ENHANCEMENT OF SOLUBILITY AND DISSOLUTION RATE OF LOPINAVIR BY USING SOLID DISPERSION TECHNIQUE WITH DIFFERENT CARRIERS

[1]Leelakrishna Chowdary Anumolu, [2]Dr. Yarlagadda Ankamma Chowdary, [3]Venkata Basaveswara Rao Mandava
[1] Research Scholar, [2] Professor, [3]Professor,
[1] Faculty of Pharmaceutical sciences, Krishna University, Machilipatnam, India.
[2] NRI College of Pharmacy, Pothavarappadu, India.
[3] Krishna University, Machilipatnam, India.

Abstract: *The solid dispersion has become an established solubilization technology for poorly water-soluble drugs to enhance absorption. Since a solid dispersion is basically a drug–polymer two-component system or dispersion of one or more active ingredients in an inert excipient or matrix, where the active ingredients could exist in finely crystalline, solubilized, or amorphous states.*

The objective of this investigation was to formulate solid dispersions of poorly water-soluble drug Lopinavir using a water-soluble or hydrophilic carriers like ***Soluplus*** *(polyvinyl caprolactam–polyvinyl acetate–polyethylene glycol graft copolymer),* ***Kollidon VA 64*** *(vinylpyrrolidone-vinyl acetate copolymers) using solvent evaporation method in various ratios of drug and carrier such as 1:1 and 1:2 and carriers like* ***Kolliphor® P188*** *(Poloxamer 188) and* ***Gelucire 50/13*** *(Polyoxylglycerides-Hydrophillic grade) using Fusion method in various ratios of drug and carrier such as 1:1 and 1:2 to improve the Solubility and dissolution rate of Lopinavir.*

The prepared solid dispersions were evaluated for pre-formulation characteristics, drug content, solubility study, dissolution behavior and SEM analysis. Based on the results, all the physical characteristics evaluated were found to be satisfactory and formulation having carrier Soluplus with drug to carrier ratio of 1:2 was found to be showing enhanced solubility results when compared to other formulations using solvent evaporation method. There is a significant increase in drug release with increase in drug to polymer ratio. Finally, Solid dispersion was formulated into controlled release dosage forms such as Tablets.

Index Terms: *Lopinavir, Soluplus, Kollidon VA 64, Kolliphor® P188, Gelucire 50/13, Solvent evaporation, Fusion, Solubility, Dissolution, Solid Dispersion, Tablet.*

I. INTRODUCTION

Solubility is a significant physicochemical factor affecting absorption of drug and its therapeutic effectiveness. The low dissolution rate and low solubility of drug substances in water in aqueous G.I.T fluid frequently leads to inadequate bioavailability. Newly discovered chemical molecules have high therapeutic activity but have low aqueous solubility which results in poor absorption and bioavailability.

Many methods were reported for solubility and dissolution enhancement of poorly soluble drug such as micronization, complexation, particle size reduction, etc. However, all these methods have limitations like micronized powder having high energetic surface, which shows poor flow property and particles often agglomerated. For solubility and dissolution rate enhancement of poorly soluble drugs, abundant commercially viable methods are such as liquisolid, in which drug in solution state or dissolved drug is adsorbed over insoluble carriers. Solid dispersion is the one of the promising method to formulators to enhance the solubility, absorption of several insoluble drugs and simplicity of preparation, ease of optimization, and reproducibility.

The term 'solid dispersion' means the drug is dispersed in a biologically inert matrix, usually with a view to enhancing oral bioavailability. A Solid dispersion generally composed of two components- the drug and the polymer matrix. Numerous methods are existing to prepare the solid dispersions such as melting method, solvent evaporation method, fusion method, kneading method, melting method, spray drying method, co-grinding method, lyophilization technique, hot melt extrusion, melt agglomeration, supercritical fluid (SCF) technology etc. A variety of hydrophilic carriers have been investigated for enhancement of dissolution characteristics and bioavailability of poorly aqueous-soluble drugs.

Lopinavir is an anti-retroviral drug of protease inhibitor used for the treatment of HIV infections. According to biopharmaceutical classification system (B.C.S)-II. It is a poorly water soluble drug, having bio-availability of less than 5% and high permeability so it was chosen as a model for this research work. Formulation development would lead to be failure if drug having poor aqueous solubility. Low oral bioavailability of drug may be due to poor aqueous solubility, high first pass metabolism and efflux transport. Lopinavir shows poor bioavailability when administered orally. The major reason for poor bioavailability is poor drug solubility characteristics, followed by its first pass metabolism.

Various carriers such as Soluplus (polyvinyl caprolactam–polyvinyl acetate–polyethylene glycol graft copolymer), Kollidon VA 64 (vinylpyrrolidone-vinyl acetate copolymers), Kolliphor® P188 (Poloxamer 188) and Gelucire 50/13 (Polyoxylglycerides-Hydrophillic grade) have been investigated for improvement of dissolution characteristics and bioavailability of poorly aqueous soluble drugs

II. MATERIALS AND METHODS

Lopinavir was obtained as a Gift sample (Microlabs Ltd. Bangalore), carrier Soluplus, Kollidon VA 64 and Kolliphor® P188 was obtained as a Gift sample (BASF SE Pharma) Gelucire 50/13 was obtained as a Gift sample from Gattefosse, Methanol were purchased from S.D Fine Chem Ltd., Mumbai and Himedia Laboratories Pvt. Ltd. Purified water obtained from Milli Q Plus (Millipore) was used for all experiments. All the carriers used were of analytical grade. Equipment's used in the formulation study are Analytical Precision Balance and UV Visible Spectrophotometer (PERKIN ELMER LAMBDA 35)

III. RESEARCH METHODOLOGY

Formulation of solid dispersions of Lopinavir was done using carriers Soluplus, Kollidon VA 64 using solvent evaporation method and carriers Kolliphor® P188 and Gelucire 50/13 using Fusion method in various ratios of 1:1 and 1:2. The study details are as follows;

3.1 Preparation of solid dispersion.

For preparation of solid dispersions, solvent evaporation method and Fusion method were selected for the Soluplus, Kollidon VA 64 and Poloxamer P188, Gelucire 50/13 respectively. In order to optimize drug to carrier ratio, solvent evaporation mixture of Lopinavir with Soluplus and Kollidon VA 64 were prepared in different ratios of 1:1 and 1:2.
Along with these mixtures solvent dispersion mixtures of Drug: Poloxamer P188, Drug: Gelucire 50/13 were prepared using fusion method in different ratios of 1:1 and 1:2.

3.1.1 Solvent Evaporation:

Solid dispersions of Lopinavir were prepared by solvent evaporation technique. Required quantities of Lopinavir and selected carriers (Soluplus, Kollidon VA 64) were weighed separately to get drug: polymer ratio of 1:1, 1:2. The mixture was prepared in ratio of 1:1, and 1:2 for each carrier were added separately in a beaker containing methanol and the solution was vigorously stirred on the magnetic stirrer until the entire methanol was evaporated to get a solid dispersion.

3.1.2 Fusion Method:

In this method, the drug and carriers were weighed. The selected carriers (Poloxamer P188 and Gelucire 50/13) were heated or melted individually with respective to their melting points of 52°C and 50 °C to accomplish a homogenous dispersion respectively. Then the weighed drug was added to the melted carriers. After the drug incorporation with carriers, mixture was dried and passed through the sieve no.80 and dispersion was collected individually.

Table 1: Formulation details of solid dispersions

S. No.:	Formulation	Drug-Carrier ratio	Formulation Code
1.	Pure Drug	-	PD
2.	API + Soluplus	1:1	LSD1
		1:2	LSD2
3.	API + kollidon VA 64	1:1	LSD3
		1:2	LSD4
4.	API + Poloxamer 188	1:1	LSD5
		1:2	LSD6
5.	API + Gelucire 50/13	1:1	LSD7
		1:2	LSD8

IV. RESULTS AND DISCUSSION.

4.2.1 Scanning Electron Microscope Study (SEM)

The electronic microscopy was carried out using a scanning electron microscope (JEOL Model JSM-6390LV) to determine the crystal shape and crystal size of solid dispersion. The samples of pure drug and selected solid dispersion were mounted on an aluminum stub using a double-sided adhesive tape and then making it electrically conductive by coating with a thin layer of gold (approximately 20 nm) in vacuum. The scanning electron microscope was operated at an acceleration voltage of 20 kV.
SEM photographs for Lopinavir and Solid dispersion was shown in Figure 1 and 2.

From the below fig 1 & fig 2, pure Lopinavir was irregular crystalline and Solid dispersion was showing uniform dispersion and drug particles are entrapped within the carrier.

Fig 1: SEM image of Pure Lopinavir

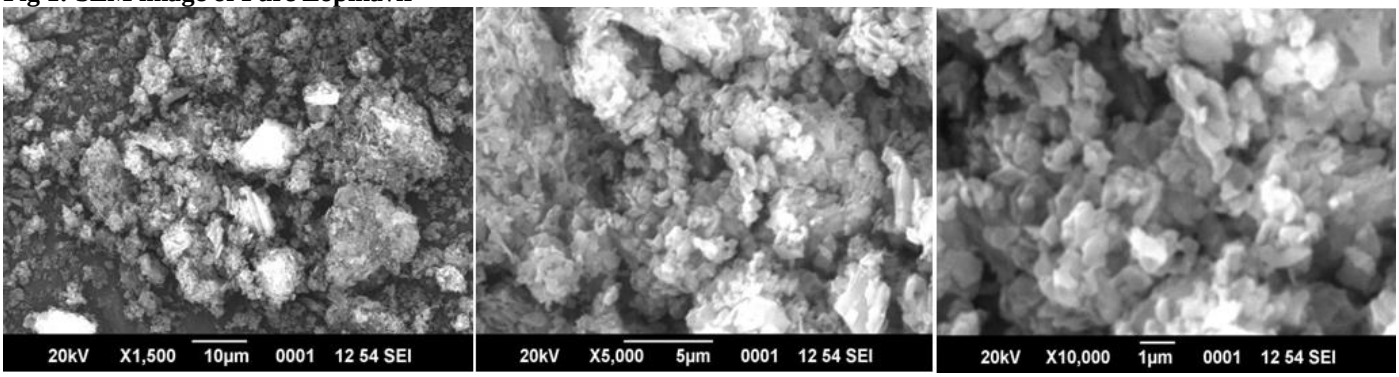
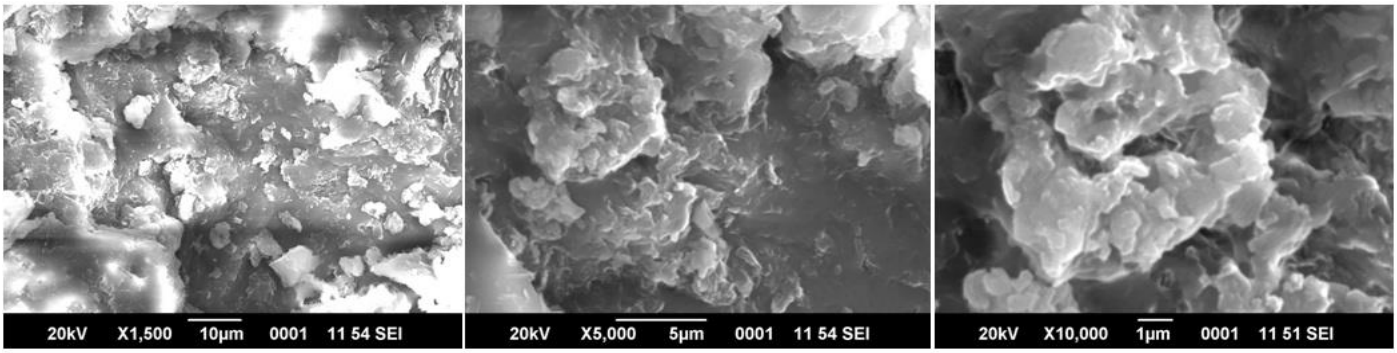


Fig 2: SEM image of Solid Dispersion (LSD2)



4.2.2 Saturation Solubility Study for Lopinavir:

Saturation solubility of lopinavir was determined by adding excess amount of Lopinavir in vials containing distilled water separately. The samples were subjected to shaking for 24 hrs. on a magnetic stirrer. The resultant suspension was then filtered through Whatmann filter paper No.1 and suitably diluted with distilled water. Finally, the samples were analyzed by UV-Spectrophotometer at 260nm.

Table 2: Saturation Solubility Study for Lopinavir and Solid Dispersion

S. No	Medium	Average Solubility (mg/ml)
1	Distilled Water	0.91
2	4.6 pH acetate buffer	3.87
3	6.8 pH phosphate buffer	6.41
4	0.1N HCl	2.91

Saturated solubility studies were conducted for Lopinavir using different dissolution media. Lopinavir showed maximum solubility in 6.8 pH phosphate buffer, which indicates that 6.8 pH phosphate buffer is ideal dissolution medium for Lopinavir.

4.2.3 Estimation of drug content

Solid Dispersion equivalent to 200 mg of Lopinavir were weighed accurately, dissolved in the 50 ml of 6.8 pH phosphate buffer and sonicated for 20 minutes. The solution was filtered, diluted suitably. Drug content was analyzed at 260 nm by UV spectrophotometer. The Drug Content was determined using the following equation:

$$\text{Drug Content} = \frac{\text{Abosrbance of Std. (Cstd.) x100}}{\text{Absorbance of Test (Ctest).}}$$

Table 3: Calibration Curve for the Estimation of Lopinavir		
S. No	**Concentration**	**Absorbance**
1.	0	0
2.	2	0.125
3.	4	0.246
4.	6	0.357
5.	8	0.475
6.	10	0.581

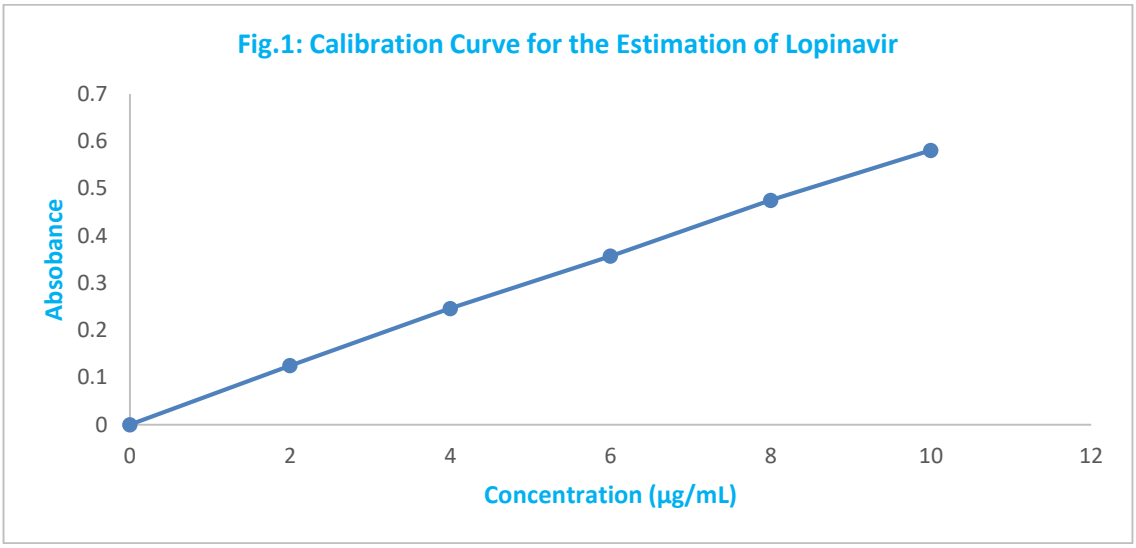


Table 4: % of drug content in solid dispersion	
Solid dispersion	**Drug Content (mg)**
LSD1	95.4±0.02
LSD2	97.8±0.02
LSD3	97.2±0.02
LSD4	95.4±0.02
LSD5	97.9±0.02
LSD6	96.8±0.02
LSD7	95.5±0.02
LSD8	97.9±0.02

4.2.4 Dissolution Study:

Dissolution rate of Lopinavir and Solid dispersion prepared by different methods in different ratios were measured by using USP type II (paddle type) dissolution test apparatus (Lab India-8 station Dissolution test apparatus) in 900 ml of 6.8 pH phosphate buffer with 50 rpm at temperature of 37 ± 0.5°C. Drug and solid dispersion equivalent to 200 mg of Lopinavir was used in each test. Aliquots of 5 ml were withdrawn through a Syringe at different time of intervals. The aliquots were assayed by UV spectrophotometer at 260 nm.

Dissolution profiles of the Lopinavir and solid dispersions was represented in Table 3 and 4. Based on the amount of drug release it was observed that, the solid dispersion technique has improved the dissolution rate of all formulations as compare to pure Lopinavir to great extent. In addition, Figures 2 and 3 represents the dissolution profiles were plotted as the percentage of dissolution from the pure drug and solid dispersions. All values expressed in percentage cumulative drug release

From the dissolution study, it is clearly observed that the dissolution rate of Lopinavir is low because of only 48.5% of drug dissolved in 45 minutes and all solid dispersions batches shows significantly enhanced dissolution rate of 14 to 95% in 45 minutes. The more improvement in a dissolution rate was observed in solid dispersion batch LSD2 which comprises of Drug: carrier (Soluplus) in the ratio of 1:2 that is prepared by solvent evaporation method.

Table 5: Dissolution profile for Lopinavir Solid Dispersions					
Time	Amount of drug dissolved (mg/mL)				
	Pure Drug	Soluplus		kollidon VA 64	
		Soluplus (1:1)	Soluplus (1:2)	Kollidon VA64 (1:1)	Kollidon vA64 (1:2)
0	0	0	0	0	0
5	12.09	20.4	28.66	30.24	32.45
10	18.99	31.2	46.05	43.22	44.85
15	26.4	43.2	68.56	55.77	58.98
20	32.33	54.6	79.88	62.22	70.04
30	40.04	64.56	83.05	70.24	75.13
45	48.94	77.32	94.6	79.88	84.45
Sample Name	-	**LSD1**	**LSD2**	**LSD3**	**LSD4**

FIG.2: DISSOLUTION COMPARISION OF LOPINAVIR SOLID DISPERSIONS USING SOLUPLUS AND KOLLIDON IN 1:1 AND 1:2 RATIO

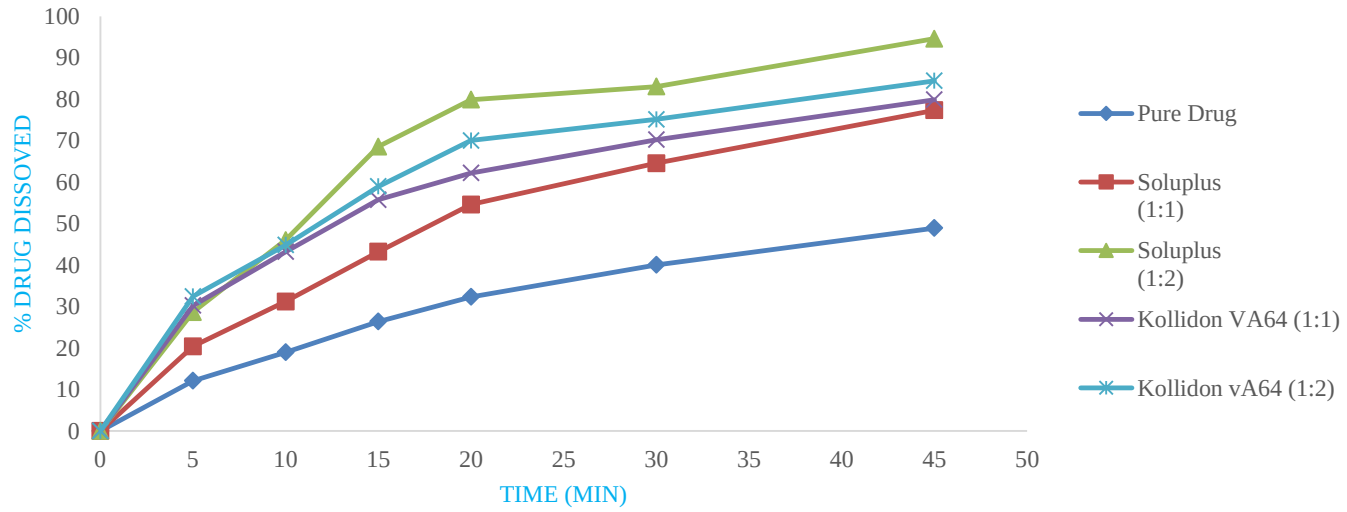
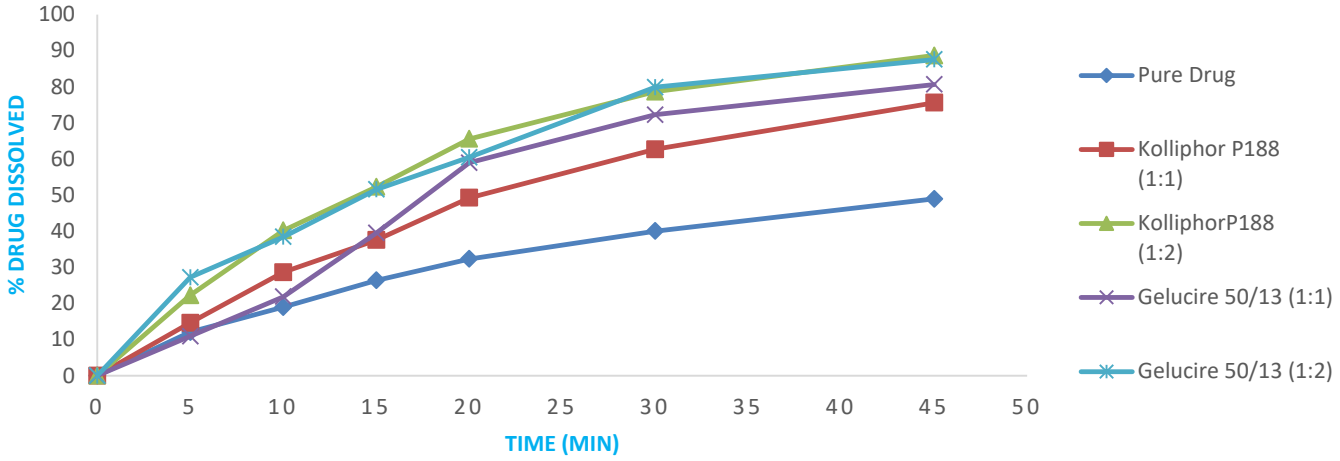


Table 6: Dissolution profile for Lopinavir Solid Dispersions					
Time	Amount of drug dissolved (mg/mL)				
	Pure Drug	Poloxamer 188		Gelucire 50/13	
		Kolliphor P188 (1:1)	KolliphorP188 (1:2)	Gelucire 50/13 (1:1)	Gelucire 50/13 (1:2)
0	0	0	0	0	0
5	12.09	14.64	22.26	10.93	27.22
10	18.99	28.66	40.22	21.88	38.45
15	26.4	37.54	52.28	39.5	51.54
20	32.33	49.24	65.54	58.94	60.45
30	40.04	62.66	78.64	72.24	79.85
45	48.94	75.55	88.64	80.62	87.54
Sample Name	-	**LSD5**	**LSD6**	**LSD7**	**LSD8**

FIG.3: DISSOLUTION COMPARISION OF LOPINAVIR SOLID DISPERSIONS USING KOLLIPHOR P188 AND GELUCIRE 50/13 1:1 AND 1:2 RATIO



V. CONCLUSION

- The physical characteristics of Solid dispersions with proposed carriers were found to be satisfactory.
- Based on the images of SEM analysis, it was found that the nature of pure Lopinavir was irregular crystalline and Solid dispersion was shown dispersion was uniform and drug particles are entrapped within the carrier.
- Saturated solubility studies were conducted for Lopinavir using different dissolution media. Lopinavir showed maximum solubility in 6.8 pH phosphate buffer, which indicates that 6.8 pH phosphate buffer is ideal dissolution medium for Lopinavir.
- Based on the dissolution results of Lopinavir with different carriers, it was observed that the % drug release is more in the Solid dispersion with Drug: Soluplus (1:2) [LSD2] when compared to other solid dispersion formulations. There is a significant increase in drug release with increase in drug to polymer ratio. It can be concluded that enhancement of solubility and dissolution rate of lopinavir was achieved using solid dispersion technique with selected carrier of Drug: Soluplus (1:2) [LSD2]
- Henceforth, the controlled release tablet formulations were formulated with the Solid dispersion with Drug: Soluplus (1:2) [LSD2] and using the polymers having the property of sustained release action.

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