The study of Dissolution Rate and Solubility of Levofloxacin Solid Dispersion Tablets.

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ABSTRACT

The main objective of present work was to study the dissolution rate and solubility of Levofloxacin Solid dispersion tablet. The solid dispersion was prepared by solvent evaporation method by using water soluble polymers as β-Cyclodextrin & PEG 6000. The prepared all Solid dispersions were comparatively evaluated for various pre-compressional parameters as Aq. solubility, Angle of Repose, Bulk Density, Tapped Density, Hausner's Ratio, Carr's Index, % Powder Yield, Phase solubility. The drug and polymer compatibility study were studied by FT-IR & DSC. The FT-IR & DSC revealed no chemical incompatibility between drug & polymer. The direct compression technique was utilized for tablet compression of all solid dispersion batches. All solid dispersion batch tablets were evaluated for post compressional parameters as hardness, friability, drug content, in-vitro dissolution profile.

The optimized batch was SE3 which released 97.57% drug within 30 min, the drug release batches of solid dispersion tablets. The SE3 batch was relatively stable at 40^0C / 75% RH condition for at least 60 days. Finally, the present study may be concluded that solid dispersion prepared by solvent evaporation method with β-CD & peg 6000 showed enhanced dissolution & solubility profile

Keywords: - Levofloxacin, Dissolution rate, PEG 6000, β-Cyclodextrin, Solubility enhancement, Bioavailability.

INTRODUCTION [1, 2]: -

Levofloxacin has moderate activity against Gram-positive, Gram-negative and anaerobic bacteria. It belongs to second-generation fluoroquinolone. Levofloxacin is used in treatments of upper and lower respiratory tract infections, urinary tract infections, skin infections[1]. The aim of this study was to formulate solid dispersion tablets of Levofloxacin. The main motto is to develop & evaluate solid dispersion tablets by using β-Cyclodextrin. The approach of complexation with β-cyclodextrins has been frequently used to increase the aqueous solubility and dissolution rate of water insoluble and slightly soluble drugs in an effort to increase oral bioavailability. However, in certain instances, this approach is also used to increase drug solubility as well as Control drug release rate, improve organoleptic properties and maximize the gastrointestinal tolerance. Generally, Beta-cyclodextrins are potential carriers for achieving such objectives but for a variety of reasons including cost, production capability and toxicity,

the amount of Cyclodextrins incorporated into a drug formulation is limited. It is therefore, important to develop methods, which can be applied in order to enhance the efficiency of drug-Cyclodextrins complexation. The complexation efficiency and solubilizing effect of Beta-cyclodextrins in aqueous solutions have been increased by addition of water-soluble polymers. This might be a useful strategy to decrease the amount of Beta-cyclodextrin needed in oral dosage forms and to increase the pharmaceutical usefulness of beta-cyclodextrins in solid oral dosage forms. Consequently, the rationale of this study was to improve the therapeutic efficacy of Levofloxacin utilizing the approach of inclusion complexation with Beta-cyclodextrins. These sorts of carriers produce crystalline or partially crystalline solid molecular dispersions, which are more thermodynamically stable than amorphous ones. The experimental verification of mechanochemical activation falls under the broad field of solid-state characterization & there are many techniques that are useful for this purpose X-ray, infrared, Raman spectroscopy, differential scanning calorimetry (DSC) & electron microscopy.

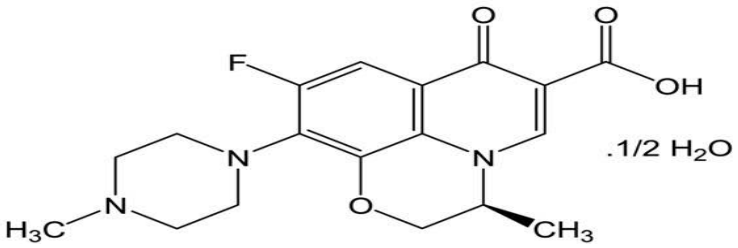


Fig.1. Levofloxacin structure

MATERIALS AND METHODS

Materials

Levofloxacin and β-Cyclodextrin was obtained from Yarrow chem products, Mumbai, India., PEG 6000, Lactose monohydrate and Methanol was obtained from Loba chemie, Mumbai, India.

Methods

Preparation of solid dispersion of Levofloxacin[3]:

Levofloxacin solid dispersions were performed by using carriers as β-CD & PEG 6000 in an appropriate ratio (SE1, SE2, SE3, SE4) by solvent evaporation method. Methanol was added to the mixture of drug and carriers, triturated in dry mortar until the solvent evaporated & a clear film of drug and carrier was obtained. The resultant solid dispersion was scrapped out with a spatula. Dispersions obtained were pulverized in a mortar-pestle and passed through a sieve no.60. Then, the prepared solid dispersion batches were stored in a desiccator until further use.

Batch	Drug(mg)	β-CD (mg)	PEG 6000(mg)
SE1	100	4.9	3.1
SE2	100	3.6	3.1
SE3	100	5.9	4.1
SE4	100	3.9	4.1

Table 1. Composition of Solid dispersion batches.

Calibration curve of Levofloxacin:

Accurately weighed 10 mg of drug (LFX) was dissolved in 10 ml of Phosphate buffer pH 6.8 to give a concentration of 1000 microgram/ml. Form the stock solution 1 ml was withdrawn and diluted up to 100 ml obtain the concentration 20 microgram/ml.(stock solution II) From stock solution II 0.2, 0.4, 0.6, 0.8 ml solution was withdrawn and diluted up to 10 ml with Phosphate buffer pH 6.8 to get subsequent concentration of 2, 4, 6, 8 microgram/ml solutions respectively. Absorbance was recorded at 295 nm using UV-spectrophotometer.

Evaluations of solid dispersion product:

Pre-compression Parameters of Solid dispersion:

Aqueous solubility[4]

It was performed according to a reported method. Solid dispersions equivalent to 100 mg of Levofloxacin were shaken with 10 ml distilled water & Phosphate buffer pH 6.8 separately in a stoppered conical flask in an orbital shaker for 24 hrs at room temperature. Subsequently, the solutions were filtered through a Whatman filter paper. Filtered solution was diluted properly. The diluted solutions were analysed for the Levofloxacin in UV-Spectrophotometer at 295 nm.

Phase solubility[5]

Phase solubility studies were carried out according to the method reported by Higuchi and Connors. An excess of LFX (200 mg) was added in 15 ml of portions of distilled water, each containing variable amount of β-CD in 0,1,2,3,4,5,6 X 10^{-3} moles/litre. All the above solutions with variable amount of β-CD were shaken for 72 hr. After shaking, the solutions were filtered and their absorbance were noted at 295 nm. The solubility of the LFX in every β-CD solution was calculated and phase solubility diagram was drawn between the solubility of levofloxacin and different concentrations of β-CD.

Percent Powder Yield

The percentage powder yield for the solid dispersion was calculated using the following equation.

$$\%\ Powder\ Yield = \frac{\text{weight of powder}}{Total\ weight\ of\ powder} X\ 100$$

Bulk Density & Tapped Density

Accurately weighed amount of solid dispersion were poured into a graduated cylinder to measure the volume (V_b). The measuring cylinder was tapped for a fixed period of time & tapped volume (V_t) occupied in the cylinder was measured. The bulk density & tapped density were calculated in gm/ml by using following formulae

$$Bulk\ density = \frac{\text{Mass of powder}}{Bulk\ volume\ of\ powder}$$

$$Tapped\ density = \frac{\text{Mass of powder}}{Tapped\ volume\ of\ powder}$$

Carr's Index and Hausner's Ratio

Carr's index and Hausner's ratio were calculated by using following formulae:

$$Carr's\ Index = \frac{\text{Tapped density} - \text{Bulk density}}{Tapped\ density} X\ 100$$

$$Hausners\ Ratio = \frac{\text{Tapped density}}{Bulk\ density}$$

Angle of Repose

A funnel was fixed in a stored in such a way that the top of the funnel was at a appropriate height from the surface. The solid dispersions were passed from the funnel so that they formed a pile. The height & the radius of the heap were measured & the angle of repose was calculated by using following formula:

$$\tan \Theta = \frac{\text{h}}{r}$$

Where,

h = Height of the heap

r = Radius of the heap Θ = Angle of repose.

Post-Compressional Parameters

Hardness[6]

Hardness indicates the ability of a tablet to withstand shocks while handling. The hardness of the tablet was determined using precision dial type hardness tester. It is expressed in Kg/cm^2. Three tablets were randomly picked and hardness of the tablet was determined.

Friability[6]

The friability of tablets was determined using Roche friabilator. It is expressed in percentage (%). 10 tablets were initially weighed and transferred into friabilator. The friabilator was operated at 25 rpm for 4 minute or run up to 100 revolutions. The tablet was weighed again, the percent friability was then calculated by following formula

$$\%\ friability = \frac{\text{W} - \text{Wo}}{W} X\ 100$$

Where,

Wo = Initial weight.

W = Weight after friability.

Drug content[7]

25 mg of solid dispersion was accurately weighed and transferred to 50 ml of volumetric flask and volume was made up to mark with Phosphate buffer pH 6.8. From this 1 ml was taken in 10 ml volumetric flask and the volume is adjusted up to mark with Phosphate buffer pH 6.8 solvent. The absorbance of the solution was measured at 295 nm using appropriate blank solution. The drug content of LFX was calculated using calibration curve showed in table no.2.

In-vitro dissolution studies[8]

In-vitro dissolution studies were performed for prepared solid dispersions. The following conditions were maintained for the dissolution process

Instrument: Electro lab USP TDL-081, India.

Apparatus: Paddle Type

Temperature: 37 ± 0.5ºC

RPM: 75

Volume of Medium:900 ml

Sample Intervals: 5, 10, 15, 20, 25 & 30 min

Sample volume: 2 ml sample withdrawn at fixed time intervals & replaced with same volume of Phosphate buffer pH 6.8

Drug release kinetics studies[9]

In order to understand the kinetics & mechanism of drug release, the results of the in vitro drug study were filled with various kinetic equations as Zero order, First order, Higuchi model, Korsmeyer-peppas model. The kinetic model that best fits the dissolution data was evaluated by comparing the regression coefficient (R^2) values obtained in various models.

Stability Studies[10]

The optimized formulations were subjected for two-month stability study according to ICH guidelines. The selected formulations were packed in aluminium foils, which were in wide mouth bottles closed tightly. They were then stored at room temperature 40^0C / 75% RH for 2 months and evaluated for their dissolution study.

Analytical Testing of Solid Dispersions

DSC analysis

DSC analysis of drug, polymer, solid dispersion was performed using Mettler differential scanning calorimeter. The samples were weighed in 40 ml aluminium pans, approximately 1-

2 mg and were sealed. An empty pan was used as a reference. The DSC Thermograms were obtained heating aluminium pans at heating rate of 10^0C/min. from 25^0C to 350^0C under nitrogen gas with flow rate 20ml/min.

RESULT AND DISCUSSION:

Calibration curve of Levofloxacin

The UV Spectrum of drug in the range of 200-400 nm on UV Spectrophotometer revealed that ג max of levofloxacin was at 295 nm. From the plot of absorbance vs Concentration of pure levofloxacin, it was observed that the drug obeys beer's-lambert's law in the concentration range of 2-8 µg/ml (r=0.999) at 295 nm. It was shown in Table 2, Figure 2.

Sr. No.	Conc.(µg/ml)	Absorbance
1.	0	0.000
2.	2	0.076
3.	4	0.151
4.	6	0.223
5.	8	0.295

Table 2 Calibration curve of Levofloxacin in Phosphate buffer pH 6.8.

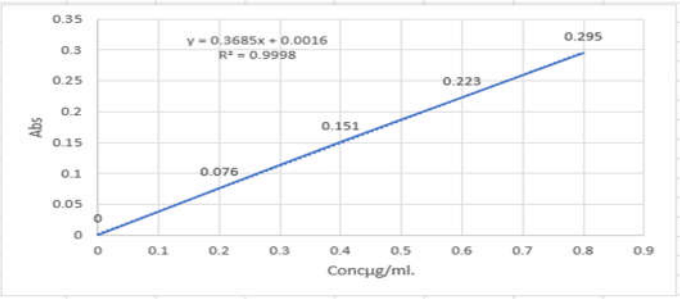


Figure 2 Calibration curve of Levofloxacin in Phosphate buffer pH 6.8.

Aq. Solubility

Aq. Solubility of levofloxacin solid dispersions in distilled water & phosphate buffer pH 6.8 were found in the range of 23.8 – 25.3 µg /ml & 27.5 -30.5 µg/ml respectively. The results found in aq. solubility study was shown in table 3.

Batch	Aq. Solubility of Drug in Dist. Water (µg/ml)	Batch	Aq. Solubility of Drug in pH 6.8 Phosphate Buffer (µg/ml)
SE 1	23.8	SE 1	27.5
SE 2	24.1	SE 2	28.6
SE 3	25.3	SE 3	30.5
SE 4	24.7	SE 4	28.9

Table 3 Aq. Solubility of Levofloxacin solid dispersions in Distilled water and Phosphate buffer pH 6.8.

Phase solubility study

The phase solubility study of the levofloxacin in various β-CD solutions was determined. The phase solubility curve for the solubility of levofloxacin & different concentration of β-CD was shown in figure3.

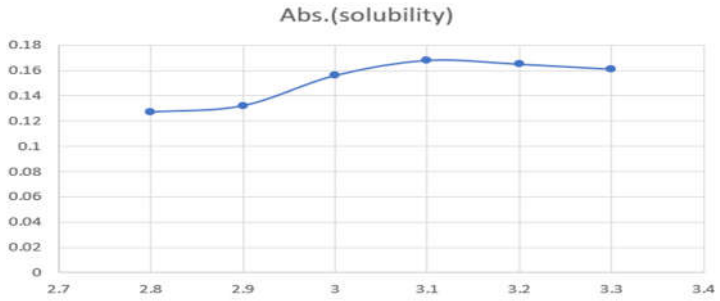


Figure 3 Phase solubility curve.

Percent powder yield

The Percent powder yield values of all prepared solid dispersion batches were shown in table4.

Batch	% Powder Yield
SE 1	94.44
SE 2	96.65
SE 3	98.18
SE 4	97.22

Table 4 % Powder yield of solid dispersions.

Bulk density & Tapped density

The results of bulk density & Tapped density of all prepared solid dispersion batches were found in the range of 0.243 - 0.277 gm/ml & 0.270 - 0.307 gm/ml respectively. The Bulk density & Tapped density values of all prepared solid dispersion batches were shown in table 5.

Carr's Index & Hausner's Ratio

The Carr's index & Hausner's ratio of all prepared solid dispersion batches were found in the range of 9.3 - 11.14 % & 1.10 - 1.12 respectively. The values of Carr's Index & Hausner's ratio were shown in table 5.

Angle of Repose

The angle of repose of all prepared solid dispersion batches were found in the range of 15.37-19.79. The values of angle of repose of all prepared solid dispersion were shown in table 5.

Batch	Bulk Density (gm/ml)	Tapped Density (gm/ml)	% Carr's Index	Hausner's Ratio	Angle of Repose (θ)
SE 1	0.255 ± 0.05	0.287 ± 0.03	11.14 ± 0.01	1.12 ± 0.01	19.79
SE 2	0.277 ± 0.01	0.307 ± 0.01	9.7 ± 0.01	1.10 ± 0.01	15.37
SE 3	0.243 ± 0.03	0.270 ± 0.01	10 ± 0.01	1.11 ± 0.01	18.43
SE 4	0.263 ± 0.01	0.290 ± 0.01	9.3 ± 0.01	1.10 ± 0.01	16.69

Table 5 Powder flow properties of solid dispersions. (SD=±, n=3)

Hardness Test

The hardness of all prepared solid dispersion tablets was found in the range of 1.5 - 2.1 kg/cm$^{2.}$ The values found for hardness test of all prepared tablets were shown in table 6.

Friability Test

The friability test of all prepared solid dispersion tablets was found in the range of 0.56-0.62 %. The values found for friability test of all prepared solid dispersion tablets were shown in table 6.

Batch code	Hardness	%Friability
SE 1	1.9±0.12	0.57
SE 2	1.7±0.09	0.59
SE 3	2.1±0.06	0.62
SE 4	1.5±0.10	0.56

Table 6 Hardness and % Friability of solid dispersion tablets.

Drug content

The drug content of the all prepared solid dispersion tablets were found in the range of 93.75-96.45 %. The values found for % drug content of all prepared solid dispersion were shown in table 7.

Batch	% Drug content
SE 1	95.74
SE 2	94.73
SE 3	96.45
SE 4	93.75

Table 7. % drug content of solid dispersion tablets.

In-vitro dissolution study

The prepared solid dispersion tablets were evaluated for In-vitro dissolution studies in pH 6.8 phosphate buffer & found results were shown in Table no.8. Among all prepared solid dispersion tablets SE3 batch shows higher % cumulative drug release it was found to be 97.57% in 30 min as compared to SE1, SE2 & SE4 batches. The plot of % cumulative drug release from all prepared solid dispersion tablets vs time in minute were shown in figure 4 and % CDR shown in table 8.

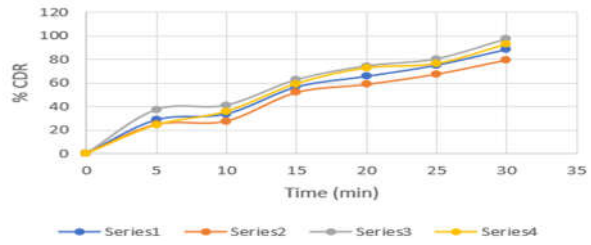


Figure 4 Plot of In-vitro dissolution profile of solid dispersion tablets.

Time (min)	SE 1	SE 2	SE 3	SE 4
0	0	0	0	0
5	28.74	24.83	37.38	24.29
10	33.72	27.66	41.13	35.74
15	56.68	52.09	62.75	59.35
20	65.82	58.97	74.49	72.74
25	75.30	67.74	80.56	76.38
30	88.78	79.75	97.57	92.84

Table 8 In-vitro dissolution profile of solid dispersion tablets.

Drug release kinetic studies

The model that gave higher regression coefficient value was considered as best fit model. The regression coefficient (v) values for formulations SE1 – SE4 were shown in table no 9. The drug release kinetic studies data obtained for all prepared solid dispersion tablets were shown in figure 5.

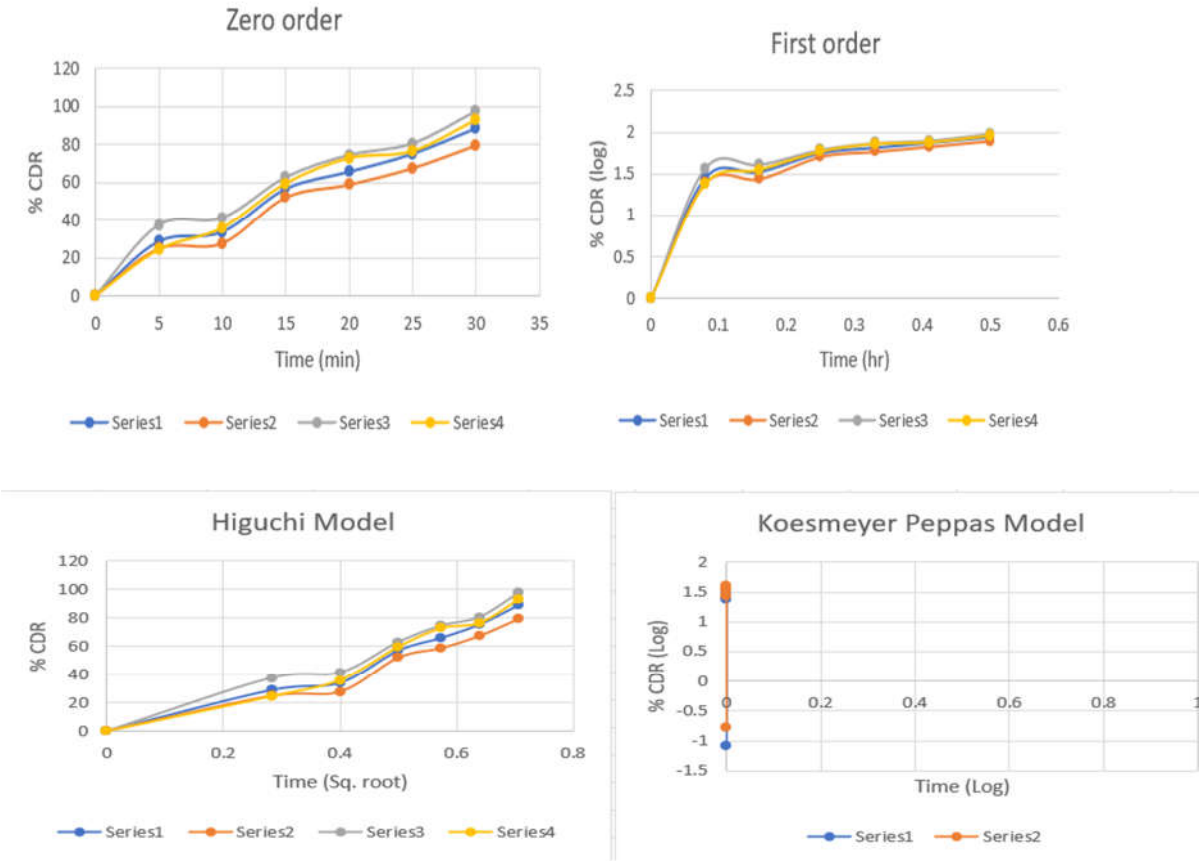


Figure 5 Drug release kinetic models for solid dispersion tablets.

Batch	Zero order model (R^2)	First order model (R^2)	Higuchi model (R^2)	Koesmeyer Peppas model (R^2)	Best fitted model
SE 1	0.968	0.622	0.967	**0.990**	Koesmeyer Peppas
SE 2	0.965	0.644	0.955	**1**	Koesmeyer Peppas
SE 3	**0.977**	0.879	0.860	0.956	Zero order model
SE 4	0.970	0.646	**0.962**	0.428	Higuchi model

Table 9. Drug release kinetic values.

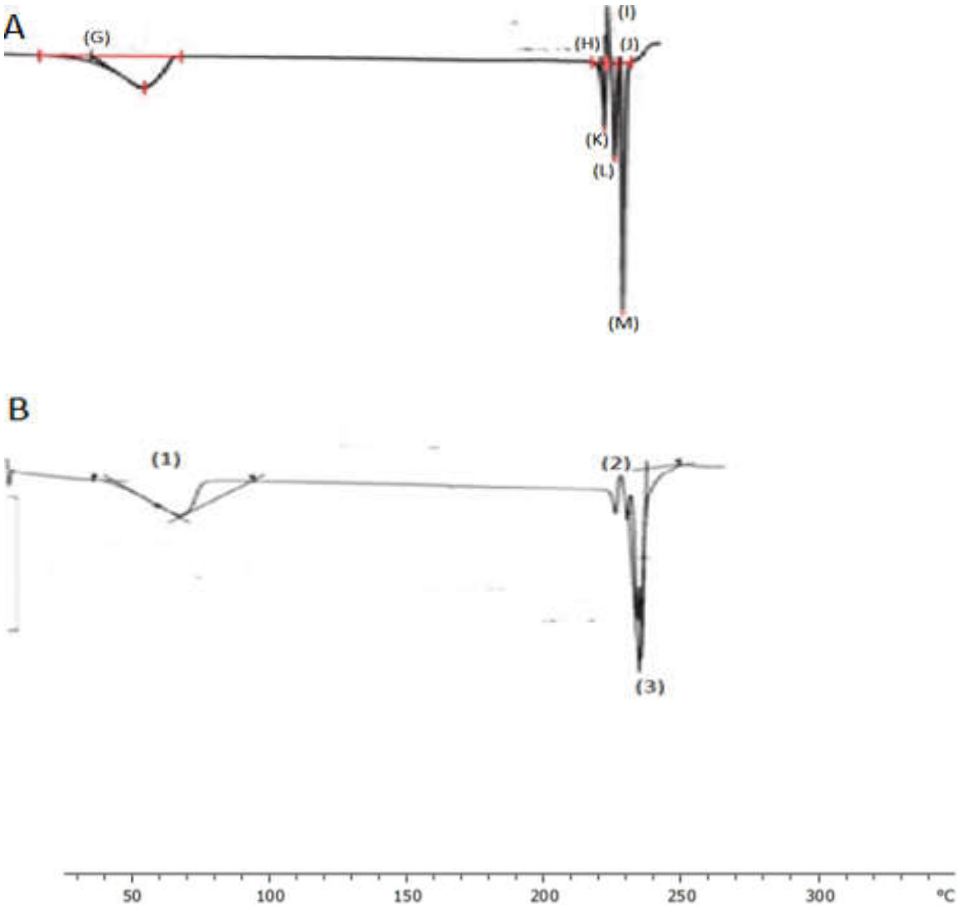
Stability Study

Stability studies were carried out according to ICH Guidelines for the selected solid dispersion tablet batch SE3 & results found were shown in table 10. The results revealed that there was no any significant change in the drug content which confirms the stability of the product after storage.

Batch SE 3	Percent drug content at Room Temperature	Percent Drug content at 40^0C Temperature
First Day	96.45 ±0. 23	96.41 ±0. 21
15th Day	96.39 ±0. 19	96.33 ±0. 17
30th Day	96.32 ±0. 18	96.29 ±0. 12
45th Day	96.26 ±0. 15	96.20 ±0. 25
60th Day	96.13 ±0. 21	96.07 ±0. 13

Table 10. Stability study of Batch SE3 at room temperature & 40ºC

DSC (Differential Scanning Calorimetry) –



(A) DSC of Pure Levofloxacin, (B) DSC OF SE3 Batch

The plain levofloxacin (A) showed an endothermic sharp peak at M (233.65ºC) & this same peak were also shown by (B) at 236.34ºC with more intensity in comparison with pure drug thermogram. (A) & (B) both thermographs have a broad peak at G & 1 with in temperature range 20 - 70ºC & 60.55ºC – 75.02ºC respectively. Both thermographs have almost similar values of Levofloxacin peaks in DSC studies. Also Both thermographs (A) & (B) shows an exothermic transition at I & 2 respectively, which is formed due to melting of crystallization form.

CONCLUSION

In present study solid dispersion tablets of levofloxacin were prepared by using β-CD & PEG 6000 carriers (polymers) by utilizing solvent evaporation method. From the results of present study, it was concluded that the solubility of drug was enhanced with β-CD & PEG 6000 polymers with increase in the carrier content i.e. β-CD there was increase in the enhanced dissolution rate. SE3 batch considered as optimized batch as it was shown highest % cumulative drug release i.e. 97.57 % in 30 min & also it was shown higher % drug content i.e. 88.78 %, 79.75 %, 92.84 % as compared to SE1, SE2, SE4 batches. The FT-IR and DSC of solid dispersion of levofloxacin β-CD & PEG 6000 shows that all the peaks of levofloxacin & polymers were as it is Hence, there was no interaction between drug & polymers & they were compatible with each other. A result of stability study indicated that the optimized solid dispersion tablet batch SE3 was stable & there was no significant changes observed in the drug content. Finally, it may be concluded that solid dispersion prepared by solvent evaporation method with β-CD & peg 6000 showed enhanced dissolution & solubility profile.

ACKNOWLEDGEMENT

Authors are very much thankful to principal of SVERI's College of Pharmacy, Pandharpur, Maharashtra, India for providing required facilities throughout present research work and constant encouragement.

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