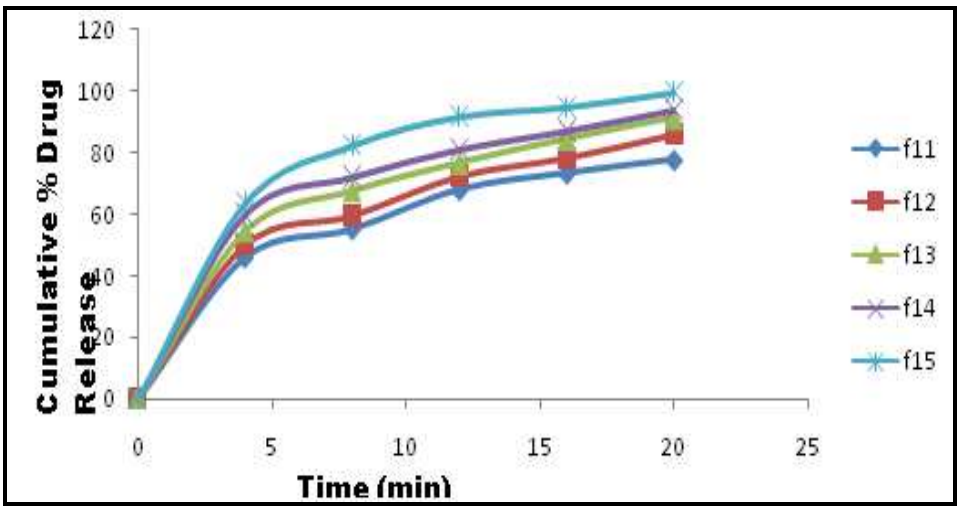

Figure No.3: Dissolution profile of lovaststin tablets F11-F15

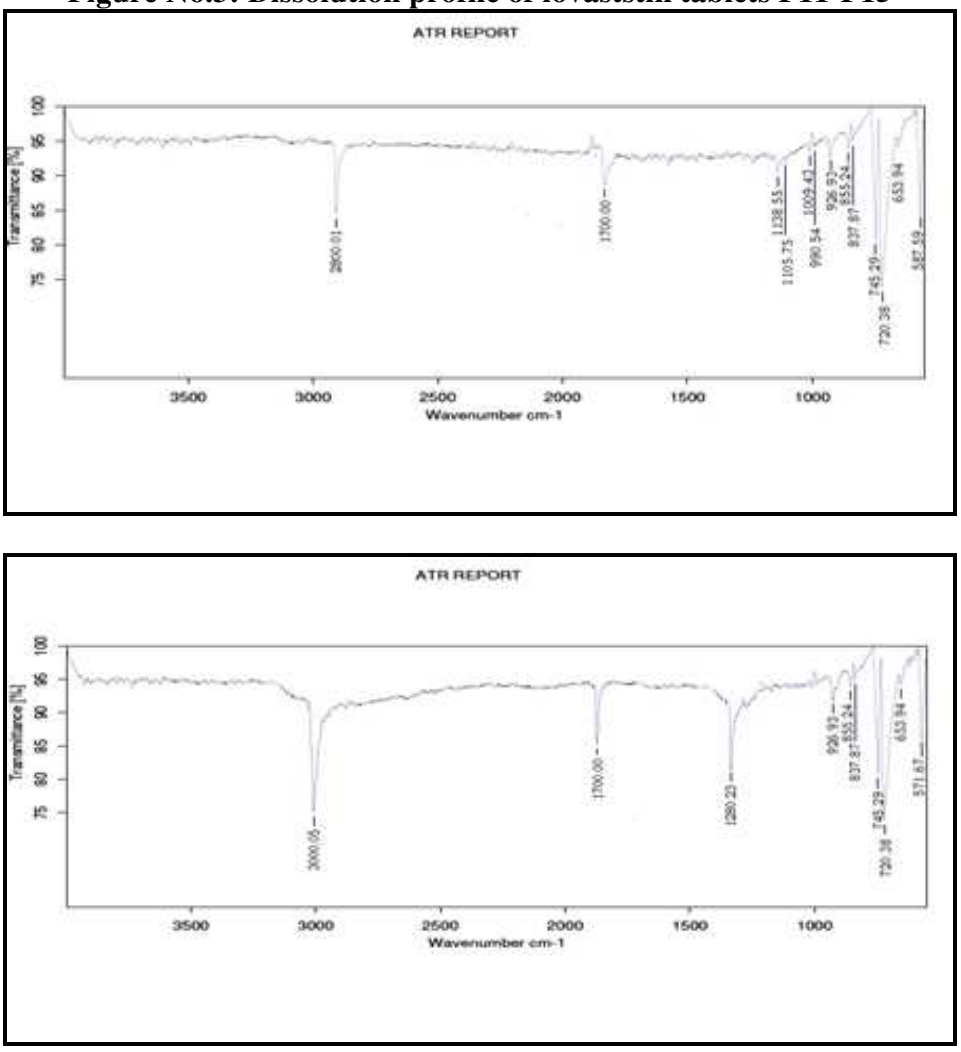

Figure No.4: FT-IR Spectra of a) Lovastatin and PVP K 30 b) Lovastatin and PEG6000

CONCLUSION

Lovastatin orally disintegration tablets were successfully prepared using solvent evaporation technique. Stability study for F4, F10, F15 and F18 were performed at temperatures (40^0C/75% RH). All the formulations showed no significant variation in all the parameters evaluated under the test period condition.

On experimental data it was concluded that Fast dissolving tablet of Lovastatin would be an effective alternative approach for management of various inflammatory disorders and pain. From the above studies it was concluded that the F15 is best formulation for Fast Dissolving Tablets of Lovastatin.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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