Physical characterization and dissolution performance assessment of Etravirine solid dispersions prepared by spray drying process

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Abstract: The aim of the current exertion was to prepare Solid Dispersion of Etravirine by Spray drying technique to enhance aqueous solubility and dissolution rate. Solid dispersions (SD) of Etravirine were prepared using Copovidone and Povidone-Copovidone in dichloromethane and physical properties were characterized by Scanning electron microscopy (SEM), X-Ray diffractometry (PXRD), Fourier Transform Infrared Spectroscopy (FTIR), Differential Scanning Calorimetry (DSC). SD's were evaluated for equilibrium solubility and *in vitro* drug release profile by dissolution testing. The diffraction and thermal patterns of solid dispersions indicated the conversion of crystalline Etravirine to amorphous form. The solubility of drug in SD's was appreciably more when evaluated against physical mixtures and intact Etravirine. Drug release characteristics were evaluated in three different media at different pH and found that drug release kinetic was best described by weibull mathematical model. Mean dissolution time (MDT) and Dissolution efficiency (DE %) in different media were evaluated for SDs. Statistical evaluation of dissolution data using Analysis Of Variance (ANOVA) single factor and t-Test: Paired Two Sample for Means was applied for better understanding and evaluation.

Keywords: Etravirine, Copovidone, Povidone, solid dispersion, Spray drying, solubility, dissolution.

INTRODUCTION

Etravirine (ETV) is a non-nucleoside reverse transcriptase inhibitor (NNRTI) used as an anti-retro viral agent and chemically known as 4-[[6-amino-5-bromo-2-[(4-cyanophenyl) amino]-4-pyrimidinyl] oxy]-3, 5dimethylbenzonitrile. ETV increases the number of CD4 or T cells there by reducing the amount of HIV in the blood (Kehr *et al.,* 2008; Eraikhuemen *et al*., 2008; Schiller & Youssef-Bessler 2009). The chemical structure of etravirine is represented in fig. 1. Etravirine is highly lipophilic (logP=5.2) and has low water solubility. As per BCS (Biopharmaceutical Classification System), ETVisa class 2 drug with poor water solubility and highly permeability (Usach *et al*., 2013; Schöller Gyüre *et al*., 2013; Mellaerts *et al*., 2013). For class 2drugs, the most important constraint of oral absorption is the rate of drug dissolution. So, its clinical performance can get better by the augmentation of the apparent aqueous solubility of the drug (Hetal *et al*., 2010; Kumavat *et al*., 2013).

Formation of amorphous forms to increase drug solubility and the reduction of particle size to expand surface area for dissolution and decrease the interfacial tension with the aid of a water-soluble carrier are among the possible mechanisms for increasing dissolution rates and improving bioavailability of poor water-soluble drugs (Shavi *et al.,* 2010). Solid dispersions (SD) are one the mostly used techniques by which solubility of poor aqueous soluble drugs can be improved (Pavan *et al.,* 2014).

Since long oral method of drug intake is a desirable route for drug administration due to ease and good patient fulfillment. When a drug is to be orally absorbed, it must be dissolved in gastric and/ or intestinal fluid. However, a number of promising drugs generated by technological innovations are poorly water-soluble and it is difficult to adopt them as candidates for new drug though they may exhibit good pharmacological activity. The poor water solubility leading to low dissolution rate in the gastrointestinal fluid often lead to insufficient bioavailability (Poddar *et al*., 2011; Rowland 1972). The improvement of dissolution from solid dispersion is attributed to drug particle size reduction, solublization effect of the carrier, generation of amorphous state and specific molecular interaction between the drug and carrier (Vasconcelos *et al*., 2007, Augustijns *et al*., 2009). Spray drying technique shows to be a resourceful technique for fabrication with significant enhancement in dissolution properties, which may be due to their potential conversion of crystalline state of drug to amorphous state, one step process, production of spherical particles with high surface area etc. (Vasconcelos *et al*., 2007; Amighi *et al*., 2005; Dress man *et al*., 2008).

Reported literatures specify that polymeric carriers have been in use for improving solubility of class 2 drugs (Torchilin *et al*., 2004; Torchilin 2004; Singh *et al.,* 2007). The improved solubility and dissolution of the drug is due

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to the molecular level dispersion of drug in polymeric carriers because of which surface area improvement and particle size diminution occurs (Vasconcelos *et al*., 2007; Dressman & Leuner 2000; Bikiaris *et al*., 2007). Etravirine is rapidly absorbed after oral administration but since it has poor aqueous solubility its dissolution rate is very low (Ter Heine *et al*., 2010). In the present work, we used spray-drying technique to prepare the SDs of Etravirine using different concentrations of Copovidone and Povidone-Copovidone. The physicochemical properties of different systems were determined from XRD, SEM, DSC and IR studies. In addition, the effect of carrier concentration on dissolution properties of Etravirine in SDs was evaluated.

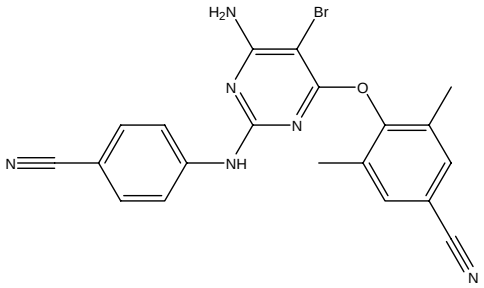

Fig. 1: Chemical structure of etravirine.

MATERIALS AND METHODS

Materials

Etravirine was provided courtesy Pharma Train, Hyderabad, India. Povidone and Copovidone was purchased from BASF India Ltd (Navi Mumbai, India). Dichloromethane were procured from Merck Company (Darmstadt Germany). All the chemicals used were of analytical grade.

Preparation of physical mixtures (PM)

ETV PM's were prepared by grinding Etravirine-Copovidone (1:1) and Etravirine-Povidone-Copovidone (1:1:1) in a mortar and pestle for 10 minutes. This mixture was screened through sieve 80 mesh to yield a product having particle size in the range of 150µm.

Preparation of spray dried powder

Feed solutions (5%, wt/vol) in methylene chloride were made for spray drying process for the solid dispersions of the binary mixtures of Etravirine-Copovidone (1:1) and Etravirine-Povidone-Copovidone (1:1:1). The formulated solution was spurted at a flow rate of 10g/min/k gusing 2.0 bar atomizing air pressure using a spray dryer with nitrogen inert loop (Labultima, Jay Instruments and Systems Pvt. Ltd., Mumbai, India). The inlet air temperature was 45^{o}C and the exhaust temperature was around 30^{o}C.The spray dried substance was kept back in vacuum oven for all night drying at 25^{o}C. The dried-up substance was accumulated in a closed vial in a desiccators to maintain them humidity free.

Characterization of SD's of etravirine

Powder X-ray diffraction (XRPD)

XRPD pattern were collected with Bruker D8 advance X-ray diffract to meter with Cu anode and Lynx eye detector. Etravirine, individual excipients, physical mixtures and solid dispersions were scanned from 3^{o}2θ to 45^{o}2θ, with step size 0.01^{o}2θ and time per step of 0.4 sec. The instruments generator voltage and current was maintained at 40kV and 40mA respectively. Variable divergent slit and Anti scattering slit were used of V20mm. Nickel filter was used in secondary beam path and the anode is copper (Cu Kα radiation =1.54 □). Eva software was used for data processing and evaluation.

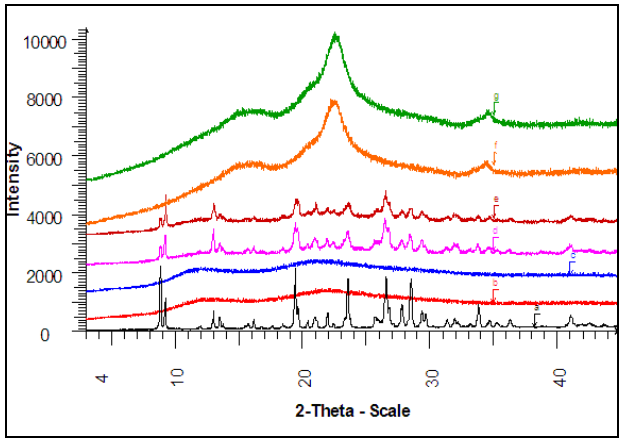

Fig. 2: Overlaid diffraction pattern of ETV (a), Povidone (b), copovidone (c), ETV: Povidone (1:1) physical mixture (d), ETV: Povidone: Copovidone (1:1:1) physical mixture (e), SDs of Etravirine-Copovidone(ETV-CO-SD) (f) and Etravirine-Povidone-Copovidone (ETV-PO-CO-SD) (g).

Thermal analysis

Differential scanning calorimetry (DSC)

DSC analysis of intact Etravirine, PM's and prepared SD's were performed by means of Mettler Toldeo Model DSC with Software: STAR^{e}. Samples of 2-4 milligrams were precisely weigh up and placed in aluminum crimped pans and thermo grams were obtained from 25°C to 300°C at 10°C per min heating ramp. Nitrogen at flow rate 50 ml/min was used as purge gas.

Modulated DSC (mDSC)

DSC Q1000 by TA instruments was used to perform mDSC experiment. Data interpretation was done with Universal Analysis 2000 thermal analysis software. All the test products were equilibrated at 25^{o}C. The samples were heated from 25^{o}C to 300^{o}C at a rate of 2^{o}C/min with modulation 0.21^{o}C every 40 s.

Infra red spectroscopy (FT-IR)

Universal Attenuated Total Reflectance (UATR) accessory attachment of Perkin-Elmer Spectrum-one FTIR spectrometer (USA) was used to collect the spectra with

number of accumulations as 4 and in the range of 4000 to 650cm-1.

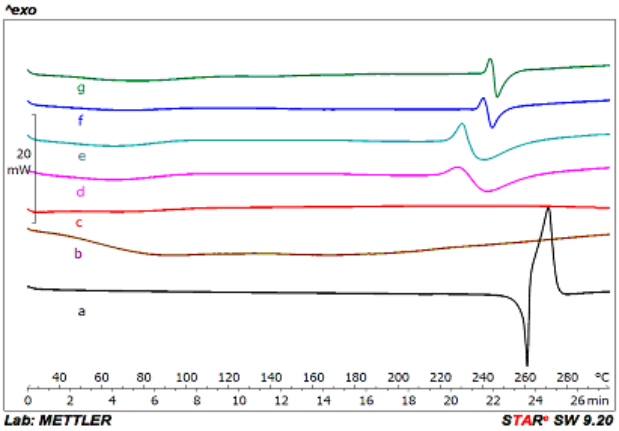

Fig. 3: Overlaid DSC pattern of ETV (a), Povidone (b), copovidone (c), ETV: Povidone (1:1) physical mixture (d), ETV: Povidone: Copovidone (1:1:1) physical mixture (e), SDs of Etravirine-Copovidone(ETV-CO-SD) (f) and Etravirine-Povidone-Copovidone (ETV-PO-CO-SD) (g).

SEM imaging

Imaging of the RPV and SDs were investigated by scanning electron microscopy (SEM, JOEL JSM-6380) at an accelerating voltage of 2.0 kV was used to generate images. Double-coated carbon conductive tabs are mounted on SEM sample stubs and samples were sprinkled uniformly and coated by Platinum Sputter Coater vacuum coater (JEOL, JFC 1600, Auto fine Coater) to minimize electrostatic charging.

Equilibrium solubility determination

The equilibrium solubility of the pure drug ETV and the prepared SDs of Etravirine-Copovidone (ETV-CO-SD) and Etravirine-Povidone-Copovidone (ETV-PO-CO-SD) were determined in Ultra-pure water (Millipore®, USA) by adding excess amount of sample in water and the samples were shaken for 24 hours at 37^0C in a horizontal shaker. The supernatant is filtered through 0.45 µm filters the filtrate was assayed spectrophotometrically at 310 nm.

Dissolution testing of ETV SDs

In order to understand the drug release properties amorphous solid dispersions of ETV, a two-stage dissolution procedure was used. In the first step, dissolution testing was conducted in 300 ml 2.25% SLS in 0.01N HCl for 10 minutes and no sampling was done during this step and in the second step added 600ml of pH 4.5 Acetate buffer (Media 1) as dissolution media in USP Type-II apparatus (Lab India) at stirring speeds of 75 rpm at 37±0.5°C. Similarly drug release testing was performed in other two dissolution media i.e. 6.8 pH phosphate buffer (Media 2) and 0.1N Hydrochloric acid (HCl) (Media 3) without altering the initial step. SD's corresponding to 20mg of ETV was put in to the dissolution medium. Aliquots of 10mL sample were withdrawn at particular time intervals and an equivalent volume of clean medium was put back with second media to keep up the volume of medium. The collected sample was filtered through 0.45µm PVDF filters and discarded first few ml of the filtrate. The pass through a filter sample was analyzed spectrophotometrically about 310 nanometres. The drug release kinetics was evaluated by applying different mathematical models.

RESULTS

The physical properties of physical mixtures of etravirine, povidone and copovidone and SDs prepared by spray drying procedure were characterized by DSC, mDSC, PXRD, SEM, FT-IR and drug release characteristics by dissolution studies. The characteristic diffraction angle values (2θ), d values (□), intensity in counts and % intensity of pure drug ETV are tabulated in table 1.

The overlaid diffraction patterns of ETV (a), Povidone (b), copovidone (c), ETV: Povidone (1:1) physical mixture (d), ETV: Povidone: Copovidone (1:1:1) physical mixture (e), SDs of Etravirine-Copovidone (ETV-CO-SD) (f) and Etravirine-Povidone-Copovidone (ETV-PO-CO-SD) (g) is represented in fig. 2.

Overlaid DSC thermo grams pattern of drug ETV (a), Povidone (b), copovidone (c), ETV: Povidone (1:1) physical mixture (d), ETV: Povidone: Copovidone (1:1:1) physical mixture (e), SDs of Etravirine-Copovidone(ETV-CO-SD) (f) and Etravirine-Povidone-Copovidone (ETV-PO-CO-SD) (g) is shown in fig. 3.

SEM photomicrographs revealed the surface morphology of the drug (A), povidone (B), copovidone (C), SDs of Etravirine-Copovidone (ETV-CO-SD) (D) and Etravirine-Povidone-Copovidone (ETV-PO-CO-SD) (E) which is shown in fig. 5.

Fig. 6 represents the dissolution profiles of ETV SDs in three different dissolution media. Here SD1MI is the dissolution profile of ETV-CO-SD in media 1 and SD2M1 is the dissolution profile of ETV-PO-CO-SD in media 1. Similarly SD1M2, SD2M2, SD1M3 and SD2M3 are the dissolution profiles of ETV-CO-SD and ETV-PO-CO-SD in media 2 and media 3 respectively.

Statistical evaluation of dissolution profiles of SDs in different media

In order to assess the performance of the two SDs systems in three different dissolution media statistically Analysis Of Variance (ANOVA) single factor has been applied. The source of variations between groups and with in groups was assessed. It is found that for ETV-CO-SD system the F value1.8890 is not well above the F critical value 3.8853 and the P-value 0.19 reflects this value by bringing significantly greater than 0.05. Thus, by accepting the null hypothesis it can be concluded that

Table 1: Characteristic peaks of drug ETV

Diffraction angle (2θ)	d value (□)	Intensity (counts)	Intensity %
8.794	10.047	4296	100
9.185	9.621	2296	53.4
11.931	7.412	314	7.3
12.989	6.81	1319	30.7
13.456	6.575	954	22.2
13.712	6.452	410	9.5
15.493	5.715	340	7.9
15.708	5.637	490	11.4
16.136	5.488	752	17.5
16.746	5.29	243	5.7
17.634	5.026	390	7.4
18.431	4.81	440	10.2
19.412	4.569	4208	97.9
19.632	4.518	1641	38.2
20.400	4.349	627	14.6
20.923	4.242	964	22.4
21.067	4.213	731	17
21.964	4.043	1225	28.5
22.434	3.959	461	10.7
23.293	3.816	780	18.2
23.544	3.776	3552	82.7
23.997	3.705	278	6.5
24.718	3.598	260	6.1
25.717	3.461	940	21.9
25.913	3.436	791	18.4
26.416	3.371	3592	45.4
26.570	3.352	1572	83.6
26.796	3.324	507	36.6
27.102	3.288	1741	11.8
27.825	3.204	3448	40.5
28.524	3.127	1281	80.2
29.387	3.036	1168	29.8
29.682	3.007	320	27.2
30.233	2.954	733	7.4

Table 2: Aqueous solubility of ETV and SDs prepared by spray dry process

Name	Solubility (mg/ml)	No of folds increase in solubility
ETR	0.0025	-
ETR + Copovidone (Solid dispersion)	0.0112	4.48
ETR + Copovidone + Polyvinylpyrrolidone (Solid dispersion)	0.0113	4.52

Table 3: Drug release kinetics of SD1M1 and SD2M1 in media 1

Kinetic Models	Correlation coefficient (r)		Root-mean-square error (RMSE)	
	SD1M1	SD2M1	SD1M1	SD2M1
Korsmeyer-Peppas model	0.8957	0.9325	8.82	6.14
Weibull model	0.9036	0.9782	9.32	2.29
Hixson-Crowell model	0.6417	0.7252	13.51	10.54
Higuchi model	0.4610	0.6371	16.24	12.47

Table 4: Drug release kinetics of SD1M2 and SD2M2 in media 2

Kinetic Models	Correlation coefficient (r)		Root-mean-square error (RMSE)	
	SD1M2	SD2M2	SD1M2	SD2M2
Korsmeyer-Peppas model	0.9450	0.9409	3.67	3.17
Weibull model	0.9885	0.9977	1.46	0.49
Hixson-Crowell model	0.7404	0.7083	7.39	6.50
Higuchi model	-0.8274	-3.8953	20.18	26.73

Table 5: Drug release kinetics of SD1M3 and SD2M3 in media 3

Kinetic Models	Correlation coefficient (r)		Root-mean-square error (RMSE)	
	SD1M3	SD2M3	SD1M3	SD2M3
Korsmeyer-Peppas model	0.9928	0.9967	1.21	0.80
Weibull model	0.9972	0.9998	0.64	0.19
Hixson-Crowell model	0.8531	0.8731	4.55	4.30
Higuchi model	-0.3880	0.2235	14.19	11.02

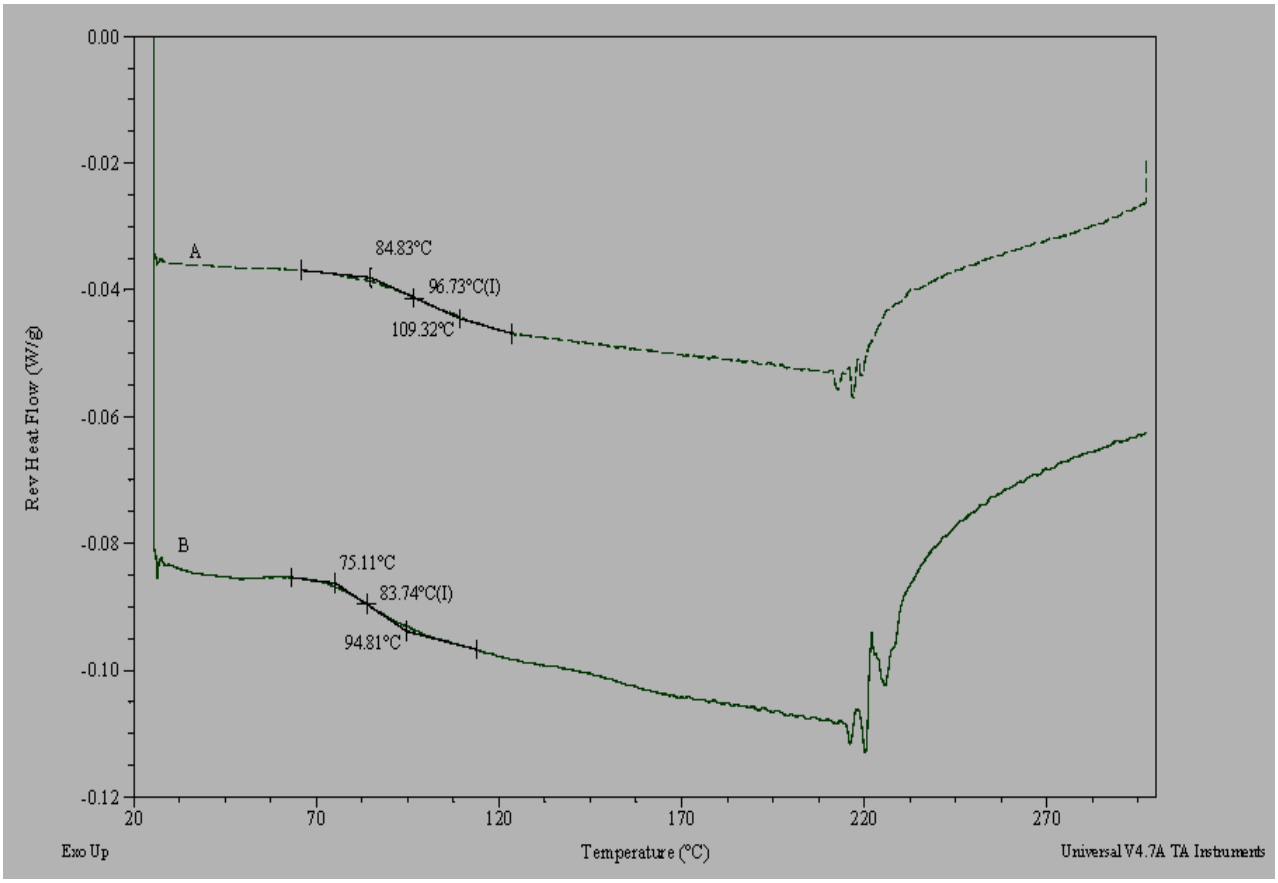

Fig. 4: Thermograms of solid dispersions of Etravirine-Copovidone (ETV-CO-SD) (A) and Etravirine-Povidone-Copovidone (ETV-PO-CO-SD) (B)

there is no noteworthy disparity between the groups. For ETV-PO-CO-SD system the F value 4.1352 is not well above the F critical value 3.8853 and the P-value 0.04 reflects this value by bringing significantly smaller than 0.05. Thus, we decline the null hypothesis, and conclude that there is a major difference between the groups.

For better clarity on the performance of SDs in different media t-Test: Paired two samples for means is performed on dissolution data (table 7). It is clear that in all the cases t critical two tail is less than the absolute value of t stat. Therefore we can decline the null hypothesis that there are no statistical differences between the two datasets.

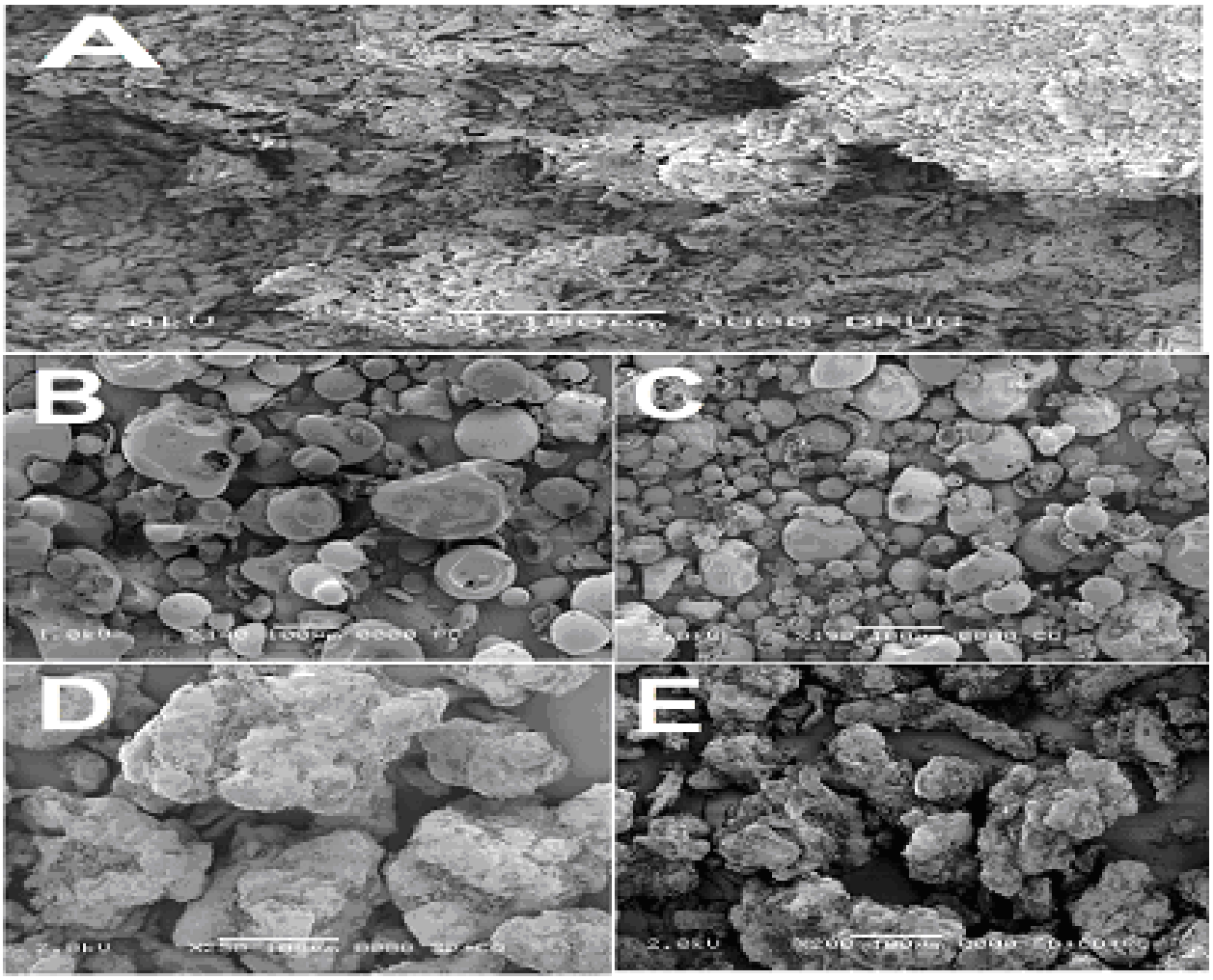

Fig. 5: Scanning electron microscopy images for spray dried dispersion

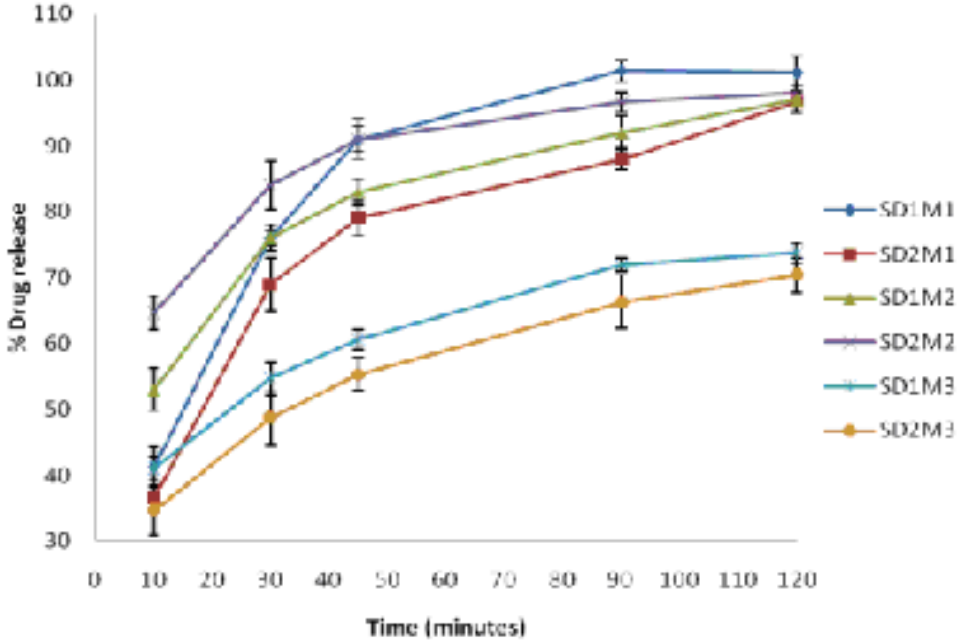

Fig. 6: Dissolution profiles of EVT SDs in different dissolution media

DISCUSSION

Form fig. 2. It is evident that ETV (a) is highly crystalline in nature and the povidone (b) and copovidone (c) are amorphous in nature. The physical mixtures ETV: Povidone (1:1) (d) and ETV: Povidone: Copovidone (1:1:1) (e) are crystalline in nature and contains peaks belonging to crystalline ETV drug only and hence it is concluded that the drug is compatible with the physical mixtures. The crystalline ETV API peaks were monitored carefully in the prepared SD's. Absence of diffraction peaks in the scanned range indicates the presence of short-range molecular order in SD's.

Table 6: Model independent parameters for the evaluation of ETV-CO-SD and ETV-PO-CO-SD systems in different dissolution media

Trial Name	Model independent Parameters	
	% DE	MDT
SD1M1	82.71	20.75
SD2M1	74.06	28.38
SD1M2	77.98	21.50
SD2M2	85.69	15.08
SD1M3	60.15	22.47
SD2M3	54.65	26.32

The thermo gram of ETV shows a pointed melting endotherm at 265°C signifying the crystalline character of the drug and no endothermic peaks for polymers indicating the amorphousness. In SDs prepared with Copovidone and Povidone-Copovidone, the melting endotherms have not appeared in as the drug is converted into amorphous form, which point towards the absence of physicochemical relations in between Polymers and ETV SD. In the modulated DSC pattern, the reversing heat signal confirmed that the ETV-CO-SD (A) and ETV-PO-CO-SD (B) (fig. 4) exhibits glass transition temperature (Tg) at about 96.73^{o}C and 83.74^{o}C respectively. The subsistence of Tg indicates the formation of an amorphous SD. The mDSC, DSC and PXRD investigation imply the formation of amorphous SD by spray drying process for binary system.

Distinguishing pine needle form crystals of ETV were examined in the photomicrograph of ETV (A). Images of the SD's disclose the lopsided particles with quite a lot of minuscule breaks and splits, which make available extra surface for deposition of the ETV particles. The absences of ETV crystals were confirmed by XRD and DSC. The SEM images also revealed that the SD's showed big sub angular asymmetrically shaped structures.

ETV has aqueous solubility of 0.0025mg/mL. The SD's of ETV demonstrated improved solubility when evaluated against pure drug. The proportion augment in the solubility are given in table 2. The enhanced aqueous solubility may be caused by superior wetting capability, a reduced amount of particle size and large surface area of SDs.

In media 1 the drug release for SD1M1 is about 40% in first 10 minutes, about 75% of the drug is released in 30 minutes, about 90% of the drug is released in 45 minutes and in 90 minutes the drug release was complete and no further release is observed when continued further for 120 minutes. For SD2M1 about 35% of the drug is released in 10 minutes, about 70% of the drug is released in 30 minutes, about 80% of the drug is released in 45 minutes, about 90% of the drug is released in 90 minutes and about 97% of the drug is released in 120 minutes. The drug release kinetics was evaluated using four different mathematical models and found that the kinetics of the drug release was best described by weibull model. According to this model the best-fit values obtained when compared to other models for root-mean-square error (RMSE) and correlation coefficient (r) for SD1M1 and SD2M1 are 0.9036, 0.9782 and 9.32, 2.29 respectively (table 3).

As compared to media 1 drug release in media 2 is a bit faster in first 10 minutes i.e. about 50% and 65% of the release is observed for SD1M2 and SD2M2 respectively. Even though the drug release was faster for ETV-CO-SD system in media 2 up to 45 minutes but complete release could not be attained as in media 1, so only 97% release is achieved. For ETV-PO-CO-SD system much faster release is observed in media 2 as compared to media 1. The drug release kinetics was best described by weibull model according to which the 'r' values for SD1M2 and SD2M2 are 0.9885 and 0.9977 respectively. The RMSE values for SD1M2 and SD2M2 are 1.46 and 0.49 respectively (table 4).

For SD1M3 and SD2M3 the drug release matched with SD1M1 and SD2M2 initially i.e. in first 10 minutes but later the drug release was slower and only about 74% and 70% of the release obtained in 120 minutes. Here the drug release kinetics were best described by weibull model and 'r' value and RMSE value for SD1M3 and SD2M3 are found to be 0.9972, 0.9998 and 0.64, 0.19 respectively.

ETV-CO-SD and ETV-PO-CO-SD systems in all the dissolution media exhibited weibull mathematical model which is an empiric model, it presents some deficiencies. This model cannot depict and characterize kinetic properties of drug dissolution and it has nominal possibility for establishing *in vivo in vitro* correlations table 6 consist the dissolution efficiency (%DE) and mean dissolution time (MDT) values. DE values are related with the real amount of drug dissolved in the dissolution medium and thus, lead to a better extrapolative for *in vivo* performance. It can be observed that for both an SD system DE was first-rate in media 1 and media 2 but not

Table 7: T-Test: Paired Two Sample for Means for two solid dispersion systems in three dissolution media

	SD1M1	SD2M1	SD1M2	SD2M2	SD1M3	SD2M3
Mean	82.13	73.87	78.8	86.87	60.4	55.07
Variance	626.37	538.37	281.53	184.53	179.97	204.3
Observations	5	5	5	5	5	5
Pearson Correlation	0.9879		0.9920		0.9984	
Hypothesized Mean Difference	0		0		0	
df	4		4		4	
t Stat	4.4300		-4.8458		10.1193	
P(T<=t) one-tail	0.0057		0.0042		0.0003	
t Critical one-tail	2.1318		2.1318		2.1318	
P(T<=t) two-tail	0.0114		0.0084		0.0005	
t Critical two-tail	2.7764		2.7764		2.7764	

up to the mark in media 3.Since the MDT values are not quite low for both the SDs, the release rate is not higher and indicates higher drug-retarding ability of the polymer.

From statistical evaluation of dissolution data we can conclude that there is a momentous variation between the two SD systems and their release profiles in different media. The drug release of ETV-CO-SD system is unswerving in all the media as compared with ETV-PO-CO-SD system.

CONCLUSION

The aim of this work is to prepare solid dispersions of practically insoluble drug etravirine using spray drying technology for enhanced aqueous solubility and dissolution rate and found the purpose is accomplished comprehensively. Different analytical techniques, kinetic models and statistical tools have been applied to understand the drug release characteristics in different media, which helps us in understanding and selecting the appropriate alternative among different variables.

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