Academic Sciences Asian Journal of Pharmaceutical and Clinical Research
Vol 6, Issue 1, 2013 ISSN - 0974-2441

Research Article

DIFFERENT TECHNIQUES TO ENHANCE THE DISSOLUTION RATE OF LOVASTATIN: FORMULATION AND EVALUATION

KARTHIK NEDURI[1], VIJAYA KUMAR BONTHA[1], SATEESH KUMAR VEMULA[1, 2]*

[1]Department of Pharmaceutics, Jangaon Institute of Pharmaceutical Sciences, Yeshwanthapur, Jangaon, Warangal, Andhra Pradesh, India-506167,[2]Department of Pharmaceutics, Chaitanya College of Pharmacy Education and Research, Kishanpura, Hanamkonda, Warangal, Andhra Pradesh, India-506001,Email: vemulasatish15@gmail.com

Received: 2 October 2012, Revised and Accepted:1 November 2012

ABSTRACT

The intent of present study is to enhance the dissolution profile, absorption efficiency and bioavailability of water insoluble drugs like Lovastatin by using various techniques. Lovastatin is a poorly soluble, highly permeable drug and the rate of its oral absorption is often controlled by the dissolution rate in the gastrointestinal tract. In this study an attempt was made to enhance the in vitro dissolution profiles of Lovastatin by using various methods like solid dispersions, superdisintegrants and sublimation with respective to conventional drug. Solid dispersions of lovastatin showed enhancement in its dissolution efficiency was 2.03%, in 5 min, where as in case of superdisintegrants method it was 4.37% in 5 min and in sublimation method was found to 4.26% in 5min compared to conventional preparation. Drug-polymer interaction studies like Differential scanning calorimetry and Fourier Transform Infrared Spectroscopy studies were performed and the results showed that there were no possible interactions between the drug and the polymer. In conclusion, the results suggest that there was satisfactory dissolution enhancement from all three methods and could potentially lead to improvement in bioavailability of oral lovastatin products, but superdisintegrant method was preferred due to its simplicity, low cost and industrial feasibility.

Keywords: Dissolution efficiency, Interaction studies, Poorly soluble, Sublimation, Superdisintegrants, Solid dispersions.

INTRODUCTION

Poorly water soluble drugs are allied to slower rate of absorption from oral route; hence dissolution is the rate limiting step for lipophilic drugs[1]. So, there is a necessity to enhance the dissolution of these drugs to ensure maximum therapeutic utility of these drugs[2, 3]. As oral route is considered most natural, uncomplicated, convenient, safe means of administering drugs due to its immense advantages like flexibility in dosage form design, ease of production and low cost e.g. tablets, capsules. But, nearly one third of drugs in development are poorly water soluble, thus these poorly water soluble drugs show slow drug absorption leading to inadequate and variable bioavailability and gastro intestinal mucosal toxicity of drugs[4]. As these solid dosage forms are convenient for many drugs but they are challenging to formulate if the active substances has poor dissolution rate or low bioavailability. Hence to overcome such problems various techniques have been introduced to enhance the dissolution rate and solubility of the drug[5]. These techniques include physical modification of lipophilic drugs using several carriers like cyclodextrins, carbohydrates, hydrotropes, dendrimers, polyglycolized glycerides, acids[6] and other methods by the use of superdisintegrants, solid dispersions, surfactants, melt granulation, particle size reduction etc[7].

The objective of the present study is to enhance the dissolution rate of lovastatin tablets (poorly soluble drug) by superdisintegrants, solid dispersions & sublimation. Superdisintegrants acts as hydrophilic carrier for poorly water insoluble drug.They provide quick disintegration due to combined effect of water absorption and swelling, thus lead to wettability and dispersibility of the system thus enhances the dissolution profile of a drug. One of the limitations, while selecting super disintegrant is that their critical concentration is to be considered[8]. Solid dispersions are product formed by converting a fluid drug-carrier combination to the solid state (Corrigan 1985) by melting solvent method or fusion method[9]. It is considered as one of the most potential method of improving dissolution and solubility of drugs. 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. Sublimation is a method in which inert solid ingredients like camphor, menthol, urea, naphthalene, ammoniumcarbonate, ammoniumbicarbonate and solvents (like benzene, cyclohexane), were added to the other tablet ingredients and mixture is compressed in to tablets. These volatile substances are then removed by sublimation, to form porous structures, thus formed porous structures impart progress in the dissolution rate[10].

Lovastatin belongs to the class of statins, used for lowering cholesterol (hypolipidemic agent) in those patients suffering with hypercholesterolemia. It was the first statin approved by the FDA. It's a prodrug and inhibitor of 3-hydroxy-3methylglutaryl coenzyme A reductase (HMG-CoA reductase). It's a poorly soluble drug, with a shorter half life of 1.1-1.7 h and less than 5% bioavailability[11]. The concept of use of above three techniques has emerged from the desire to provide patients with more conventional means of taking their medication.

MATERIALS

Lovastatin is obtained as a gift sample from MSN laboratories, Hyderabad, India. Sodium starch glycolate, Crosspovidone, and Crosscarmellose were gift samples from Matrix laboratories, Hyderabad, India. All other chemicals used were of analytical grade.

METHODS

Preparation of solid dispersion by melt solvent method

Lovastatin and different carriers like PEG 4000 & 6000 are weighed accurately in the ratio of (1:1, 1:2, 1:3 and 1:4). Carriers were melted at 60°C. To this melted carriers, solution containing lovastatin previously dissolved in small quantity of acetone was added. It was mixed well and immediately cooled in an ice bath. The prepared solid dispersion was then grounded by using mortar and pestle, sieved through mesh 40 & stored for further use in a desiccator[12]. The solid dispersion equivalent to 20 mg of drug was taken according to the ratios and then mixed with directly compressible diluent and disintegrant. Magnesium stearate and talc were mixed with the intial mixture and blended, followed by compression (Table 1).

Preparation of tablets by superdisintegrants

The drug is properly mixed with various proportions (2%, 4% and 8%) of superdisintegrants like crospovidone, croscamerllose and sodium starch glycolate. Then the other excipients except the glidant and lubricant were added and mixed in a plastic bag for 5-10 min. The obtained blend was mixed with magnesium stearate and talc for another 5min. The resultant mixture was directly compressed in to tablets (Table 1) with 6mm round flat punches using 16 station rotary compression machine (Cmach, Ahmedabad, India).

Table 1: Formulation of Lovastatin tablets prepared by various techniques

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Lovastatin	20	20	20	20	20	20	20	20	20	20
PEG 6000	40	-	-	-	-	-	-	-	-	-
PEG 4000	-	40	-	-	-	-	-	-	-	-
Crospovidone	-	-	9.6	-	-	-	-	-	-	-
Croscamerllose	-	-	-	9.6	-	-	-	-	-	-
Sodium starch glycolate	-	-	-	-	9.6	-	-	-	-	-
Camphor	-	-	-	-	-	12	-	-	-	-
Benzoic acid	-	-	-	-	-	-	12	-	-	-
Urea	-	-	-	-	-	-	-	12	-	-
Naphthalene	-	-	-	-	-	-	-	-	12	-
Phthalic anhydride	-	-	-	-	-	-	-	-	-	12
Starch	6	6	-	-	-	6	6	6	6	6
Lactose	70.4	70.4	86.8	86.8	86.8	78.4	78.4	78.4	78.4	78.4
Magnesium stearate	2.4	2.4	2.4	2.4	2.4	2.4	2.4	2.4	2.4	2.4
Talc	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2
Total tablet weight	120 mg									

Preparation of tablets by sublimation

Accurately weighed quantity of drug, volatile ingredients like camphor, benzoicacid, naphthalene, pthalic anhydride, urea are added in their respective formulations along with other excipients like disintegrant, diluent are properly mixed, following addition of magnesium stearate as lubricants. The powder mixture was subjected to compression in to tablet (Table 1). Then these tablets were subjected to sublimation, by placing in a hot air oven at 60°C for 30 min. Thus generates a porous matrix, due to removal of volatilizable component[13, 14].

Pre compression parameters

Angle of repose: It was determined by fixed funnel method. Accurately weighed quantity of blend was taken in a funnel; the height of the funnel is adjusted such that the tip of the funnel just touches the apex of heap of the blend. Then the blend is allowed to flow through the funnel freely on to the surface[15]. The diameter is then measured and angle of repose was calculated by following equation.

$$\text{Tan } \theta = h/r \qquad (1)$$

Where θ is angle of repose, h is height of the cone and r is radius of the cone base.

Bulk density: It was determined by pouring a weighed quantity of blend in to a graduated cylinder and measuring the bulk volume.

$$\text{Bulk density} = \text{weight of the powder} / \text{bulk volume} \qquad (2)$$

Tapped density: It was determined by pouring a known mass of blend in a measuring cylinder and tapped for fixed time. Then the final volume occupied by the blend was measured.

$$\text{Tapped density} = \text{weight of the blend} / \text{final volume} \qquad (3)$$

Compressibility index: The compressibility index (Carr's index) is a measure of propensity of a powder to be compressed.

$$\text{Carr's compressibility index} = [(\text{tapped density} - \text{bulk density} / \text{tapped density})] \times 100 \qquad (4)$$

Post compression parameters

The designed formulations were studied for their physical properties like weight variation, hardness and friability. For estimating weight variation, 20 tablets of each formulation were weighed using an electronic weighing balance (AW 120, Shimadzu Corporation, Japan). The hardness of six tablets was measured using Monsanto tablet hardness tester. Friability was determined on ten tablets in a Roche friabilator (Electrolab, Mumbai, India).

Determination of drug content

Ten tablets were powdered and the blend equivalent to 20mg of lovastatin was weighed and dissolved in methanol/0.1N HCl buffer. The solution was then filtered, diluted and drug content was then determined by UV-Visible spectrophotometer at 238 nm.

***In vitro* disintegration time**

In vitro disintegration time is determined by following procedure, 10ml of water was taken in a petridish of 10cm diameter. The tablet was then carefully placed in the centre of petridish and time required for the tablet to completely disintegrate in to fine particles was noted[16].

Wetting time & Water absorption ratio

A linear relationship exists between wetting time and disintegration time. It is closely related to the inner structure of tablets and hydrophilicity of excipients. A piece of tissue paper folded twice was placed in small Petri plate containing 10ml of water of internal diameter 10cm.A tablet was placed on the paper and time for complete wetting of the tablet was measured in seconds. The same procedure was followed for determining the water absoption ratio[17]. The wetted tablet was weighed and water absorption ratio R, was determined by following equation

$$R = \{(Wa - Wb) / Wb\} \times 100 \qquad (5)$$

Where, Wa and Wb were weights of the tablets after and before study.

***In vitro* dissolution studies**

In vitro dissolution studies were carried out in USP Type II apparatus (USP XXIV dissolution test apparatus) at 50rpm in 900ml of 0.1N HCl containing 1% of Sodium laurlyl sulphate, maintained at 37 ± 0.5ºC. 5ml aliquot was with drawn at the specified time intervals and replaced with fresh dissolution media (5 ml), then these samples were filtered through whatmann filter paper and analyzed spectrophotometrically at 238nm. Dissolution studies were performed in triplica.

Calculation of dissolution parameters

Cumulative percent drug release was plotted as a function of time and percent drug release in 5 minutes (Q_5) was calculated. Initial dissolution rate (IDR) was calculated as percentage dissolved of drug over the first 5 min per minute. Dissolution efficiency (DE) was calculated from the area under the dissolution curve at time t (measured using the trapezoidal rule) and expressed as a percentage of the area of the rectangle described by 100% dissolution in the same time. Relative dissolution rate (RDR) is the ratio between amount of drug dissolved from optimized formulation and that dissolved from the conventional formulation at 5 min[18].

Drug-Polymer Interaction Studies

By the means of spectroscopic and thermal analysis drug-polymer interaction between lovastatin and excipients of formulations of various techniques are conducted. These studies determine the physical stability of a drug. DSC studies were carried out on pure dug and optimized formulations and the thermograms were obtained using DSC (Perkin-Elmer, Shelton, USA). The analysis were performed under nitrogen (nitrogen flow rate 50 ml/min) in order to get rid of oxidative and pyrrolytic effects at a standard heating

rate of 15ºC/min over a temperature range of 50ºC-350ºC. Further the infrared spectra studies of lovastatin and optimized formulations recorded between 400 to 4000 cm^{-1} on FTIR spectrometer (Perkin Elmer FTIR, Perkin Elmer Inst. USA) to detect the drug-excipient interactions using KBr disk method. The resultant spectra obtained, were compared for any possible changes in the peaks of the spectra.

RESULTS AND DISCUSSION

Pre compression parameters

The powder mixtures of different formulations were evaluated for angle of repose, bulk density, tapped density, compressibility index. Bulk density, tapped density values ranged from 0.294 to 0.338 and 0.342 to 0.396 for solid dispersions, 0.294 to 0.338 and 0.354 to 0.401 for superdisintegrants, 0.288 to 0.328 and 0.342 to 0.394 for tablets prepared by sublimation respectively. Angle of repose and compressibility index (%) ranged from 27.1±0.72 to 30.26±0.94 and 16.7 to 20.37 for solid dispersions,25.18±0.72 to 29.48±0.87 and 15.67 to 19.36 for super disintegrants,26.7±0.673 to 32.55±0.50 and 18.39 to 20.96 for tablets prepared by sublimation respectively.

Post compression parameters

The physical properties of lovastatin tablets are given in Table 2. In weight variation test, the pharmacopoeial limits of the tablets are not more than 10% of the average weight. The average percentage deviation of all the tablet formulations was found to be within the above mentioned limits hence all the formulations passed the uniformity of weight as per official requirements. The hardness of tablets was found to be in the range of 3.3±0.2 to 3.7±0.30 for solid dispersions, 3.06± 0.25 to 3.63 ±0.41for superdisintegrants and 2.93±0.32 to 3.5±0.2 for tablets prepared by sublimation. Another measure of tablet strength is friability; the percentage friability for all the formulations was below 1%, indicating that the friability is with in prescribed limits. The tablets were found to contain 98.13±0.83 to 99.13±0.81 for solid dispersions, 97.8± 0.6 to 99.13± 0.81 for superdisintegrants, 97.4 ± 0.95 to 99.2 ± 0.81 for tablets prepared by sublimation of labeled amount indicating uniformity of drug content.

Table 2: Physical properties of Lovastatin tablets

Formulation	Weight variation*	Hardness**	Friability	Drug content uniformity***
F1	121.1±0.94	3.5±0.26	0.37	99.1±0.81
F2	121.1±1.73	3.3±0.20	0.31	98.6±1.05
F3	121.1±1.01	3.6±0.41	0.32	99.1±0.81
F4	120.4±0.76	3.5±0.26	0.37	97.7±1.35
F5	119.6±0.57	3.7±0.30	0.29	99.3±0.66
F6	119.6±1.52	3.2±0.15	0.44	99.2±0.81
F7	120.2±1.06	2.9±0.32	0.37	97.7±1.35
F8	120.4±1.12	3.5 ±0.20	0.33	98.6±1.05
F9	120.3±1.52	3.2±0.26	0.34	97.4±0.95
F10	119.7±1.73	3.3± 0.55	0.26	98.1±1.06

***All values represent mean standard deviation, n=20**
****All values represent mean standard deviation, n=6**
*****All values represent mean standard deviation, n=3**

Disintegration time for all the formulations was found to be the range of 33.17±0.90 to 47.87±0.71 for solid dispersions (F1), 30.47±1.02 to 48.63±0.55 for superdisintegrants (F3), 35.31±0.80 to 48.7±0.98 for tablets prepared by sublimation (F6) (Table 3). Among the three methods superdisintegrants (F3) showed rapid disintegration (30 sec) and all the tablets disintegrated with in 48 sec. Wetting time for all the formulations was found to bein the range of 25.19±0.42 to 35.38±1.60 for solid dispersion, 23.34±0.98 to 35.58±1.19 for superdisintegrants, 28.16±0.76 to 36.26±0.64 for tablets prepared by sublimation. The combined effect of swelling and water absorption lead to quick wetting in almost all the formulations of the three methods, from these we infer that all the formulations were within the accepted physical characteristics.

Table 3: Physical properties of Lovastatin tablets

Formulation	Disintegration time (sec)*	Wetting time (sec)*	Water absorption time (sec)*
F1	33.17±0.90	25.19±0.42	78.83±1.05
F2	35.41±0.97	26.92±0.45	68.02±0.60
F3	30.47±1.02	23.34±0.98	80.83±0.72
F4	40.31±1.28	32.04±0.56	66.74±0.38
F5	33.22±1.16	24.68±0.98	78.93±0.55
F6	35.31±0.80	28.16±0.76	73.94±0.79
F7	36.04±0.94	32.21±1.04	71.29±1.62
F8	48.72±0.98	35.63±1.26	58.22±1.34
F9	45.53±1.05	36.26±0.64	60.51±0.63
F10	47.44±0.77	32.04±0.56	63.23±0.43

.* All values represent mean ± standard deviation, n= 3

In vitro dissolution study

The cumulative mean percent of lovastatin tablets for 5 min containing various proportions of solid dispersions (F1 toF2) was found to show a discrepancy from 34.78±0.12 to 55.4±0.4, where as in case of superdisintegrants (F3 to F5) 65.64±0.26 to 96.23±0.30 and 34.4±0.51 to 93.4±0.90 for tablets prepared by sublimation (F6 to F10). The optimized formulations for solid dispersions (F1) 55.4±0.40, superdisintegrants (F3) 96.23±0.30 and sublimation (F6) 93.4±0.90 showed drug release in 5 min where as the conventional formulation showed 29.32±0.58 in 5 min (Figure 1). Thus the tablets prepared by the use of soliddispersions, superdisintegrants and sublimation methods showed enhancement of the dissolution rate. They even can be well correlated with the evaluation parameter like disintegration time and wetting time.

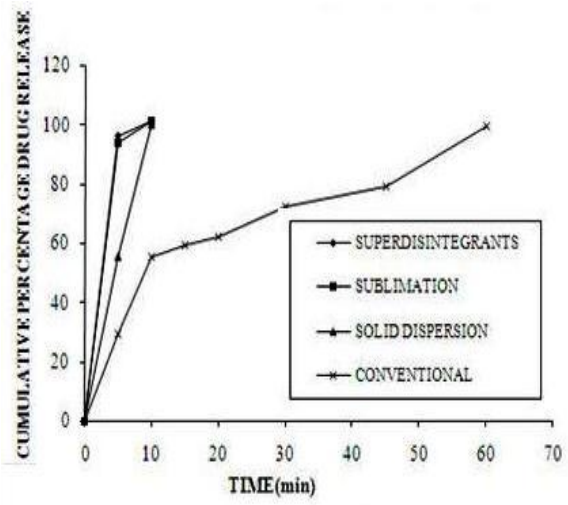

Figure 1: Dissolution profile of optimized and conventional Lovastatin formulations

The percent drug release in 5 min (Q_5) and initial dissolution rate (IDR) for optimized formulations were 55.4±0.40%, 11.08%/min for

solid dispersions (F1), 96.23±0.30%, 20.24%/min for superdisintegrants (F3), 93.4±0.90%, and 18.68%/min for tablets prepared by sublimation technique (F6) respectively (Table 4). Comparitively these methods showed higher dissolution rate with respective to conventional tablet (29.32±0.58%, 5.86%/min). The improvement in the dissolution characteristics of a drug described in terms of dissolution efficiency (DE) and relative dissolution rate (RDR). The RDR was found to be 1.89±0.06 for solid dispersions (F1), 3.28±0.06 for superdisintegrants (F3) and 3.18±0.06 (F6) for tablets prepared by sublimation. The DE was found to be 26.79 for solid dispersions (F1), 57.70 for superdisintegrants (F3), and 56.19 for tablets prepared by sublimation (F6). Hence, overall increase in the dissolution rate of all the optimized formulations described in terms of dissolution parameters with respect to conventional tablet possibly due to shorter disintegration time and improved solubility of drug.

Table 4: Dissolution parameters of optimized and conventional Lovastatin formulations

Optimized Formulation	(Q_5)*	IDR(%/min)	DE	RDR
Solid dispersion (F1)	55.4±0.40	11.08	26.79	1.89±0.06
Superdisintegrants (F3)	96.23±0.30	20.24	57.70	3.28±0.06
Sublimation (F6)	93.4±0.90	18.68	56.19	3.18±0.06
Conventional	29.32±0.58	5.86	13.18	--

Q_5-Percent drug release in 5 min, IDR-Initial dissolution rate, DE-Dissolution efficiency and RDR-Relative dissolution rate

Drug polymer interaction studies

DSC studies were performed to understand the nature of the drug in the formulated tablets. Thermograms obtained for pure drug, crosspovidone, PEG6000, camphor and optimized formulations of three methods were shown in Figure 2. The DSC of lovastatin showed endothermic peaks equivalent to its melting point at 172.210C where as thermograms of the optimized formulations did not show any significant shift in the endothermic peak. The FTIR spectrum (Figure 3) of above mentioned excipients and optimized formulations of three methods were compared to that of pure lovastatin. The FTIR spectra of pure lovastatin and optimized formulation of solid dispersions, superdisintegrants, sublimation technique exhibit peak at 1275 cm^{-1}, 1050 cm^{-1} is due to lactone and ester C-O-C bending vibration stretching and peaks at 2930cm^{-1} is due methyl and methylene C-H stretching, though additional peaks were observed with optimized formulation which could be due to the presence of polymers. Incorporation of lovastatin in to the carrier, superdisintegrants and sublimating agent didn't change the nature of its functional groups. Thus, confirms the structure of lovastatin drug.

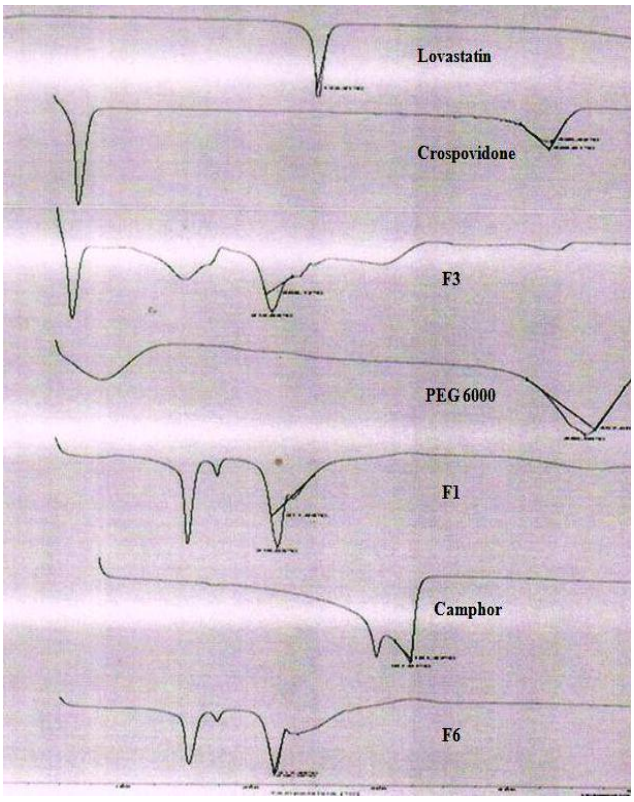

Figure 2: DSC thermograms of the pure drug, polymers and optimized formulations

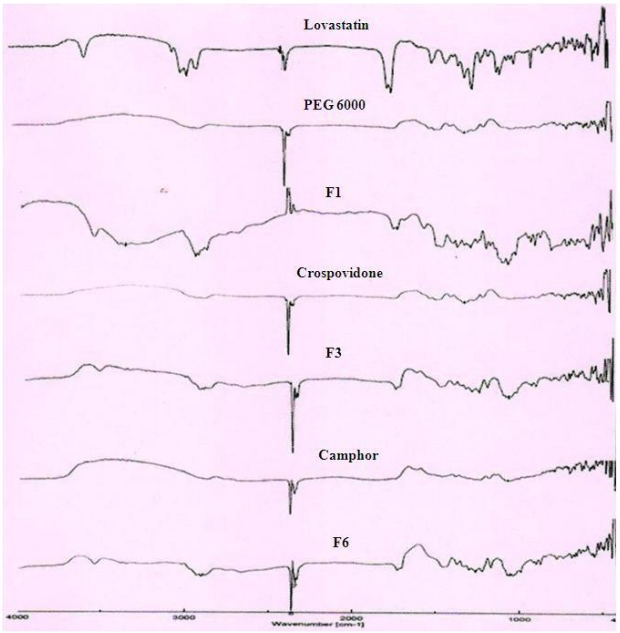

Figure 3: FTIR studies of pure drug, polymers and optimized formulations

CONCLUSION

Different attempts were made to improve the dissolution rate of Lovastatin. Lovastatin tablets were successfully formulated by using solid dispersions, superdisintegrants and sublimating agents by direct compression method. From the *in vitro* dissolution studies, three methods enhanced the dissolution rate when compared to conventional tablets. When comparing three methods, superdisintegrants method was superior in physical properties as well as dissolution rate and also it was simple method to prepare the tablets. In conclusion, formulation of lovastatin tablets with superdisintegrants is considered as suitable and feasible method to enhance the dissolution rate of lovastatin. Further efficacy must be assessed by performing pharmacokinetic studies in humans.

ACKNOWLEDGEMENTS

The authors thankful to MSN laboratories (Hyderabad, India) and Matrix laboratories (Hyderabad, India) are gratefully acknowledged for providing gift samples of lovastatin and superdisintegrants. The authors also thankful to principal and management of Jangaon institute of pharmaceutical sciences for providing the facilities.

REFERENCES

1. Charman WN. Lipids, lipophilic drugs, and oral drug delivery-some emerging concepts. J Pharm Sci 2000; 89(8): 967-78.
2. Meyer MC. Bioavailability and bioequivalence of drugs. In: Swarbik J, editors. Encyclopedia of Pharmaceutical

Technology. 2nd ed. New York: Marcel Dekker Inc; 1998. p. 33-58.
3. Shargil L. Applied Biopharmaceuitcs. 2nd ed. Norwalk: Appleton-Century Crofts; 1985.
4. Yu LX. An integrated model for determining causes of poor oral drug absorption. Pharm Res 1999; 16(12): 1883-88.
5. Mohanachandran PS, Sindhumol PG. Enhancement of solubility and dissolution rate: an overview. Int J Cph Pharm 2010; 4(11): 1-10.
6. Vikas AS, Vipin K, Mahesh K. Dissolution Enhancement of Drugs Part II: Effect of Carriers. Int J Health Res 2009; 2(2): 207-23.
7. Patel TB, Patel LD. Formulation and development strategies for drugs insoluble in gastric fluid. Int Res J Pharm 2012; 3(1): 106-13.
8. Gohel MC. Preparation and Assessment of Novel Co-processed Superdisintegrant Consisting of Crospovidone and Sodium Starch Glycolate: A Technical Note. AAPS Pharm Sci Tech 2007 8(1): E1-E7.
9. Renu K, Sushma P. Solid dispersion: A method for enhancing drug dissolution. Int J Drug Res 2010; 1(3): 1-14.
10. Debjit B, Chiranji B, Jyoti J. Fast dissolving tablet: A review on revolution of novel drug delivery system and new market opportunities. Der Pharmacia 2009; 1(2): 262-76.
11. Slater EE, MacDonald JS. Mechanism of action and biological profile of HMG Co A reductase inhibitors: a new therapeutic alternative. Drugs 1998; 36(3): 72-82.
12. Leuner C, Dressman J. Improving drug solubility for oral delivery using solid dispersions. Eur J Pharm Biopharm 2000; 50: 47-60.
13. Zajc N, Obreza A, Bele M, Srcic S. Physical properties and dissolution behavior of nifedipine/mannitol solid dispersions prepared by hot melt method. Int J Pharm 2005; 291: 51-58.
14. Guyot M, Fawaz F, Bildet J, Bonini F, Lagueny AM. Physicochemical characterization and dissolution of norfloxacin/cyclodextrin inclusion compounds and PEG solid dispersions. Int J Pharm 1995; 123: 53-63.
15. Wikberg M, Aiderborn G. Compression characteristics of granulated materials IV. The effect of granule porosity on the fragmentation propensity and the compatibility of some granulations. Int J Pharm 1991; 69: 239-53.
16. Koizumi KY, Watanabe K, Morita N, Utoguchi, Matsumoto M. New method of preparing high porosity rapid saliva soluble compressed tablet using mannitol with camphor, a subliming material. Int J Pharm 1997; 152: 127-44.
17. Ganesh MC, Pramod GY, Ashok VB, Sharwaree RH. Effect of some physical parameters and crospovidone on directly compressed frusemide tablets. Asian J Pharm 2008; 235-40.
18. Vemula SK, Veerareddy PR. Fast disintegrating tablets of flurbiprofen: Formulation and characterization. Lat Am J Pharm; 2011; 30(6): 1135-41.