CODEN [USA]: IAJPBB ISSN: 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

http://doi.org/10.5281/zenodo.1231008

Available online at: http://www.iajps.com Research Article

FORMULATION AND EVALUATION OF SOLUBILITY ENHANCEMENT OF LOVASTATIN FAST DISSOLVING TABLETS BY USING ION EXCHANGE RESINS

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Abstract:

*The present study investigated that the fast dissolving tablets of Lovastatin by ion exchange resin. DRC prepared by physical mixing and solvent evaporation method. Sodium starch glycolate and Crospovidone were used as super disintegrants. Formulations prepared by physical mixing and solvent evaporation blends were taken for pre and post compression studies. Those all found to be within limits. From dissolution data among all formulations **I11** formulation containing DRC with solvent evaporation method along with CP as super disintegrant has shown maximum drug release within **10 min**. Hence it considered as optimised formulation. From the FTIR studies it has known as good compatability between drug and excipients. XRD studies of pure drug showed crystalline nature. XRD studies have shown when drug mixed with the resin by solvent evaporation has shown good dispersion. Optimised formulation was taken for Accelerated stability studies. From these studies It has known good stability over 3 months.*

Key words: *Lovastatin, Ion exchange resin, Physical mixing, Solvent evaporation method, Fast dissolving tablets.*

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Please cite this article in press Karike Girija et al., ***Formulation and Evaluation of Solubility Enhancement of Lovastatin Fast Dissolving Tablets by Using Ion Exchange Resins,*** *Indo Am. J. P. Sci, 2018; 05(04).*

INTRODUCTION:

The oral route of administration is considered as the most widely accepted route because of its convenience of self-administration, compactness and easy manufacturing.[1-2] But the most evident drawback of the commonly used oral dosage forms like tablets and capsules is difficulty in swallowing, leading to patients incompliance particularly in case of paediatric and geriatric patients1, but it also applies to people who are ill in bed and to those active working patients who are busy or travelling, especially those who have no access to water.[2]

For these reasons, tablets that can rapidly dissolve or disintegrate in the oral cavity have attracted a great deal of attention. Oral dispersible tablets are not only indicated for people who have swallowing difficulties, but also are ideal for active people.[3]

Fast dissolving tablet (FDT)is a solid dosage form that contains medicinal substances and disintegrates rapidly (within seconds) without water when placed on the tongue. The drug is released, dissolved, or dispersed in the saliva, and then swallowed and absorbed across the GIT.[4] US FDA defined FDT tablets as "A solid dosage form containing medicinal substances which disintegrates rapidly usually within a matter of seconds, when placed upon the tongue".

Recently European Pharmacopoeia used the term 'Fast dissolving tablet' as a tablet that is to be placed in the Mouth.Where it disperses rapidly before swallowing.

Fast dissolving tablets are also called as Fast - dissolving tablets, fast disintegrating tablets, fast dissolving tablets, Fastdissolving tablets, rapimelts, porous tablets, quick dissolving tablet[5].

The US Food and Drug Administration responded to this challenge with the 2008 publication of Guidance for Industry: Fast dissolving Tablets[6].Three main points stand out in the final guidance:

- FDTs should have an *in vitro* disintegration time of approximately 30sec or less.
- Generally, the FDT tablet weight should not exceed 500 mg, although the combined influence of tablet weight, size, and component solubility all factor into the acceptability of an FDT for both patients and regulators.
- The guidance serves to define the upper limits of the FDT category, but it does not supersede or replace the original regulatory definition mentioned. In other words, disintegration within a matter of seconds remains the target for an FDT.

Mechanism of action of FDT in oral Mucosa:

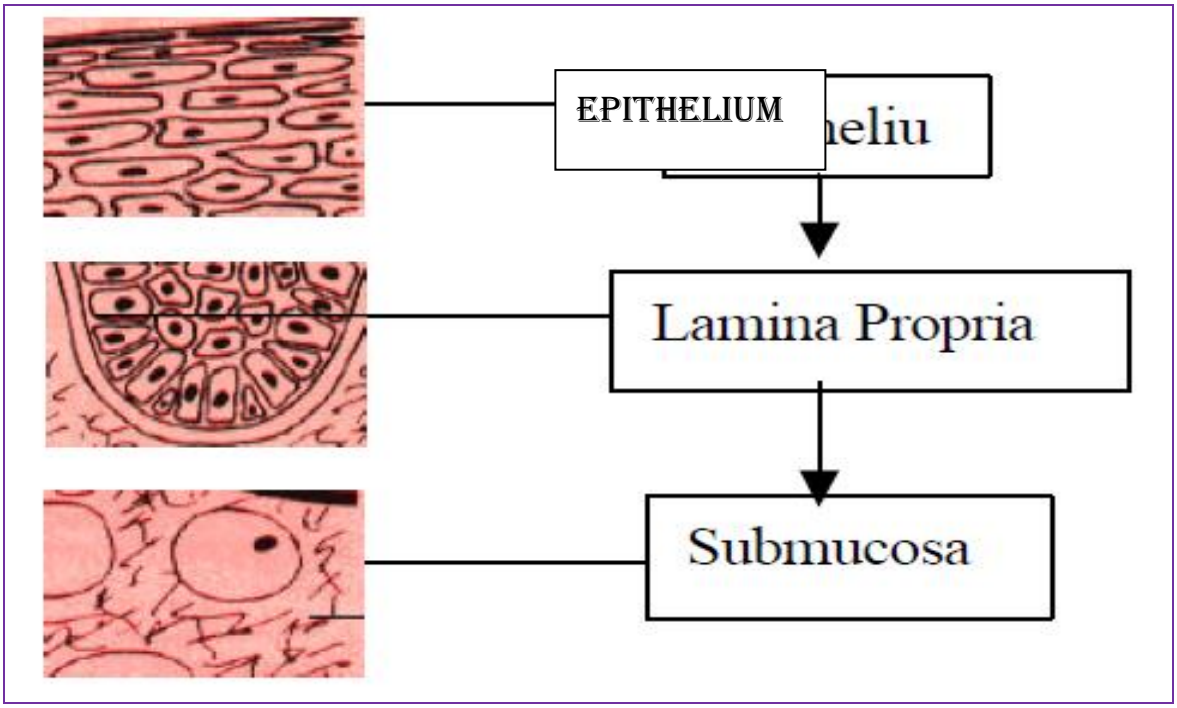

Fig: 1. Different layers of oral mucosa[7]

Mechanism of action: The FDT is placed upon patient's tongue or any oromucosal tissue. It instantly get wet by saliva due to presence of hydrophilic polymer and other excipients, then the tablet rapidly hydrates and dissolves to release the medication for oromucosal absorption

Advantages of FDTS:

Advantages of FDTs include:

- Ease of administration to geriatric, paediatric, mentally disabled, and bed-ridden patients, who have difficulty in swallowing the tablet.
- The FDTs do not need water for swallowing unlike conventional dosage forms. This is very convenient for patients who are travelling or do not have immediate access to water, and thus, provide improved patient compliance.
- Being unit solid dosage forms, provide luxury of accurate dosing, easy portability and manufacturing, good physical and chemical stability and an ideal alternative for paediatric and geriatric patients.

MATERIALS AND METHODS:

Materials used:

Lovastatin was a gift sample Provided by Sura Labs, Dilsukhnagar. Sodium starch glycolate, Crospovidone, Magnesium stearate , Talc, MCC pH 102were obtained from Sd fine Chem.Ltd. Mumbai, India.

Formulation of Lovastatin Fast dissolving tablets:

Table 1: Formulation chart of Lovastatin Fast dissolving tablets

Formulation Code	Drug Resin Complex (Equivalent to 20mg)	SSG (mg)	CP (mg)	Mg. Stearate (mg)	Talc (mg)	MCC pH 102 (mg)
I1	P1	7	-	2	2	QS
I2	P2	7	-	2	2	QS
I3	P3	7	-	2	2	QS
I4	P1	-	7	2	2	QS
I5	P2	-	7	2	2	QS
I6	P3	-	7	2	2	QS
I7	SV1	7	-	2	2	QS
I8	SV2	7	-	2	2	QS
I9	SV3	7	-	2	2	QS
I10	SV1	-	7	2	2	QS
I11	SV2	-	7	2	2	QS
I12	SV3	-	7	2	2	QS

Total weight of tablet is considered as 200 mg.

METHODOLOGY

Determination of UV Absorption maxima:

10mg of pure drug was dissolved in 10ml methanol (primary stock solution - 1000 µg/ml). From this primary stock solution 1 ml was pipette out into 10 ml volumetric flask and made it up to 10ml with the media (Secondary stock solution – 100µg/ml). From secondary stock solution again 1ml was taken it in to another volumetric flask and made it up to 10 ml with media (working solution - 10µg/ml). The working solution was taken for determining the wavelength.

Preparation of Standard Calibration Curve:

10mg of pure drug was dissolved in 10ml methanol (primary stock solution - 1000 µg/ml). From this primary stock solution 1 ml was pipette out into 10 ml volumetric flask and made it up to 10ml with the media (Secondary stock solution – 100µg/ml). From secondary stock solution required concentrations were prepared (shown in Table 7.1) and those concentrations absorbance were found out at required wavelength.

Table 2:*Invitro* dissolution study test parameters

Instrument	Labindia-USP type 2 dissolution test apparatus.
Dissolution medium	pH 6.8 Phosphate buffer
Apparatus	Paddle type.
Temperature	37±0.1oC
RPM	50
Volume of medium	900ml
Sampling intervals	5,10,20,30,45 and 60 minutes
Sample volume	5ml withdrawn and replaced with 5ml of dissolution medium.

Fourier transform Infrared spectroscopy (FTIR)

Fourier transform infrared (FTIR) spectroscopy was employed to characterize further the possible interactions between the drug and the carrier in the solid state on a FTIR spectrophotometer by the ATR (attenuated total reflectance) technique. For this technique ZnSe crystal was used to know the wavelength of those drug and carriers. The spectra were scanned over a frequency range 4000-550 cm-1 .

Differential Scanning Calorimetry (DSC) :

The possibility of any interaction between the drug and the carriers during preparation of solid dispersion was assessed by carrying out thermal analysis of drug and polymer alone as well as physical mixture and solid dispersion using DSC. DSC analysis was performed using Hitachi DSC 7020, on 5 to 15 mg samples. Samples were heated in sealed aluminum pan at a rate of 10°C/min conducted over a temperature range of 30 to 350°C under a nitrogen flow of 50 mL/min.

X-ray powder diffractometry (XRD):

To determine the powder characteristics, X-ray powder diffraction studies of drug and polymer alone as well as solid dispersion was performed. X-ray powder diffraction patterns were recorded on Bruker AXS, DH Advance, Germany. The scanning rate employed was 6° min–1 over 10 to 50° diffraction angle (2θ) range.

Accelerated stability studies:

Stability is defined as the extent to which a product retains with in specified limits and throughout its period of storage and use *i.e.,* shelf life. Stability studies were carried out on optimized formulation according to International Conference on Harmonization (ICH) guidelines. The formulation packed in aluminium foil was subjected to accelerated stability testing for 3 months as per ICH norms at a temperature 40 ± 2oC and relative humidity 75 ± 5%. Samples were taken at regular time intervals of 1month for over a period of 3months and analyzed for the change in physical appearance and drug content by procedure stated earlier. Any changes in evaluation parameters, if observed were noted. Tests were carried out in triplicate and mean value of the observed values was noted along with standard deviation.

RESULTS AND DISCUSSION:

Spectrum of Lovastatin:

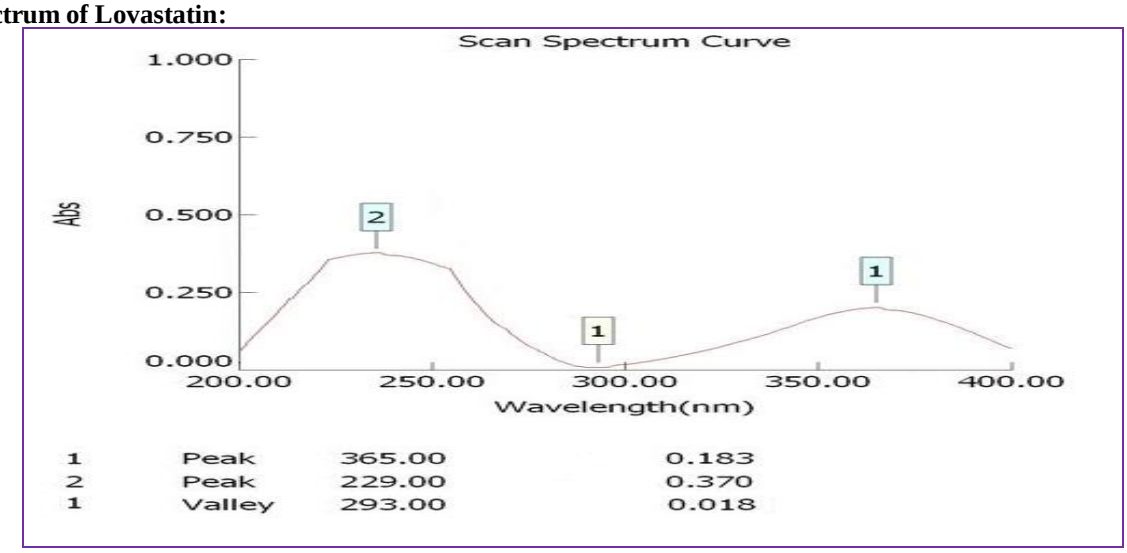

Fig 2: UV Spectrum of Lovastatin

Standard graph in phosphate buffer pH 6.8 at 229 nm

Standard graph of Lovastatin was plotted as per the procedure in experimental method and its linearity is shown in Table7.1 and Fig 7.2**.** The standard graph of Lovastatin showed good linearity with R2 of 0.998, which indicates that it obeys "Beer- Lamberts" law.

Table 3: Standard graph values of Lovastatin in pH 6.8 phosphate buffer

S.No	Concentration (µg/mL)	Absorbance
0	0	0
1	5	0.115
2	10	0.237
3	15	0.341
4	20	0.489
5	25	0.586

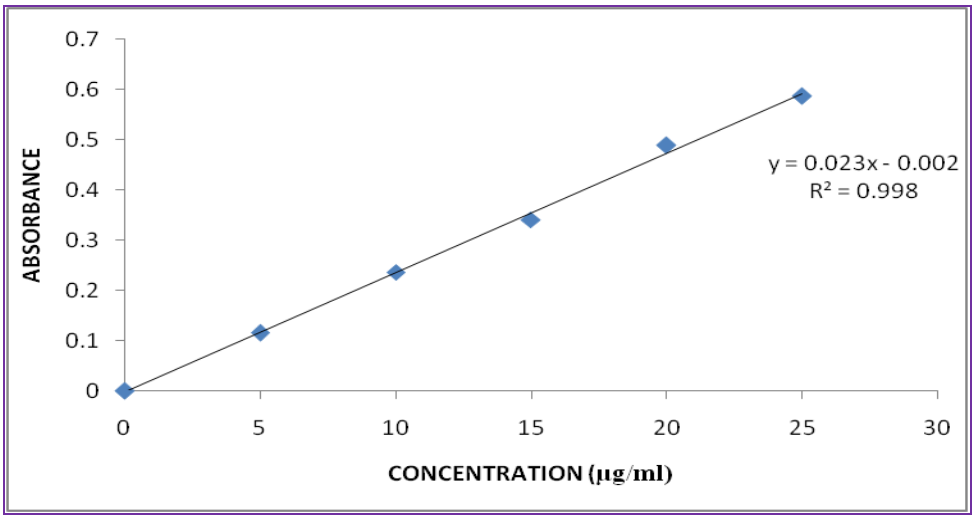

Fig 3: Standard graph of Lovastatin in pH 6.8 phosphate buffer

Pre-compression parameters:

The data were shown in Table 7.2. The values for angle of repose were found below 28o which means powder has good flow properties. Bulk density and tapped density of various formulations were found to be in the range of 0.74±0.06 to 0.89±0.09 (gm/ml) and 0.86±0.05 to 0.99±0.01 (gm/cc) respectively. Carr's index of the prepared blends was found below 18% and Hausners ratio was below 1.2. From the result it was concluded that the powder blends had good flow properties and these can be used for tablet manufacture.

Table 4: Pre-compression parameters

Formulations	Bulk Density (gm/ml)	Tap Density (gm/ml)	Carr's Index (%)	Hausners ratio	Angle Of Repose(Θ)
I1	0.82±0.06	0.93±0.08	11.82±0.08	1.13±0.04	26.14±0.04
I2	0.76±0.08	0.89±0.06	14.60±0.09	1.17±0.08	27.52±0.08
I3	0.81±0.01	0.88±0.04	7.95±0.05	1.08±0.09	24.17±0.05
I4	0.75±0.05	0.86±0.07	12.79±0.04	1.14±0.06	21.05±0.06
I5	0.84±0.04	0.93±0.06	9.67±0.07	1.10±0.01	22.69±0.09
I6	0.88±0.07	0.99±0.01	11.11±0.08	1.12±0.04	24.81±0.07
I7	0.89±0.09	0.98±0.09	9.18±0.01	1.10±0.07	27.58±0.02
I8	0.75±0.08	0.86±0.07	12.79±0.06	1.14±0.05	25.41±0.03
I9	0.74±0.06	0.87±0.04	14.94±0.04	1.17±0.06	24.18±0.07
I10	0.76±0.08	0.86±0.05	11.62±0.04	1.13±0.07	25.18±0.06
I11	0.78±0.04	0.87±0.08	10.34±0.06	1.11±0.04	27.09±0.09
I12	0.75±0.09	0.87±0.06	13.79±0.07	1.16±0.03	24.87±0.05

Drug and Excipient Compatability Studies:

FTIR:

From the FTIR studies it has known as good compatability between drug and excipients.

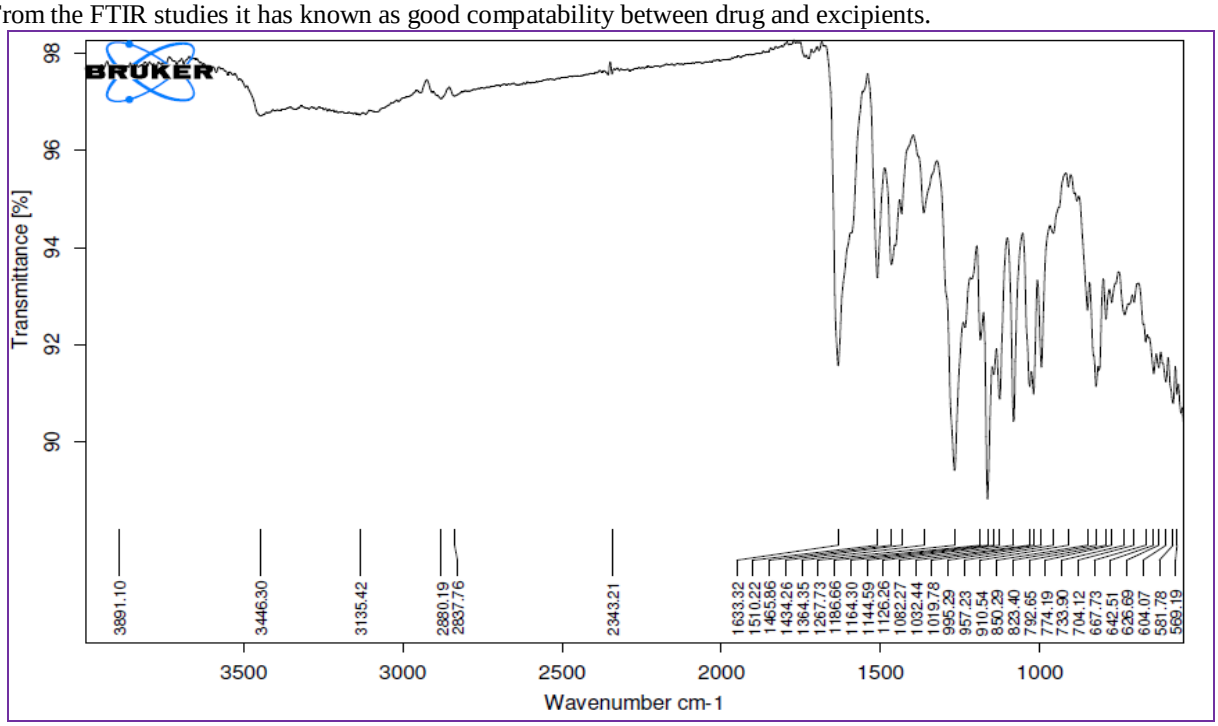

Fig 4: FTIR Spectrum of Lovastatin

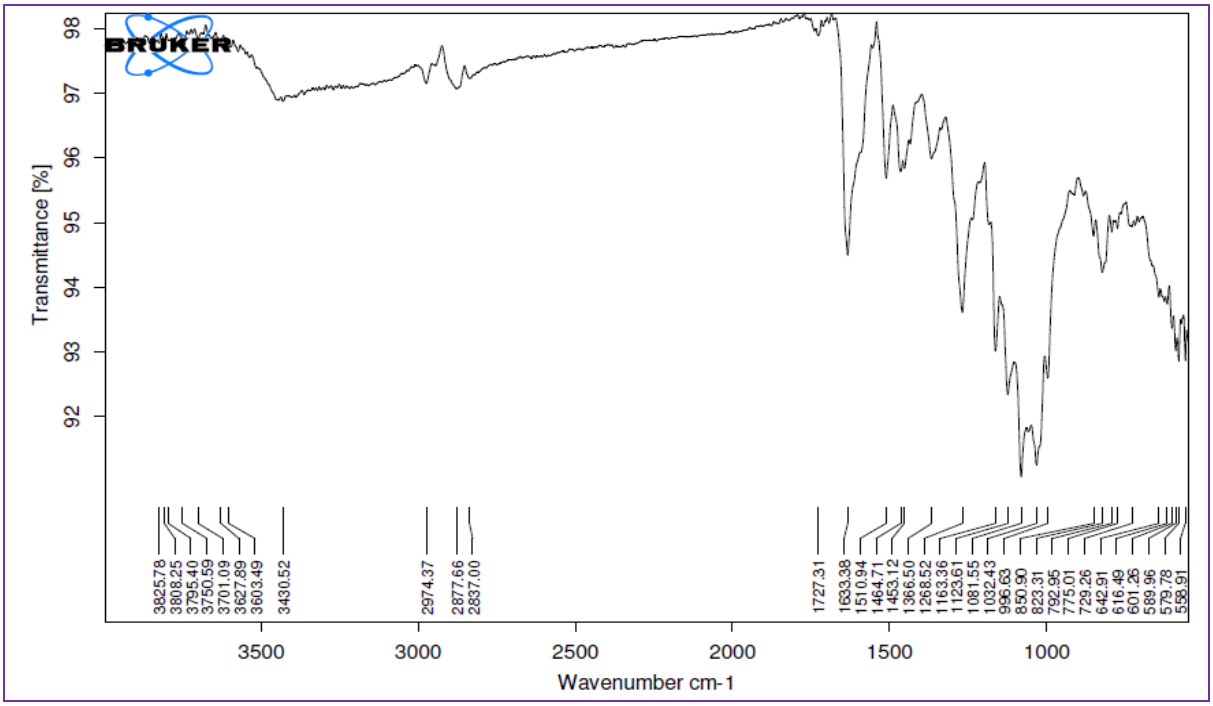

Fig 5: FTIR Spectrum of Optimised formulation

XRD Studies:

XRD studies of pure drug showed crystalline nature. XRD studies have shown when drug mixed with the resin by solvent evaporation has shown good dispersion.

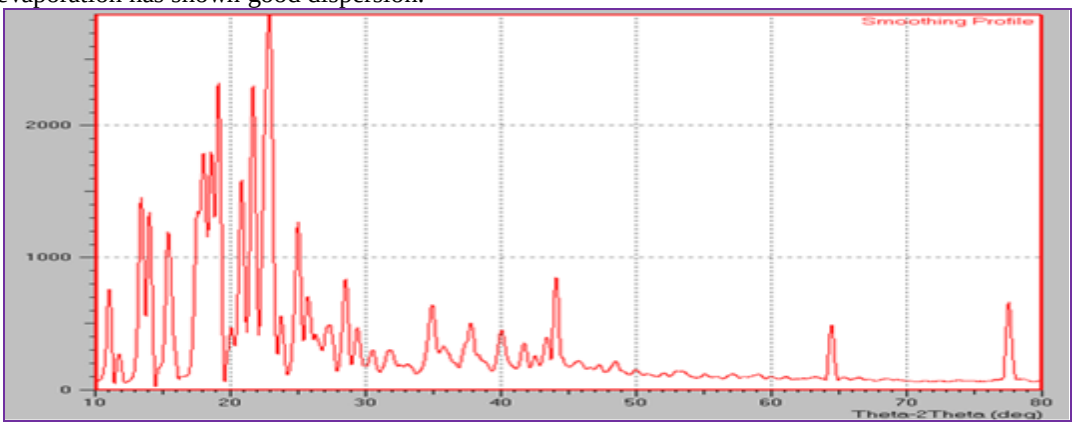

Fig 6. XRD studies of Lovastatin

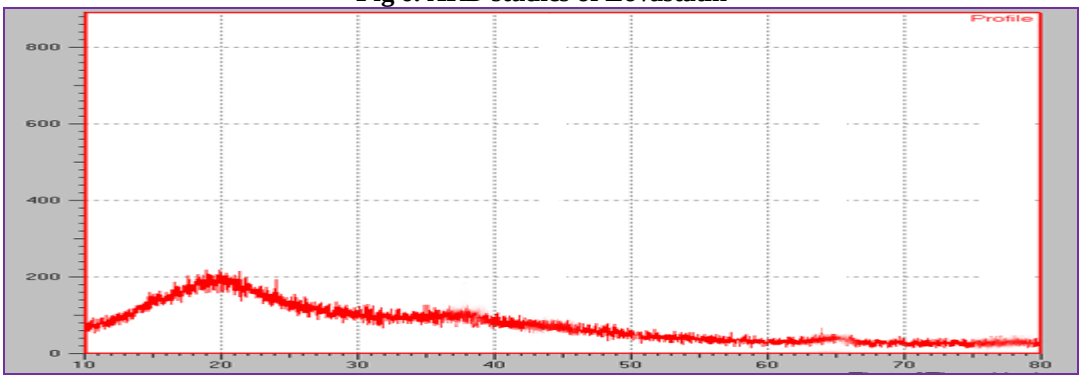

Fig 7. XRD studies of optimised formulation

Quality Control Parameters For tablets:

Table 5:Invitro quality control parameters for tablets

Formulation codes	Weight variation(mg)	Hardness (kg/cm2)	Friability (%loss)	Thickness (mm)	Disintegration Time (sec)	Drug content (%)
I1	198.65±0.82	2.5±0.06	0.50±0.04	3.7±0.04	21.15±0.04	99.12±0.14
I2	197.91±0.91	2.5±0.08	0.51±0.08	3.7±0.01	22.14±0.06	96.47±0.29
I3	200.84±1.08	2.4±0.05	0.51±0.05	3.8±0.05	29.26±0.08	98.85±0.48
I4	201.33±0.67	2.5±0.07	0.55±0.09	3.6±0.01	20.08±0.07	98.46±0.51
I5	199.79±0.85	2.4±0.09	0.56±0.02	3.6±0.01	26.34±0.02	97.17±0.49
I6	203.21±1.46	2.5±0.04	0.45±0.07	3.8±0.06	27.51±0.04	99.04±0.16
I7	198.36±0.76	2.1±0.03	0.51±0.08	3.7±0.03	21.05±0.03	96.91±0.54
I8	200.43±0.91	2.3±0.08	0.49±0.04	3.9±0.04	20.14±0.05	99.13±0.81
I9	199.41±0.75	2.5±0.04	0.55±0.07	3.8±0.02	24.19±0.07	98.09±0.39
I10	199.28±1.06	2.3±0.08	0.61±0.06	3.8±0.07	20.59±0.04	96.41±0.95

I11	201.09±0.92	2.2±0.06	0.58±0.09	3.6±0.05	19.84±0.08	98.12±0.36
I12	200.95±0.74	2.5±0.07	0.55±0.04	3.8±0.01	22.91±0.07	97.46±0.41

Weight variation test:

Tablets of each batch were subjected to weight variation test, difference in weight and percent deviation was calculated for each tablet and was shown in the Table 7.3. The average weight of the tablet is approximately in range of 197.91±0.91 to 203.21±1.46 mg. The permissible limit is ±7.5%. The results of the test showed that, the tablet weights were within the pharmacopoeia limit.

Hardness test:

Hardness of the three tablets of each batch was checked by using Pfizer hardness tester and the data were shown in Table 7.3. The results showed that the hardness of the tablets is in range of 2.1±0.03 to 2.5±0.08 kg/Cm2, which was within IP limits.

Thickness:

Thickness of three tablets of each batch was checked by using Vernier Caliper and data shown in Table-7.3. The result showed that thickness of the tablet is raging from 3.7±0.01 to 3.9±0.04.

Friability:

Tablets of each batch were evaluated for percentage friability and the data were shown in the Table 7.3. The average friability of all the formulations lies below 1%, as per official requirement of IP indicating a good mechanical resistance of tablets.

Drug content:

Drug content studies were performed for the prepared formulations. From these studies, it was concluded that all the formulations were showing the % drug content values between 95 to 100%.

Disintegration time:

Disintegration studies were performed for the prepared formulations. From these studies, it was concluded that all the formulations were showing the disintegration time below 30 seconds.

***Invitro* drug release studies:**

Table 6. Invitro drug release data of Physical mixture of DRC

Time	Pure Drug	I1	I2	I3	I4	I5	I6
5	0.92	8.14	13.72	6.59	12.67	16.48	10.54
10	1.57	15.98	25.49	10.96	27.12	30.94	19.86
15	2.96	26.84	47.14	19.63	40.08	52.83	29.47
20	4.18	39.57	62.49	28.15	63.91	75.16	38.59
30	6.49	51.63	79.86	39.82	78.14	91.54	50.29
45	8.63	72.48	95.63	51.08	87.66	94.81	62.51
60	14.96	85.19		63.47	94.81		76.13

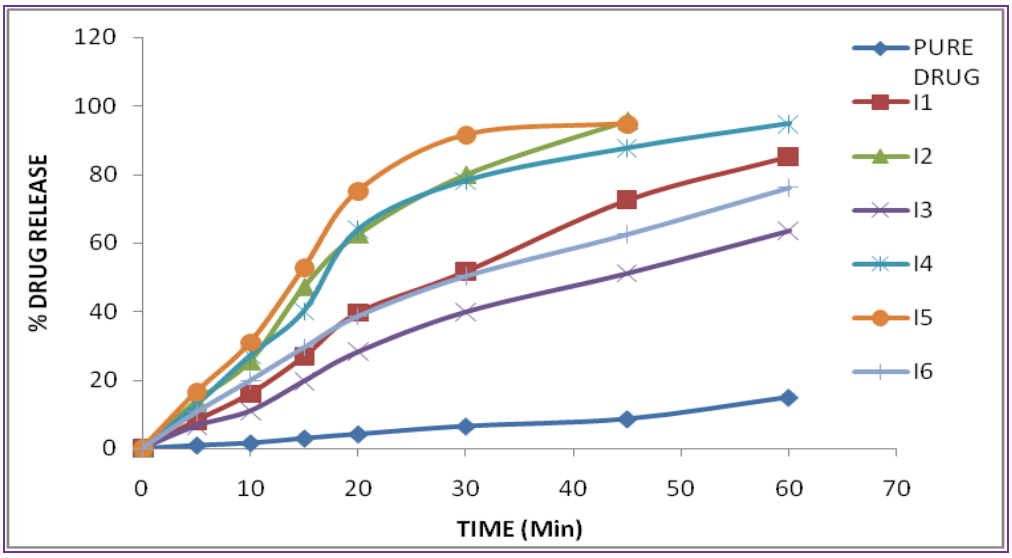

Fig 8. Comparison of invitro drug release of Physical mixture of FDT with pure drug

Table 7. Invitro drug release data of Slovent evaporation of DRC

Time	Pure Drug	I7	I8	I9	I10	I11	I12
5	0	0	0	0	0	0	0
10	0.92	24.69	39.41	19.87	35.41	68.42	21.54
15	1.57	52.87	63.47	31.68	72.84	94.75	46.09
20	2.96	79.84	86.49	42.51	96.15		62.34
30	4.18	96.31	94.87	59.74			79.12
45	6.49			67.13			86.14
60	8.63			76.89			94.08

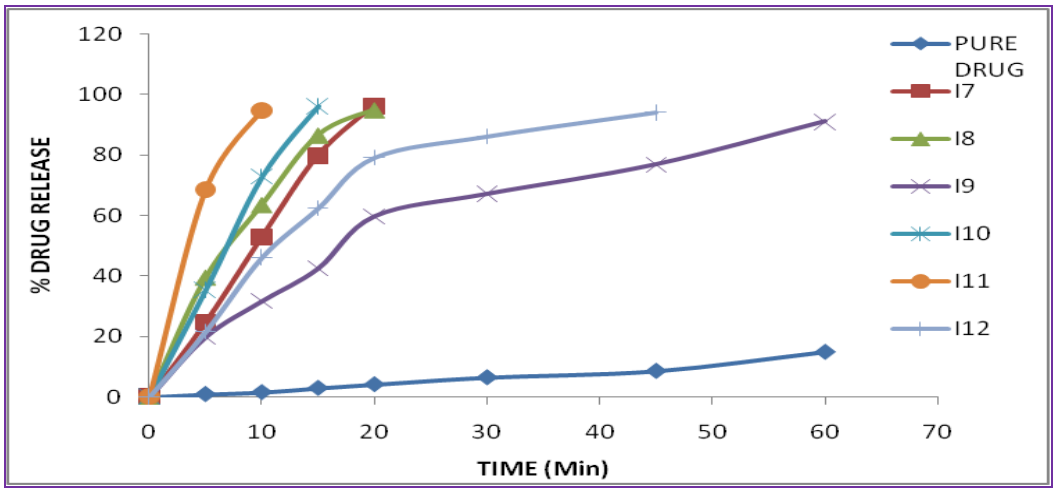

Table 9. Comparison of invitro drug release of Solvent evaporation of FDT with pure drug

From dissolution data it was evident that DRC in the ratio of 1:3 in both physical mixture and solvent evaporation method retards the drug release. Physical mixture and Solvent evaporation of DRC formulations were compared with pure drug to know whether dissolution enhancement.

Formulations prepared with Physical mixture have taken more time to release the drug when compared with the solvent evaporation method. Among all formulations I11 formulation containing DRC with solvent evaporation method along with CP as super disintegrant has shown maximum drug release within 10 min. Hence it considered as optimised formulation.

ACCELERATED STABILITY STUDIES:

Optimised formulation was taken for Accelerated stability studies. From these studies It has known good stability over 3 months.

Table 8: Accelerated Stability Studies

Parameters	Initial	After 1 month	After 2 month	After 3 month
Drug Content	98.12	98.08	97.94	97.90
Colour	White	No change	No change	No change

CONCLUSION:

The presentwas carried out on fast dissolving tablets of Lovastatin by employing Ion Exchange resins and Super disintegrants. The standard graph of Lovastatin showed good linearity with R2 of 0.998, which indicates that it obeys "Beer- Lamberts" law.The values for angle of repose were found below 28o which means powder has good flow properties. Bulk density and tapped density of various formulations were found to be in the range of 0.74±0.06 to 0.89±0.09 (gm/ml) and 0.86±0.05 to 0.99±0.01 (gm/cc) respectively. Carr's index of the prepared blends was found below 18% and Hausners ratio was below 1.2. From the result it was concluded that the powder blends had good flow properties and these can be used for tablet manufacture.

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ACKNOWLWDGEMENT:

The authors are thankful to SURA LABS Dilshukhnagar, Hyderabad, T.S., India for providing the necessary facilities for the research work.

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