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Enhancement of Solubility, Dissolution and Absorption Rate of Tenofovir by using Solid Dispersion Technique with Different Carriers

Leelakrishna Chowdary Anumolu[1], Yarlagadda Ankamma Chowdary[2]*, Venkata Basaveswara Rao Mandava[3] and R. L. C. Sashidhar[4]

1. Department of Pharmaceutical Sciences, KrishnaUniversity, Machilipatnam, Andhra Pradesh, **INDIA**
2. NRI College of Pharmacy, Pothavarappadu, Andhra Pradesh, **INDIA**
3. Krishna University, Machilipatnam, Andhra Pradesh, **INDIA**
4. Chebrolu Hanumaiah Institute of Pharmaceutical Sciences, Guntur,Andhra Pradesh, **INDIA**

Email: yarlagaddaac@yahoo.co.in

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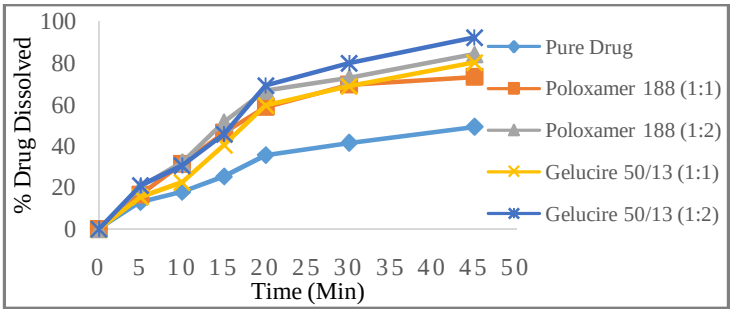
ABSTRACT

The solid dispersion has become an established solubilization technology for poorly water-soluble drugs to enhance drug absorption ability. 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 etc. A variety of solubility enhancement carriers have been investigated for enhancement of dissolution characteristics and bioavailability of poorly aqueous-soluble drugs. The objective of this investigation was to formulate solid dispersions of poorly water-soluble drug tenofovir using a water-soluble or hydrophilic carriers like Soluplus, Kollidon VA 64 using solvent evaporation method in various ratios of drug and carrier such as 1:1 and 1:2 and carriers like Poloxamer188 and Gelucire 50/13using fusion method in various ratios of drug and carrier such as 1:1 and 1:2 to improve the solubility and dissolution rate of tenofovir. The prepared solid dispersions were evaluated for pre-formulation characteristics, drug content, solubility study, and dissolution behavior. Based on the results, all the physical characteristics evaluated were found to be satisfactory and formulation having carrier Gelucire 50/13 with drug to carrier ratio of 1:2 was found to be showing enhanced solubility results when compared to other formulations using fusion 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 with rate limiting natural polymers.

Graphical Abstract



Dissolution comparison of tenofovir solid dispersions using Poloxamer 188 and Gelucire 50/13, 1:1 and 1:2 ratio.

Keywords: Tenofovir, Soluplus, Kollidon VA 64, Poloxamer P188, Gelucire 50/13, Fusion, Solvent evaporation, Solubility, Dissolution, Solid Dispersion, Tablets.

INTRODUCTION

Solubility is a significant physicochemical factor affecting absorption of drug and its therapeutic effectiveness. 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 with respect to their methodology. 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' [1] 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 [2], 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 and ampiphilic have been investigated for enhancement of dissolution characteristics and bioavailability of poorly aqueous-soluble drugs.

Tenofovir is an anti-retroviral drug of protease inhibitor used for the treatment of HIV infections [3, 4]. It is slightly soluble in water, having bio-availability of less than 25% and low permeability so it was chosen as a model for this research work. Low oral bioavailability of drug may be due to poor aqueous solubility, high first pass metabolism and efflux transport. Tenofovir shows poor bioavailability [5] when administered orally. The major reason for poor bioavailability is poor drug solubility characteristics, followed by its first pass metabolism.

Various carriers [6] 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.

Gelucire 50/13 (selected carrier for solid dispersions): Poly ethylene glycol (PEG) ester surfactants are synthesized by reacting polyethylene glycol with fatty acid. The polyethylene glycol comprises the hydrophilic part of the surfactant and the fatty acid is the lipophilic part. By varying the molecular weight of the PEG and the fatty acid, surfactants covering wide range of hydrophilic lipophilic balance (HLB) values can be produced. Gelucire is the family of vehicle derived from mixtures of mono, di and triglycerides with PEG esters of fatty acids [7]. These are available with range of properties depending on their HLB and melting point range (33°C to 65°C). They have a wide variety of application in oral and topical formulations. The applications of oral formulation include solubility and bioavailability enhancement, sustain drug release, taste masking and active pharmaceutical ingredient (API) protection from oxygen, light and humidity. Gelucire containing only PEG esters are generally used in the preparation of fast release formulations. Gelucire containing only glycerides or a mixture of glycerides and PEG esters are used in the preparation of sustained release formulations. Owing to their extreme hydrophobicity and low density, are considered as appropriate carriers for designing sustained release drug delivery systems [8, 9].

MATERIALS AND METHODS

Tenofovir was obtained as a Gift sample (Shilpa Medicare limited, Raichur), carrier Soluplus, Kollidon VA 64 and Poloxamer 188 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)

Formulation of solid dispersions of tenofovir was done using carriers Soluplus, Kollidon VA 64 using solvent evaporation method and carriers Poloxamer 188 [**10**] and Gelucire 50/13 using Fusion method in various ratios of 1:1 and 1:2.

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 tenofovir 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 was prepared using fusion method in different ratios of 1:1 and 1:2 (Table 1).

Table 1. Formulation details of solid dispersions

S. No.	Formulation	Drug-Carrier ratio	Formulation Code
1	Pure Drug	-	PD
2	API + Soluplus	1:1	TSD1
		1:2	TSD2
3	API + Kollidon VA 64	1:1	TSD3
		1:2	TSD4
4	API + Poloxamer 188	1:1	TSD5
		1:2	TSD6
5	API + Gelucire 50/13	1:1	TSD7
		1:2	TSD8

Solvent Evaporation: Solid dispersions of tenofovir were prepared by solvent evaporation technique. Required quantities of tenofovir 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.

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.

RESULTS AND DISCUSSION

Saturation solubility study for tenofovir: Saturation solubility of tenofovir was determined by adding excess amount of tenofovir in vials containing selected media separately. The samples were subjected to shaking for 24 h. on a magnetic stirrer. The resultant suspension was then filtered through Whatmann filter paper No.1 and suitably diluted with respective media. Finally, the samples were analyzed by UV-Spectrophotometer at 260 nm [**11-14**].

Table 2. Saturation solubility study for tenofovir

S. No	Medium	Average Solubility (mg mL^{-1})
1	Distilled Water	1.3
2	4.6 pH acetate buffer	3.46
3	6.8 pH phosphate buffer	2.92
4	0.1N HCl	6.43

Saturated solubility studies were conducted for tenofovir using different dissolution media. Tenofovir showed maximum solubility in 0.1N HCl, which indicates that 0.1N HCl is ideal dissolution medium for tenofovir. As per FDA Dissolution Methods data base guidance [**15**] 0.1N HCL was used as a dissolution medium for tenofovir (Table 2).

Construction of standard graph of tenofovir: The stock solution of tenofovir was prepared by accurately dissolving 100 mg in 100 mL of 0.1N HCl. From this 10 mL was taken and diluted up to 100 mL with 0.1N HCl. From this 10 µg mL^{-1} solution was prepared by diluting 10 mL to 100 mL with 0.1N HCl. From this 2, 4, 6 and 8 to 10 mL with 0.1N HCl. Absorbance was measured at 260 nm and results were tabulated in table 3 and constructed standard graph of tenofovir (Figure 1)

Table 3. Calibration curve for the estimation of tenofovir

S. No	Concentration	Absorbance
1	0	0
2	2	0.123
3	4	0.249
4	6	0.376
5	8	0.486
6	10	0.592

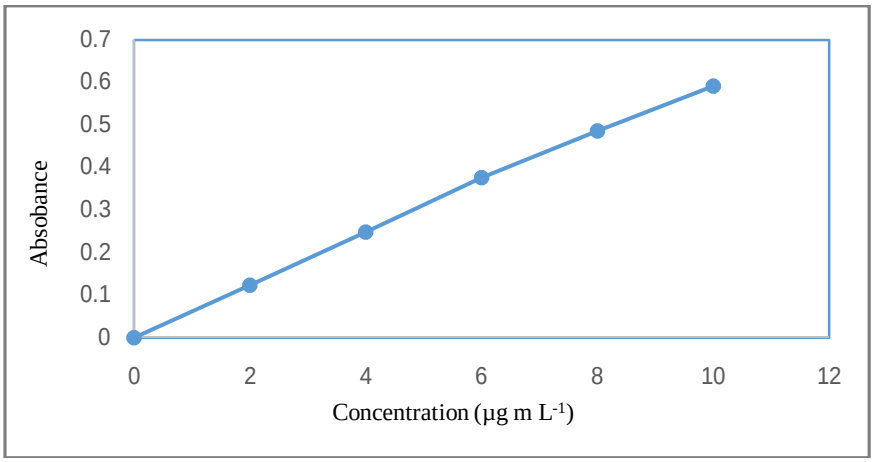


Figure 1. Calibration curve for the estimation of tenofovir.

Estimation of drug content: Solid Dispersion equivalent to 100 mg of tenofovir were weighed accurately, dissolved in the 100 mL of 0.1N HCl and sonicated for 05 min. The solution was filtered, diluted suitably. Drug content was analyzed at 260 nm by UV spectrophotometer (Table 4). The Drug Content was determined using the following equation

$$\% \text{ Drug content} = \frac{\text{Actual tenofovir content in weighed quantity of solid dispersion}}{\text{Theoretical amount of tenofovir in solid dispersion}} \times 100$$

Table 4. % of drug content in solid dispersion

Solid dispersion	Drug content (mg)
TSD1	96.4±0.02
TSD2	97.2±0.02
TSD3	95.2±0.02
TSD4	96.4±0.02
TSD5	98.6±0.02
TSD6	98.3±0.02
TSD7	99.9±0.02
TSD8	99.3±0.02

Dissolution study: Dissolution rate of tenofovir 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 0.1N HCl with 50 rpm at temperature of 37 ± 0.5°C. Drug and solid dispersion equivalent to 150 mg of tenofovir 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 tenofovir and solid dispersions were represented in table 5 and 6. 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 tenofovir 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

Table 5. Dissolution profile for tenofovir solid dispersions

Time	Amount of drug dissolved (mg mL^{-1})				
	Pure Drug	Soluplus		Kollidon VA 64	
		(1:1)	(1:2)	(1:1)	(1:2)
0	0	0	0	0	0
5	13.05	18.2	26.8	14.25	20.45
10	17.89	28.6	43.2	21.25	32.22
15	25.3	45.3	53.6	32.36	44.62
20	35.6	53.2	63.5	46.68	53.22
30	41.5	63.2	70.24	54.52	65.54
45	49.2	74.22	79.5	66.62	74.22
Sample Name	-	TSD1	TSD2	TSD3	TSD4

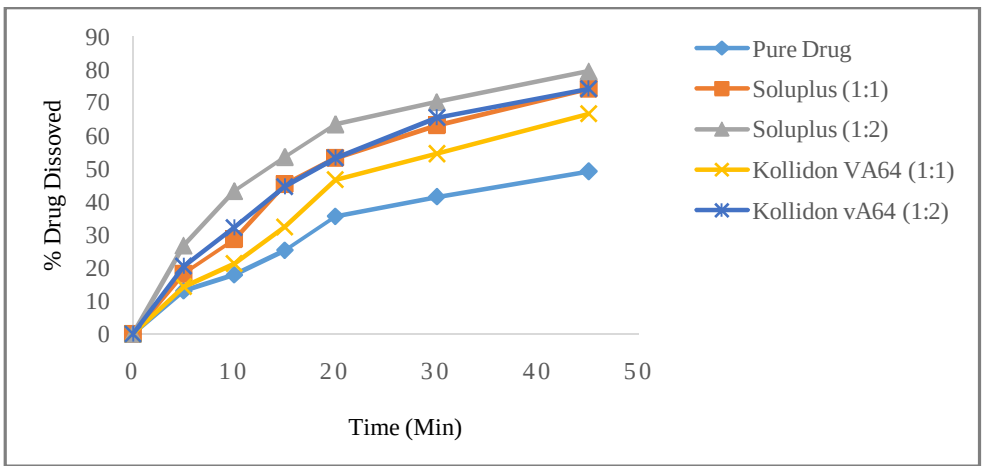


Figure 2. Dissolution comparision of tenofovir solid dispersions using Soluplus and Kollidon in 1:1 and 1:2 ratio.

From the dissolution study, it is clearly observed that the dissolution rate of tenofovir is low because of only 49.2% of drug dissolved in 45 min and all solid dispersions batches shows significantly enhanced dissolution rate of 14 to 92% in 45 mins. The more improvement in a dissolution rate was observed in solid dispersion batch TSD8 which comprises of Drug: carrier (Gelucire 50/13) in the ratio of 1:2 that is prepared by fusion method.

Table 6. Dissolution profile for tenofovir solid dispersions

Time	Amount of drug dissolved (mg mL^{-1})				
	Pure Drug	Poloxamer 188		Gelucire 50/13	
		(1:1)	(1:2)	(1:1)	(1:2)
0	0	0	0	0	0
5	13.05	16.66	20.24	15.3	20.9
10	17.89	31.5	32.22	22.6	30.5
15	25.3	46.42	51.47	40.5	45.7
20	35.6	58.9	66.68	59.4	69
30	41.5	69.66	72.88	68.66	80
45	49.2	73.32	84.28	80.22	92.24
Sample Name	-	TSD5	TSD6	TSD7	TSD8

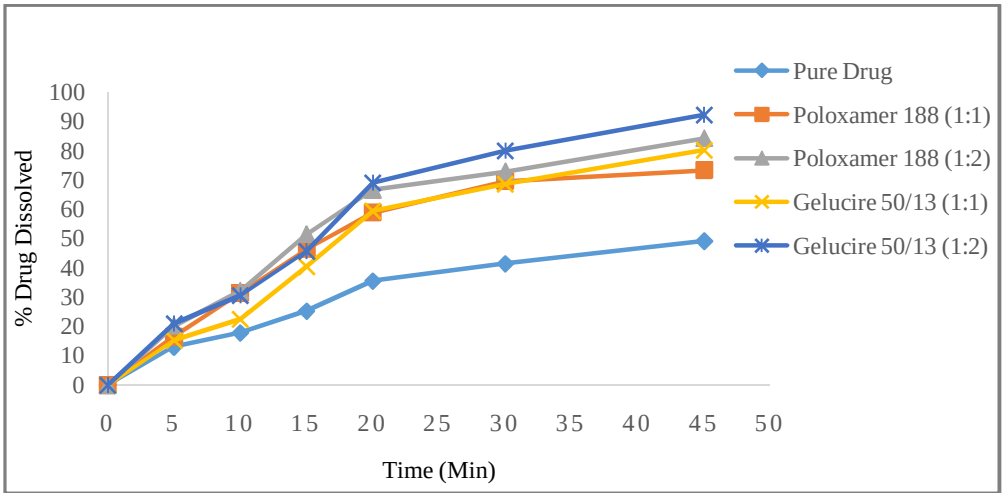


Figure 3. Dissolution comparision of tenofovir solid dispersions using Poloxamer188 and Gelucire 50/13 1:1 and 1:2 ratio.

APPLICATION

Based on the results we found that solid dispersions prepared using carrier Gelucire 50/13 at the ratio of 1:2 by fusion method shows better solubility and dissolution. Hence the increase in solubility using solid dispersion method is to be economic method compared other methods like micronization, lyophilization and other mechanical methods. The increase in solubility should leads to better drug absorption followed by better bioavailability when the drug was administered as a sustained release form.

CONCLUSION

The physical characteristics of Solid dispersions with proposed carriers were found to be satisfactory. Saturated solubility studies were conducted for tenofovir using different dissolution media. Tenofovir showed maximum solubility in 0.1N HCl, which indicates that 0.1N HCl is ideal dissolution medium

for tenofovir. Based on the dissolution results of tenofovir with different carriers, it was observed that the % drug release is more in the Solid dispersion with Drug: Gelucire 50/13 (1:2) [TSD8] 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 tenofovir was achieved using solid dispersion technique with selected carrier of Drug: Gelucire 50/13 (1:2) [TSD8]. Henceforth, the controlled release tablet formulations were formulated with the Solid dispersion with Drug: Gelucire 50/13 (1:2) [TSD8] and using the polymers having the property of sustained release action.

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