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Particle Engineering and Spray Drying Process designing for Solubility Enhancement of Lopinavir

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ABSTRACT

To improve the solubility enhancement of solid dispersion of Lopinavir by spray-drying by adding the Soluplus as polymer that is compatible with Lopinavir, was evaluated and the process used for preparation of Spray dried solid dispersion was validated and the 1:3 ratio used for preparation of solid dispersion. Dissolution tests were carried out on several spray dried solid dispersion of Lopinavir and physical mixture. The solid dispersion characterized by DSC, XRD, % Entrapment Efficiency, solubility study, drug content determination, practical yield, dissolution studies.

Keyword: Lopinavir, Soluplus, Spray Drying Technique, Dissolution studies.

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INTRODUCTION

A significant portion of recently developed pharmaceutical molecules suffer from poor solubility and consequently low bioavailability, i.e., they belong to the bio pharmaceutics classification system (BCS) class IV. In a solid dispersion, the API and the polymer may interact by several mechanisms, including hydrogen bonds[1].The small particle size and better wettability of the drug–polymer solid dispersion are also important reasons that contribute to the observed improvements in bioavailability. Solid dispersion is defined as the dispersion of one or more active ingredients in an inert excipients or matrix (carrier), where the active ingredients could exist in finely crystalline, Solubilized or amorphous state [2].Spray drying technology can be defined as a unit operation in which a liquid stream (solution, suspension or emulsion)is constantly divided into very fine droplet (by a process known as atomization) into a glass compartment where they come in contact with hot gas and get dried into fine particles, which are further separated from the drying gas using a cyclone or a bag-filter. Spray drier scan operate in open cycle mode for aqueous based or in closed-loop mode for organic based system[3].spray drying is one of the most common techniques used to prepare solid dispersions due to the possibility of continuous manufacturing, ease of scalability, good uniformity of molecular dispersion and cost-effectiveness in large scale production with high recoveries (more than 95%) [4].Lopinavir is a poorly water-soluble drug and used for treatment of Anti-HIV drug [5].The Process validation is establishing documented evidence which provides a high degree of assurance that a specific process (such as the manufacture of pharmaceutical dosage forms) will consistently produce a product meeting its predetermined specifications and quality characteristics[6].Reason for process validation new product, change in site of manufacturing, change in batch size, change in equipment, change in the critical control parameters, change in vendor of API or critical Excipients, change in specification on input material [7].The HPLC provides not only useful quantitative information on drug loss but also insights into the number of degradation products formed and their corresponding amounts. Chromatographic method development can be a time-consuming and subjective process [8].

MATERIALS AND METHOD

Material

Lopinavir was kindly provided by Glenmark and the Polymer soluplus was provided by BASF (Thane) and the solvent ethanol, Acetonitrile and Methanol purchased through S.D. fine chemicals and Spray dryer (LabultimaLU 222 Advanced), HPLC (water 600 controller), FT-IR Spectrophotometer (Bruker-α), Dissolution Apparatus (Electrolab-TDT-08L), Water heater cum

shaker bath(Classic-Scientific), pH Meter (Hanna instrument,HI2211), Digital weighing Balance (Shimadzu, AUX220)

Experimental

Quantitative determination of lopinavir [9]

Method- HPLC

Accurately weighed amount (25 mg) of drug was dissolved in Methanol in a volumetric flask and the volume was made up to 25 ml with methanol. This stock solution (solution A) containing 1000µg/ml of Lopinavir. From stock solution making various dilutions in the concentration range 75-175 µg/ml for Lopinavir by adjusting the volume with water and 20µl solution was injected in HPLC, column used for HPLC analysis was Inertsil ODS C_{18} and particle size 4.6 mm, length of column is 25cm and the HPLC used for analysis was manufacturer by Water 600 controller. The mobile phase used for quantitative determination of Lopinavir was Buffer (pH3.0): MEOH: ACN (50:20:30) and flow rate was 1.2 ml/min and UV detector at 240 nm.

PREPARATION OF SOLID DISPERSION BY SPRAY DRYING TECHNIQUE[10, 11]

a) Screening of polymer

b) Preparation of solid dispersion by spray drying technique

c) Identification of drug polymer ratio

d) Identification of Critical process parameter

(I) Inlet temperature, (II) Solvent volume and (III) Flow Rate

The solid dispersion was prepared by using the spray drying technique (Labultima LU 222 Advanced) by Drug and polymer as 1:3 ratios. The weighed amount of Lopinavir and polymer dissolved in 20 ml ethanol solvent, the mixture stirred on magnetic stirrer at 520 rpm. Then the mixture spray through the spray dryer by setting critical process parameter shown in above Table 1

Table 1: Critical process parameter (CPP) of spray drying technique

Inlet temperature	45^0c
Outlet temperature	40^0c
Feed flow rate	1 ml/min
Solvent volume	20 ml

Solubility study[12]

The prepared Solid dispersion of Lopinavir was added in 10 ml of different solvent like 0.1N HCL, 7.2 buffer, 6.8 buffer and 5.4 buffer then the mixture kept in water heater cum shaker bath at temperature 37^0C for 48 hrs. The solution was removed and diluted up to 4 ml methanol and 20 ml injected in HPLC, column used for HPLC analysis was ODS C_{18} and particle size 4.6 mm, length of column is 25cm and the HPLC used for analysis was manufacturer by Water 600 controller. The

mobile phase used for quantitative determination of Lopinavir was Buffer (PH3.0): MEOH: ACN (50:20:30) and flow rate is 1.2 ml/min at 240 nm.

Preparation of physical mixture[13]

In vitro dissolution studies for physical mixture (1:3 ratio) were carried out using USP apparatus method with 900 ml of 0.1 N HCl as dissolution media, maintained at temperature 37±0.5^{0}C at100 rpm for 60 min. The 5 ml sample were withdrawn at 5, 10, 15, 20, 25, 25, 30, 35, 40, 45, 50, 55 and 60 minutes and replaced by 5 ml of fresh 0.1 N HCL dissolution media. The collected sample filtered and 20 µl samples injected in HPLC.

EVALUATION OF VALIDATED SOLID DISPERSION AND PHYSICAL MIXTURE

Practical Yield[14]

Percentage practical yield was calculated to know about percent yield of any method, thus its help in selection of appropriate ratio for preparation of Solid Dispersion (SDs).

$$\text{PY (\%)} = \frac{\text{Actual weight of solid dispersion}}{\text{Theoretical weight(Drug + carrier)}} \times 100$$

Drug content determination

Drug content was calculated by dissolving Solid Dispersion(SDs) equivalent to 20 mg SD in 20ml 0.1N HCL and filtered the solution, suitably diluting with up to 4ml Methanol (the 1ml filtrate dilute with 3 ml methanol) the dilute solution directly injected in HPLC and the mobile phase used as 50:20:30 (Buffer pH 3.0: MEOH: ACN) and the flow rate was 1.2 ml/min at wavelength 240 nm.

$$\text{Drug content (\%)} = \frac{\text{Amount of drug in SD}}{\text{Amount of Solid dispersion}} \times 100$$

Solubility study

The prepared Solid dispersion of Lopinavir was add in 10 ml of different solvent like 0.1N HCL, 7.2 buffer, 6.8 buffer and 5.4 buffer then the mixture kept in water heater cum shaker bath at temperature 37^{0}C for 48 hrs. The solution was removed and diluted up to 4 ml methanol and 20 ml injected in HPLC, column used for HPLC analysis was ODS C_{18} and particle size 4.6 mm, length of column is 25cm and the HPLC used for analysis was manufacturer by Water 600 controller. The mobile phase used for quantitative determination of Ritonavir was Buffer (PH3.0): MEOH: ACN (50:20:30) and flow rate is 1.2 ml/min at 240 nm.

Dissolution Studies

The dissolution profile of physical mixture (PM) and Solid dispersion were studied up to Time point (min) 5min to 100min with respect to % drug release hence the difference evaluated namely physical mixture (PM) and Solid Dispersion (SD).

Physical mixture

In vitro dissolution studies for physical mixture (1:3 ratio) were carried out using USP apparatus method with 900 ml of 0.1 N HCl as dissolution media, maintained at temperature 37±0.5^{0}C at100 rpm for 60 min. The 5 ml sample were withdrawn at 5, 10, 15, 20, 25, 25, 30, 35, 40, 45, 50, 55 and 60 minutes and replaced by 5 ml of fresh 0.1 N HCL dissolution media. The collected sample filtered and 20 µl samples injected in HPLC.

Solid Dispersion

In vitro dissolution studies for physical mixture were carried out using USP apparatus method in 900 ml of 0.1 N HCL dissolution media, maintained at temperature 37±0.5^{0}C at100 rpm for 60 min. The 5 ml sample were withdrawn at 5, 10, 15, 20, 25, 25, 30, 35, 40, 45, 50, 55 and 60 minutes and replaced by 5 ml of fresh 0.1 N HCL dissolution media. The collected sample filtered and 20 µl samples injected in HPLC.

% Entrapment Efficiency [15, 16]

Prepared Solid Dispersion (SDs) adds in 6.8 buffers in test tubes the mixture kept in water heater cum shaker bath at 37^0 for 48 hrs. Then the solution filtered, suitably dilution with Methanol and phosphate buffer and the solution injected in HPLC.

$$\%EE = \frac{\text{Calculated drug concentration}}{\text{Theoretical drug concentration}} \times 100$$

Differential scanning Calorimetry

Differential scanning Calorimetry (DSC) has been a widely used calorimetric tool to study the solid-state interaction of drug and Soluplus polymer. Modulated temperature DSC equipped with an intercooler (DSC Q20 V24.11 build 124) to calibrate the temperature and enthalpy scale. The heat flow range 0.5-4.5 w/g over a temperature range is 40-390^{0}C.

X-ray diffraction

X-RD analysis was carried out on Peak Data ASC II Dump (XRD) instrument with scan range 10.000-80.000, scan speed 5. 000 degree/min, sampling pitch and sampling pitch preset time 0.0200 (deg), 0.24 sec.

RESULTS AND DISCUSSION

QUANTITATIVE DETERMINATION OF LOPINAVIR

Method- HPLC

The stock solution was used to prepare 75, 100, 125, 150, 150 µg/ml concentration of Lopinavir in Methanol, then the solution diluted and 20 µl injected in HPLC. Whenever Lopinavir drug solution analyzed by HPLC it shows sharp peak at retention time 2.1 min. From above calibration curves of Lopinavir in methanol it was concluded that when graph of AUCVs. Concentration is plotted the graph shows that Lopinavir shows linearity in 75-175 ppm concentration and shows linearity when AUC was taken at 240 nm and for details See Figure 1 and 2 and Table 2

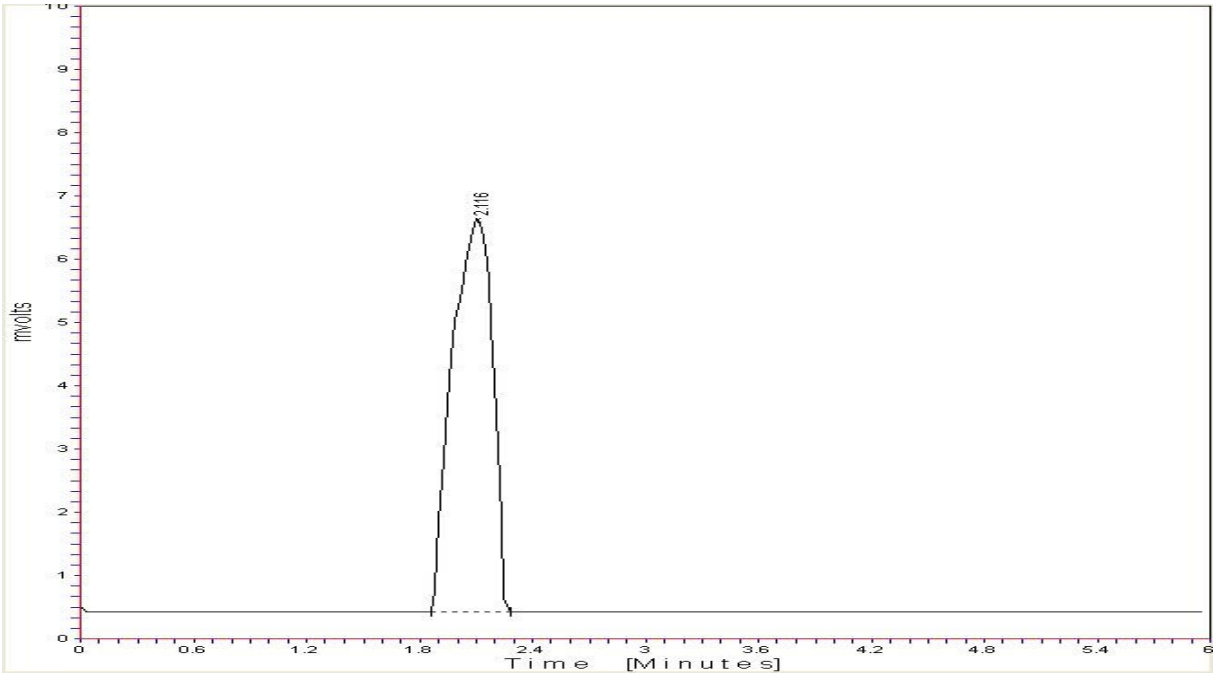

Figure 1: HPLC Chromatogram of Lopinavir in Methanol

Table 2: AUC of different Lopinavir solutions

Sr. No.	Concentration µg/ml	AUC
1	75	60350.56
2	100	78067.44
3	125	99009.06
4	150	115073.5
5	175	135157.9

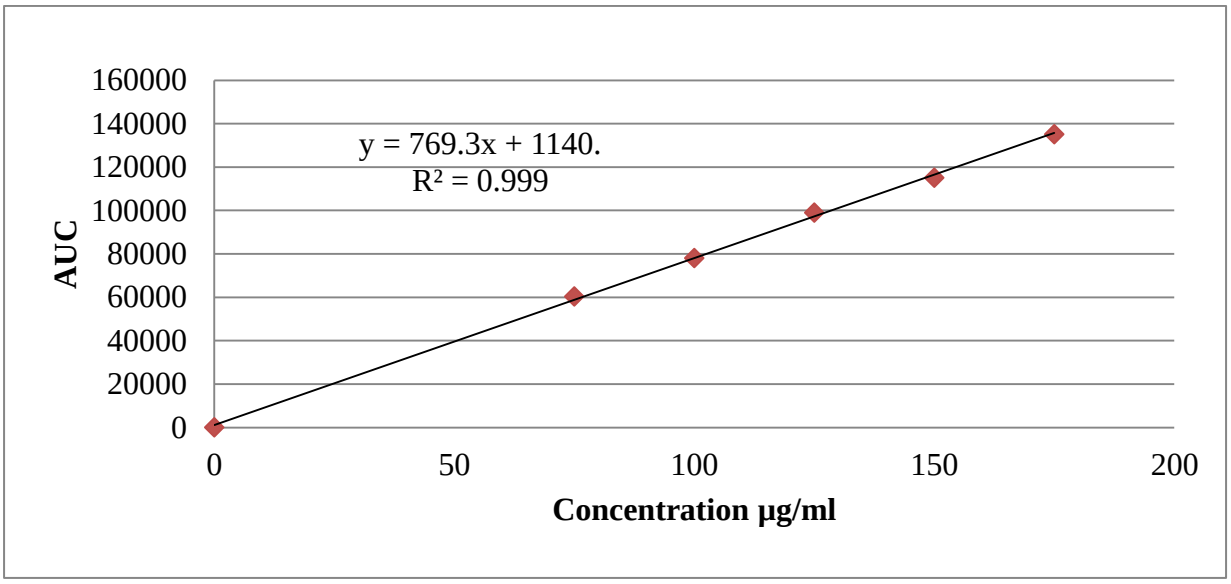

Figure 2: Calibration Curve of Lopinavir

Preparation of solid dispersion by spray drying technique

Solubility study

The final batch of solid dispersion of Lopinavir with Soluplus shows the higher solubility in 0.1 N HCL, pH 7.2 buffer compare with pH 6.8 buffers and pH 5.4 buffers compare with Poloxamer 407, Poloxamer 188 and Kollidon VA 64. The description of solubility study refers Table no.4 and Figure No. 3, hence for details of Critical Process Parameters (CPP) given in Table no. 1 and 3.

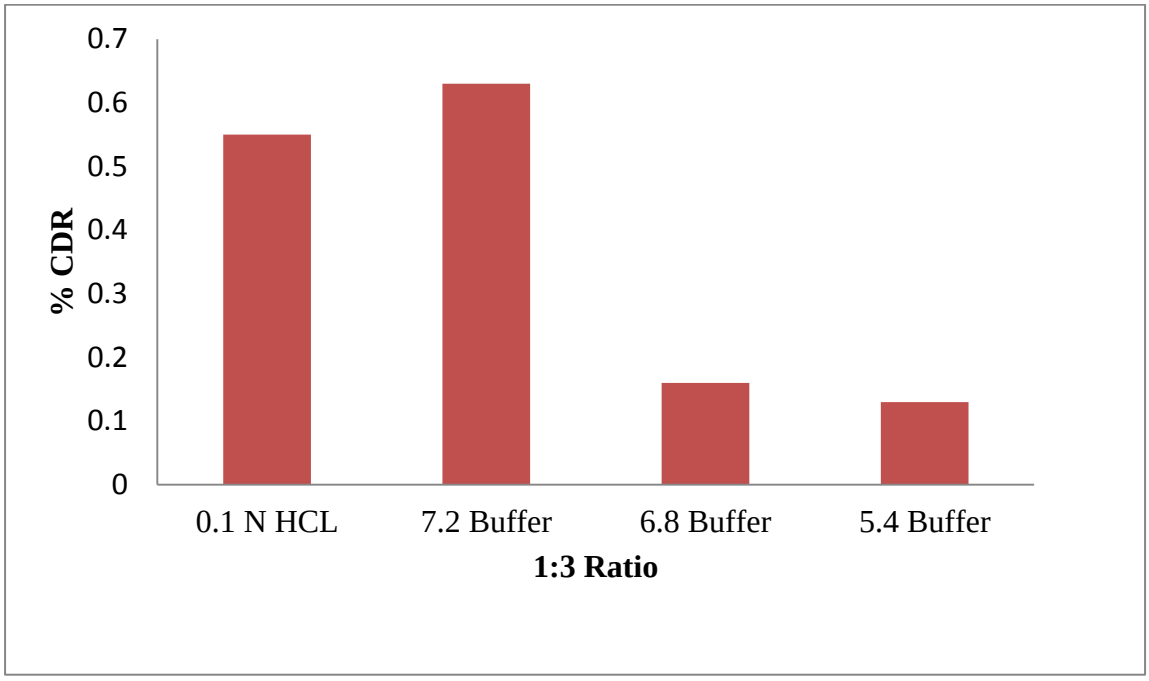

Figure 3: Solubility of Prepared Lopinavir Solid Dispersion (SD)

Table 3: Solid dispersion prepared by spray drying technique

Batch	Ratio	Inlet temperature (^{0}C)	Outlet temperature (^{0}C)	Solvent volume (ml)	Flow rate (ml/min)	Yield (%)
A	1:3	45^{0}C	40^{0}C	20 ml	1	14.66

Table 4: Solubility of optimized batch

Batch	Solubility (µg/ml)			
	0.1N HCL	7.2 Buffer	6.8 Buffer	5.4 Buffer
A	0.55	0.63	0.16	0.12

EVALUATION OF VALIDATED SOLID DISPERSION BATCH

Practical yield

The practical yield of solid dispersion was found to be 14.5 %w/w. in Table No. 5

Determination of Drug content

The drug content of Lopinavir Solid Dispersion prepared using Soluplus (1:3 ratios) in 20 ml ethanol at 45^{0}C and 1 ml/min flow rate Refer Table No.3.

Solubility study

The final batch of solid dispersion of Lopinavir with Soluplus shows the higher solubility in 0.1 N HCL, pH 7.2 buffers, pH 6.8 buffer and pH 5.4 buffers compare with Poloxamer 407, Poloxamer 188 and Kollidon VA 64

% Entrapment Efficiency

The entrapment efficiency of Lopinavir in 6.8 buffers was found to be satisfactory. The % Entrapment Efficiency of in 6.8 phosphate buffer found to be 48% see Table 5

Dissolution Studies

The dissolution profile of physical mixture (PM) and Solid dispersion (SD) were studied up to Time point (min) 5min to 100min with respect to % drug release in Table 6 hence the difference evaluated namely physical mixture (PM) and Solid Dispersion (SD). The release graphical presentation refers Figure 4

Table 5: % Entrapment Efficiency (% EE)

Sr. No.	Buffer Media	% Entrapment Efficiency
1	6.8 Phosphate Buffer	48

Table 6: Dissolution studies of physical mixture and solid dispersion

Time (Min)	% of Drug Release (PM)	% of Drug Release (SD)
5	0.844	26.50
10	1.368	36.00
15	1.711	46.50
20	2.139	51.00
25	2.441	59.25

30	2.880	60.75
35	3.031	63.75
40	3.233	65.25
45	3.362	68.25
50	3.642	70.50
55	3.933	72.75
60	4.362	75.50
65	4.441	78.62
70	4.721	81.25
75	4.880	84.00
80	5.243	86.87
85	5.683	87.55
90	6.052	91.00
95	6.601	97.45
100	7.101	99.88

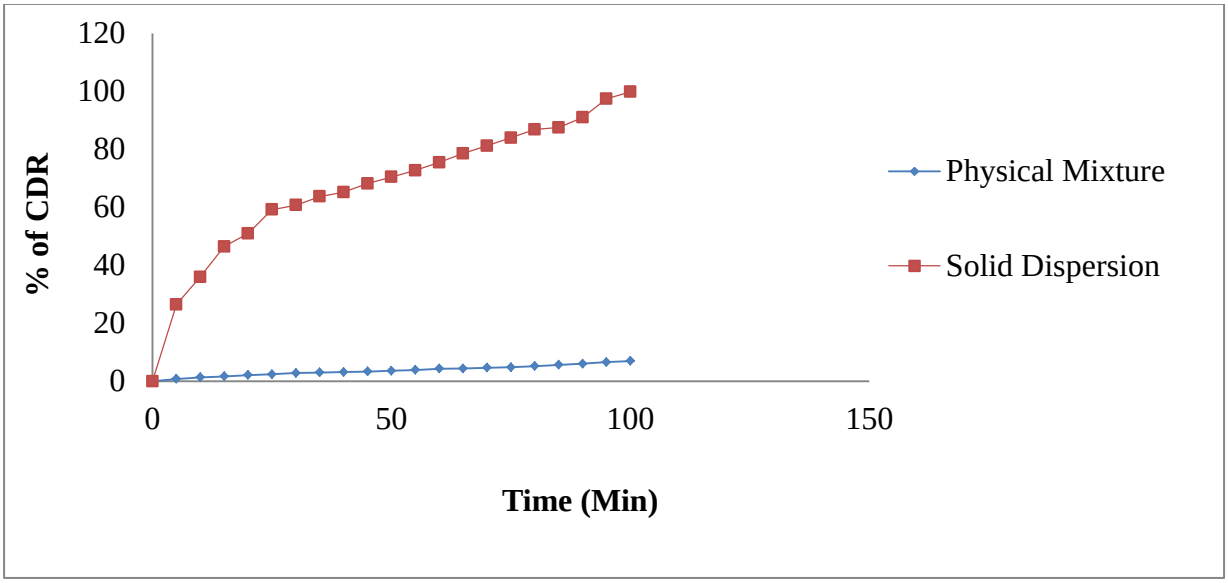

Figure 4: Drug Release Profile of Lopinavir and Physical Mixture with Soluplus and Solid Dispersion

Physical mixture and Solid dispersion

The dissolution studies of physical mixture were carried out by using USP paddle apparatus, in 900 ml 0.1 N HCL and release profile data was analyzed at different time interval and the dissolution studies of solid dispersion was carried out by using USP paddle apparatus, in 30 ml 0.1 N HCL and release profile data was analyzed at different time interval shown in bellows table No.6 and for graphical presentation refer Figure 4.

Differential scanning Calorimetry

a) Physical Mixture

b) Solid dispersion

The physical mixture of Lopinavir with Soluplus (1:3 ratios) shows sharp endothermic peak at 125.79 ^{0}C indicating unchanged form of drug whereas polymer Soluplus transition peaks at 326.68 ^{0}C and 358. 86 ^{0}C. In DSC thermogram of Solid Dispersion (SD) (See Figure No: 5 and 6) the Lopinavir not shown sharp peak indicating its entrapment polymer.

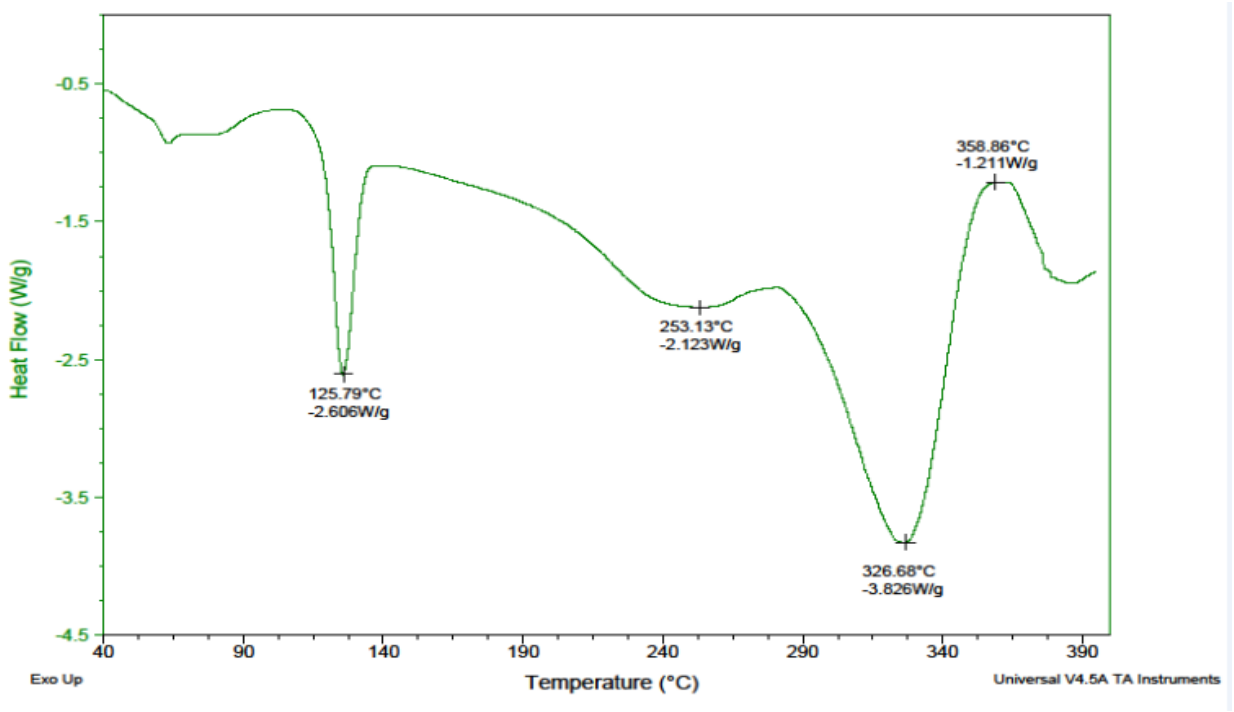

Figure 5: a) DSC Thermo gram of Physical Mixture

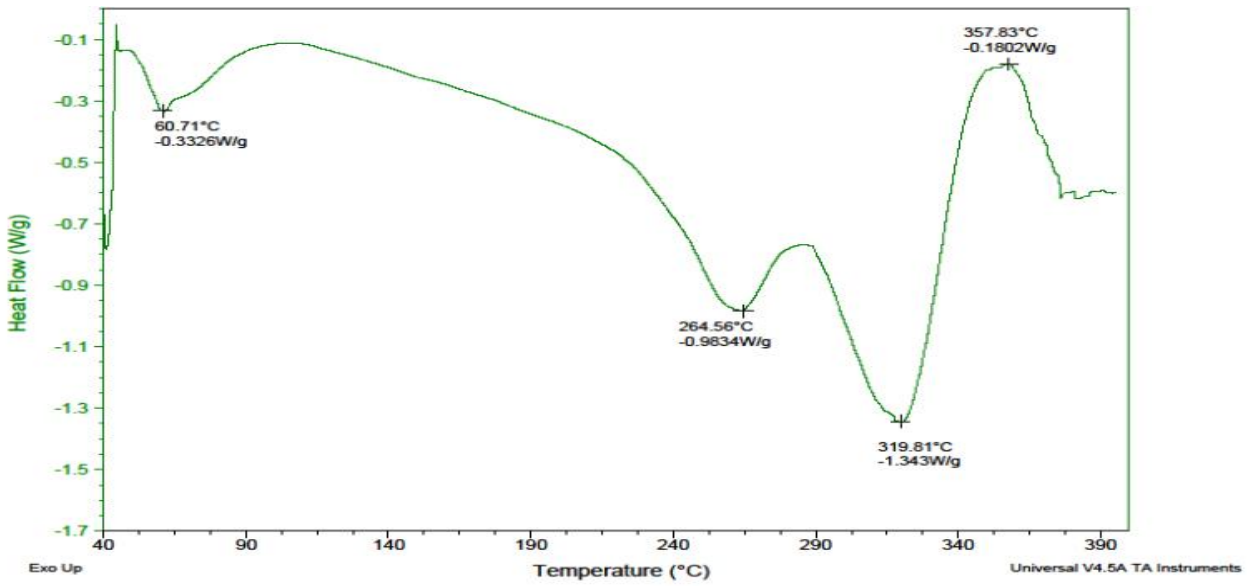

Figure 6: b) DSC Thermogram of Solid Dispersion

X- Ray diffraction

Lopinavir and Physical Mixture

The graphical analysis it was found that given sample of drug was amorphous in nature because peaks pattern was random in nature and as physical mixture contains drug as well as excipients it shows variations in the XRD graph. Because drug is amorphous in nature & excipients is crystalline in nature. But physical mixture was found to be amorphous in nature. See Figure No.7.

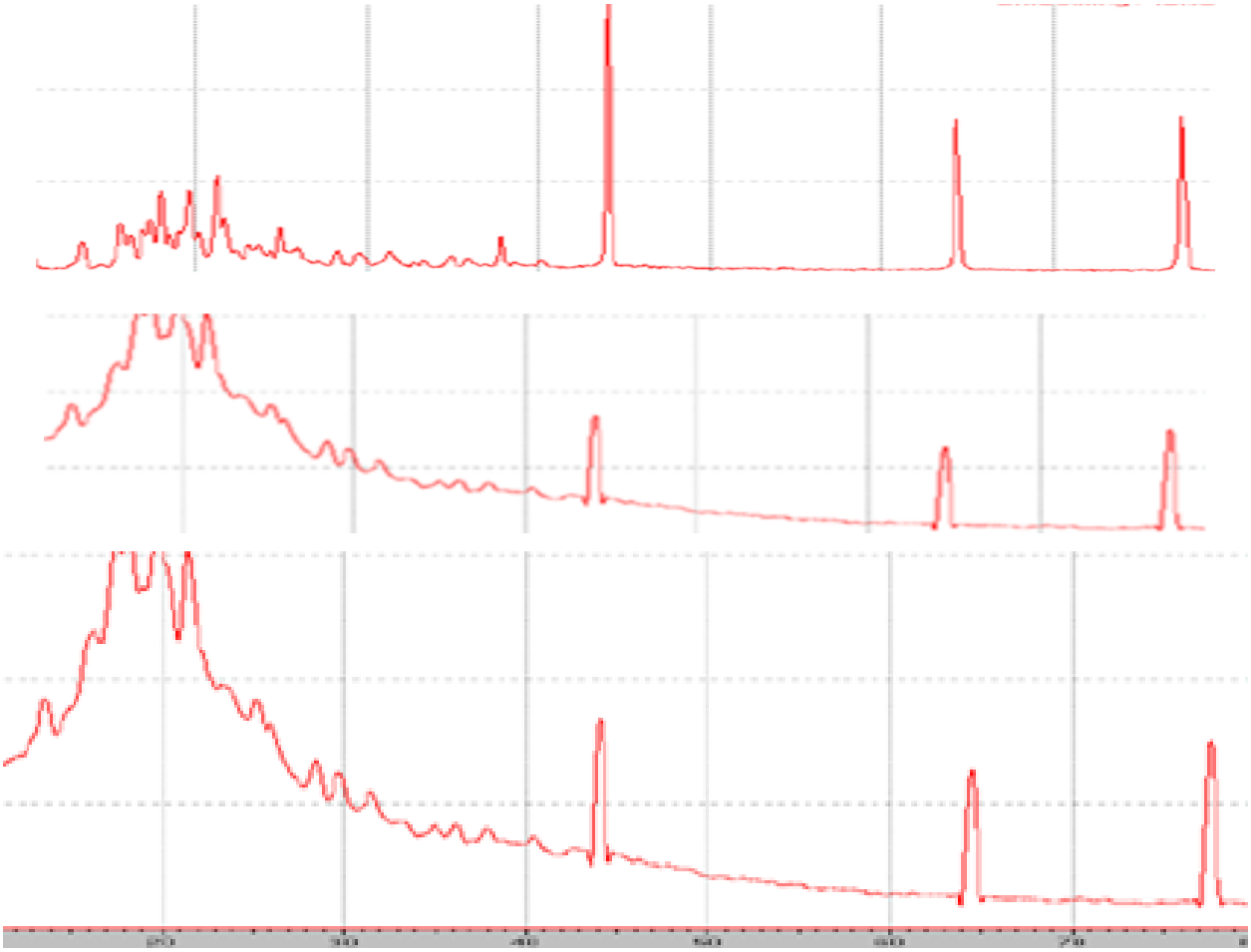

Figure 7: X-ray Diffraction Spectra of Lopinavir and Physical Mixture

CONCLUSION

A significant portion of recently developed pharmaceutical molecules suffer from poor solubility and consequently low bioavailability, i.e., they belong to the biopharmaceutical classification system (BCS) class II and class IV drugs. In a solid dispersion, the API and the polymer may interact by several mechanisms, including hydrogen bonds. To improve the solubility enhancement of solid dispersion of Lopinavir by spray-drying by adding the Soluplus as polymer

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