RESEARCH ARTICLE

Stable Amorphous Solid Dispersion of Eplerenone Prepared with Water Soluble Polymer by Spray Drying Technique

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ABSTRACT

Class II in the Biopharmaceutical Classification System, eplerenone (EPL) is a selective aldosterone antagonist. Due to its poor solubility, EPL has limited bioavailability. Here, an innovative spray-drying method was used to transform a water soluble polymer into an amorphous dispersion of the EPL. Different polymer SOL/EPL ratios were tested to determine EPL's solubility and dissolution enhancement properties. In order to learn more about the physical and chemical properties of this novel amorphous solid dispersion (ASD), methods like powder X-ray diffraction spectroscopy (PXRD), differential scanning calorimetry (DSC), fourier transform infrared spectroscopy (FTIR), particle size distribution (PSD) using a Malvern instrument, and scanning electron microscopy (SEM) were used. There was no chemical interaction between the binary mixture of EPL and SOL which was confirmed from the FTIR spectra obtained. The enhancement in the solubility and dissolution of EPL and binary mixture prepared were due to the amorphous conversion of EPL in the SOL polymer (amorphous solid dispersion), which was confirmed from DSC thermogram, PXRD spectra obtained and was also confirmed from the solubility study, *in-vitro* dissolution study. Finally, *ex-vivo* intestinal absorption study performed on the goat intestine using amorphous solid dispersion and pure EPL, also improved intestinal absorption of EPL through amorphous solid dispersion prepared.

Keywords: Amorphous solid dispersion, Eplerenone, *Ex-vivo* intestinal absorption study, Low soluble drugs, Solubility, Soluplus, Spray drying.

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INTRODUCTION

Solubility is simply the amount of solute that dissolves in the available solvents at standard temperature conditions. The dissolution process can be described as the process which measures the rate and extent of solution formation of solute into the given solvents under a standard temperature condition. Almost 40–60% of the new pharmaceutical, chemical entity falls under the biopharmaceuticals classification systems (BCS) class II. BCS class II drugs are the drug entities with low solubility and high permeability *in-vivo*. Permeability is the process by which the dissolved drug entity can pass through the cell membrane. Solubility is the step that slows down the rate of *in-vivo* absorption for BCS class II drugs/permeability through cell membrane.[1,2]

Eplerenone (EPL) ($C_{24}H_{30}O_6$) (Figure 1) is the selective aldosterone antagonist used for treating heart failure and essential hypertension along with the diuretics (potassium sparing diuretics), which binds to the mineralocorticoid receptors, ultimately blocks the aldosterone binding to the same receptors which decline the sodium resorption and increasing the water outflow in the body. Eplerenone can also help lower the risk of dying from an acute myocardial infarction in people who have heart failure and left ventricle dysfunction. The side effects like gynecomastia and vaginal bleeding are less with EPL-treated patients than with spironolactone treated patients. These less side effects are associated due to the EPL is selective aldosterone antagonists.[3]

Numerous water-soluble polymers are commercially available. Soluplus (SOL) is selected as a novel water-soluble polymer with spray drying technique. The chemical formula for Soluplus® is "polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer." SOL's amphiphilic chemical structure is used to the creation of solid solutions of low soluble pharmaceuticals like BCS class II and IV medications, which boosts their bioavailability *in-vivo*.[4]

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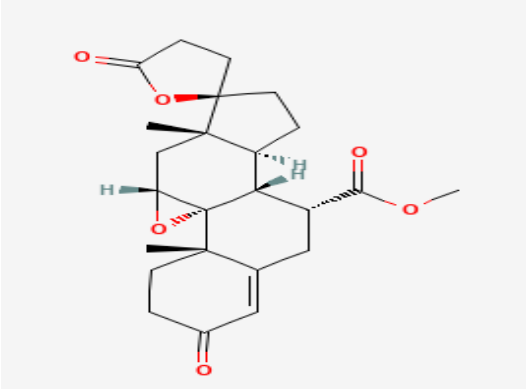

Figure 1: Eplerenone Structure.

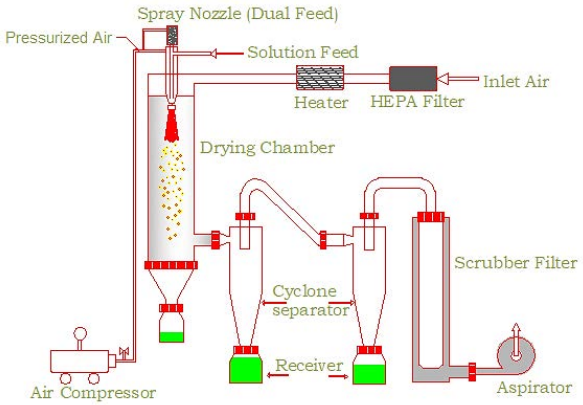

Figure 2: Graphical representation of the lab Spray dryer

MATERIALS AND METHODS

Materials

Glenmark Pharmaceuticals Ltd (Nashik, Maharashtra, India) gifted sample of Eplerenone (EPL), BASF Co. (Mumbai, India) provided for evaluation purpose sample of Soluplus® (SOL). Analytical grade of experimental materials and reagents were used.

Compatibility Study of Drug Substance and Excipients

Studies were conducted on drug substance-excipients compatibility to ensure there would be no adverse effects from combining the medicine with its selected excipients. EPL-SOL and the active pharmaceutical substance were mixed in a sealed glass vial at a 1:5 ratio and stored at 40°C and 75% relative humidity for a month to test their stability. The capacity of the EPL and polymer to interact was tested with an assay. An ultraviolet (UV) spectrophotometric test was used to examine the materials.

Solid Dispersion of EPL-SOL Preparation Methods

Preparation of the EPL-SOL Binary Physical Mixture

EPL and polymer SOL were simply combined into a physical mixture (PM) by mixing, followed by sieving through #80 sieve. The mixture was again mixed and shifted using #80 sieve to get a uniform mixture.

Analytical Method Development

To analyze assay and dissolution (% drug release) from the amorphous solid dispersion (ASD), a UV-vis spectroscopic method (Jasco V-630, Tokyo, Japan) was developed. In a 100 mL volumetric flask, precisely 10 mg EPL was taken and dissolved using solvent methanol: 0.1N HCl (80:20%) by stirring the flask. Above filtered (using 0.45 µm filter) solution then suitably diluted and analyzed using analytical technique i.e. measuring absorbance (λ_{max}= 245 nm).

Amorphous Solid Dispersion (ASD) (EPL-SOL) Preparation

Preparations of EPL-SOL amorphous solid dispersions with various EPL-SOL to amorphous solid ratios were made by using an industrial feasible solvent evaporation technique, i.e., Spray drying technique (Table 1). In a suitable beaker, a mixture of solvents [Isopropyl alcohol (90%) and dichloromethane (10%)] was taken and kept under a mechanical stirrer. Under covered slow stirring, SOL was added slowly to the solvent to get clear solution, followed by the addition of EPL to it. Once the solution has become clear, spray it with a lab spray dryer (Lab model: Spray Mate, Mfg. by: JISL, Mumbai, India) according to the process parameters specified in Table 2. A lab model co-mill fitted with a circular 0.5 mm screen was run at the correct speed to produce a powder. (Mfg. by: Bowman and Archer, Mumbai, India). For solvent free powder, the #60 sieved powder was additionally dried out in tray dryer at 60 ± 2°C for 24 hours (Figure 2).

Optimal Amorphous Solid Dispersion Characterization

Assessment of Drug Content

The %assay/%drug content in the ASD prepared was calculated using Jasco's UV–vis spectrophotometer (Model V-630, Tokyo, Japan). ASDs containing 25 mg equivalent EPL were placed in the 100 mL volumetric flask containing a solvent mixture (80 mL methanol and 20 mL 0.1N HCl). Flask constantly agitated to get a clear solution. The filtered (using 0.45µm filter) solution was then suitably diluted and analyzed at λ_{max} = 245 nm in UV–vis spectrophotometer (Figure 3).

Table 1: Formulae for amorphous solid dispersion of EPL-SOL

Mixture	*Weight ratios*	*Solvent evaporation Technique*	*Dissolution enhancement*
EPL:SOL	1:1	Spray drying technique	Yes
EPL:SOL	1:2		Yes
EPL:SOL	1:3		Yes
EPL:SOL	1:4		Yes

Table 2: Process parameters for Spray drying technique

Processing condition (Parameters)	*Set parameter*
% Solid in solution (% w/w)	5 % w/w
Nozzle diameter (mm)	1.0 mm
Inlet temperature (°C)	45 ± 5°C
Atomization pressure (kg/cm^2)	1.5–2.0
Outlet temperature (°C)	35 ± 5°C
Aspirator speed (rpm*)	2000 ± 200
Feed pump speed (rpm)	3 RPM to 10
Spray rate (g/min)	02.5 to 010

Revolution per minute means rpm

Table 3: Assay results for Drug excipients compatibility study

Sample	*Ratio used*	*Initial (T0)*	*30 days (40°C/75% RH) (T1)*
EPL	NA	100.12 ± 2.35	99.06 ± 0.03
EPL + Soluplus	1:5	100.85 ± 0.31	100.86 ± 0.03

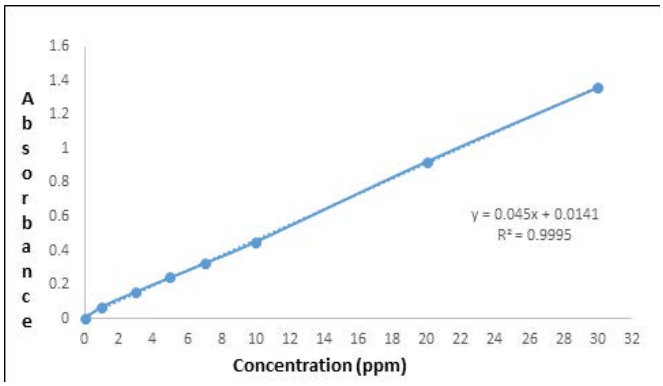

Figure 3: Calibration curve of EPL in Methanol and 0.1 N HCl.

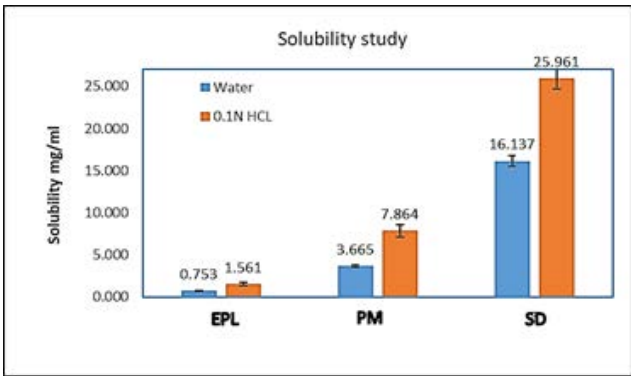

Figure 4: Comparative solubility study in water and 0.1N HCl.

%Yield calculation

The %yield of ASD was computed using the following formula.

$$\% \text{ yield} = \frac{\text{Practical yield in g}}{\text{Theoretical yield in g}} \times 100$$

Saturation Solubility Study

Saturation solubility of EPL, physical mixture of EPL-SOL and ASD prepared by spray drying technique were studied in 0.1N HCL and water. For this, excess sample was taken in 10 mL volumetric flasks with a glass stopper. The volumetric flasks were kept at 37 ± 1°C for 24 hours in a glass shaking apparatus. After proper dilution, the filtered solution's absorbance (filtered using a 0.45 µm membrane filter) was measured using a UV-vis spectrophotometer with a max reading of 245 nm.

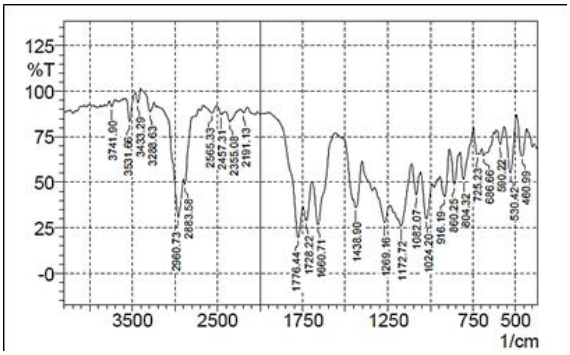

Figure 5: Eplerenone drug's FTIR spectra

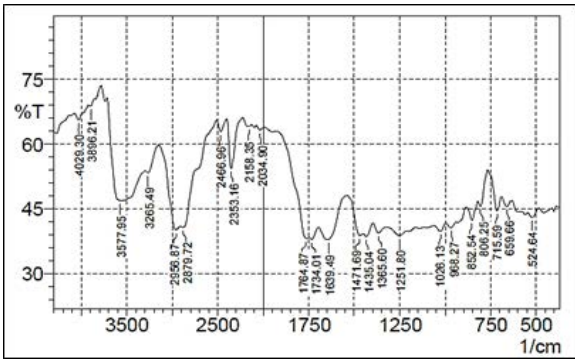

Figure 6: ASD (EPL-004)'s FTIR spectra

Fourier Transform Infrared Spectroscopy

FT-IR spectra of EPL and prepared ASD were achieved using FTIR spectrophotometer (Model no.: FTIR-8400; Mfg. by: Shimadzu, Asia Pacific Pvt. Ltd. Singapore).

Differential Scanning Calorimeter Study

Thermogravimetric analysis of EPL, physical mixture, and ASD was performed in a nitrogen atmosphere using a differential scanning calorimeter (DSC; manufacturer: Mettler Toledo, Switzerland) at a heating rate of 10°C/minute between 30 to 350°C.

P-X-ray Diffraction Evaluation

Using a diffractometer (Model no. PW 1140, Mfg. by: Mettler Toledo, Columbus, OH, USA) and Cu-K radiation, a PXRD diffractogram of EPL, SOL, physical mixture, and ASD was obtained. The diffractometer functioned optimally at a chart speed of 2°/2 cm per 2, with a scanning speed of 2°/mm.

Particle size distribution (PSD) investigation

Mastersizer 2000S (Mfg. by: Malvern Instruments Ltd. UK) was used. A uniform paste of 50 mg ASD powder was prepared using 25 mL of sunflower oil in a beaker. This mixture was sonicated for 1-minutes in a sonicator (PCI Analytics, India).

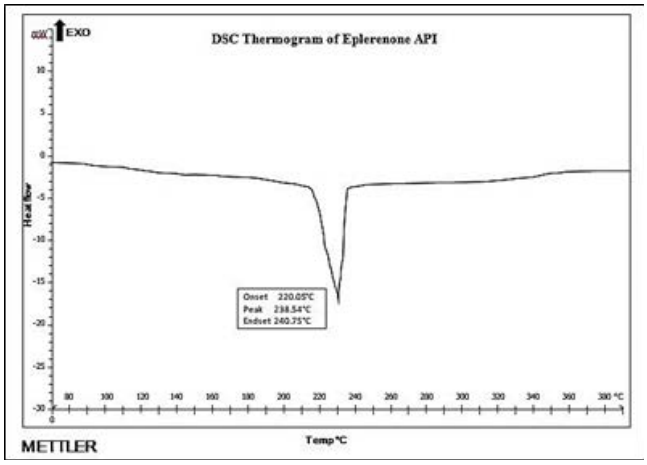

Figure 7: Eplerenone drug substance's DSC Thermogram.

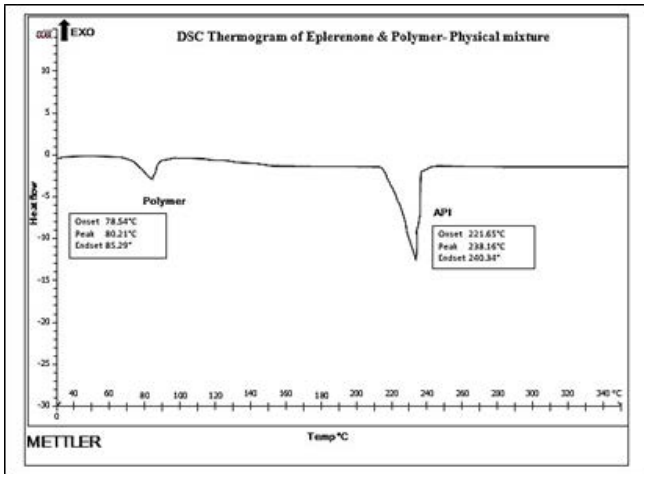

Figure 8: Physical mixture (PM) 's DSC Thermogram.

Table 4: % yield and drug content of the ASD

Batch number	*Binary mixture*	*Ratio used for EPL:SOL*	*%yield obtained*	*%drug content analyzed*
EPL-001	EPL: SOL	1:1	80.56% ± 2.14	98.56% ± 1.66
EPL-002	EPL: SOL	1:2	81.45% ± 1.56	99.12% ± 2.78
EPL-003	EPL: SOL	1:3	83.65% ± 0.92	96.76% ± 0.69
EPL-004	EPL: SOL	1:4	84.99% ± 2.35	99.26% ± 1.71

Table 5: Flow properties of Spray dried ASD (EPL-004)

Flow Property	*Practical value*
(BD) Bulk density in g/mL	0.420
(TD) Tapped density in g/mL	0.600
(CI) Compressibility index in %	30.000
(HR) Hausner ratio	01.429
(PSD) Particle size distribution (in µm)	
d_{10}	3.418
d_{50}	6.539
d_{90}	12.177

Transferring the paste into the master sizer chamber and waiting for the obscuration level to stabilise allowed us to calculate the PSD. Assessments of PSD at the D10, D50, and D90 levels were made.

Dissolution Study (in-vitro)

The USP type II (paddle) dissolving device was used for the *in-vitro* dissolution profile analysis of both pure EPL medication and produced ASDs (Mfg. by: Electrolab dissolution tester, Mumbai). The dissolution media consists of 900 cc of 0.1N HCl and is kept at 37 ± 1°C while being spun at 75 rpm. At regular intervals, 5 mL of dissolution media were taken from each flask and replaced with 5 mL of fresh dissolution medium to maintain the sink condition. Absorption of the obtained samples was measured spectrophotometrically at max = 245 nm after they were filtered through filter paper. The percent of medication release was calculated using a calibration curve equation. Six sets of results were obtained for this experiment[5].

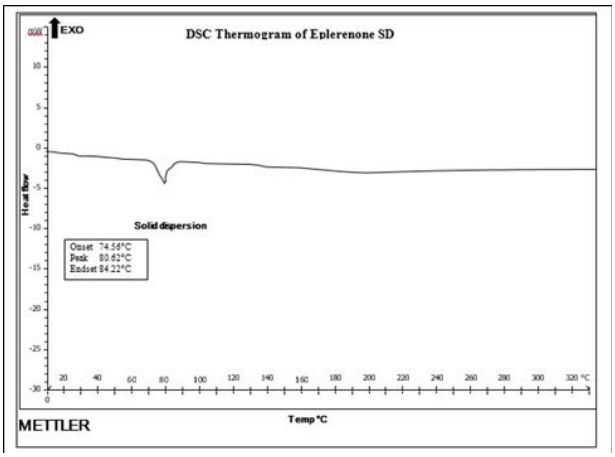

Figure 9: ASD (EPL-004)'s DSC Thermogram.

Intestinal Medication Absorption of EPL

The intestinal medication absorption of EPL was evaluated in an *ex-vivo* duodenal drug absorption investigation employing everted goat intestine hung on modified apparatus in a USP type II dissolving apparatus. The *ex-vivo* study used fresh goat intestines procured from a nearby slaughterhouse. Fresh goat intestine was chopped into 6 cm pieces and washed in a saltwater solution to remove any debris. This cleansed section then moved into a salty, oxygenated environment. After clamping the everted intestine to a redesigned apparatus, we immersed it in a 900 cc of 37 ± 1°C , 0.1N HCl dissolving buffer, spinning it at 75 rpm. Pure drug EPL and ASDs powder were transferred to the dissolution medium. The drug

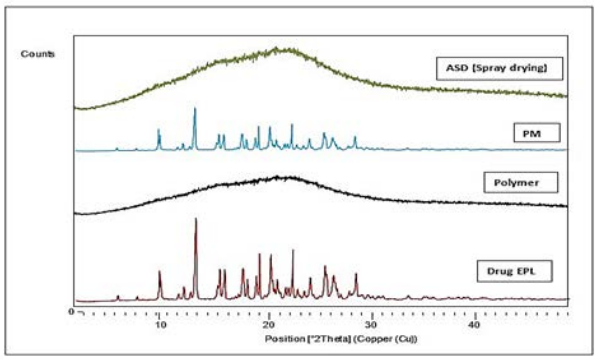

Figure 10: PXRD diffractogram: from bottom drug EPL, polymer SOL, physical mixture, ASD (EPL-004) prepared by spray drying technique.

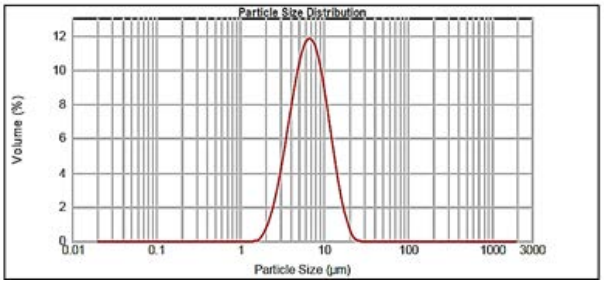

Figure 11: PSD histogram: ASD (EPL-004) manufactured by Spray drying technique

absorption/ diffusion through the goat intestine was measured by collecting the sample at 5, 10, 20, 30, 40, 50, 60, 90 and 120 minutes from the modified apparatus, followed by dissolution medium replenishment. The collected sample were analyzed spectrophotometrically at λ_{max} = 245 nm. The experimentation was performed in triplicate (n = 3)[6].

Stability Study

A stability study of the prepared ASDs were done. %Assay and *in-vitro* dissolution profile determination of the stability samples were done. The optimized ASD stability study was continued upto 3 months[7].

RESULT AND DISCUSSION

Compatibility Study (Drug-excipients)

As per the assay results obtained from the drug excipients compatibility study samples kept on stability, to check the compatibility between EPL and SOL, it demonstrates that there is no substantial change in the assay test values of initial and 1-month samples, which indicates that there is no interaction between the EPL and SOL. The initial and 1-month assay (40°C/75% RH condition) results were presented below in Table 3.

Assessment of Drug Content

Spray-dried ASDs had an EPL content ranging from 96.76 to 99.22%, as measured by their drug assay potency (as depicted in Table 4). These findings show that EPL is distributed consistently over the ASD and is within acceptable pharmacopoeial ranges.

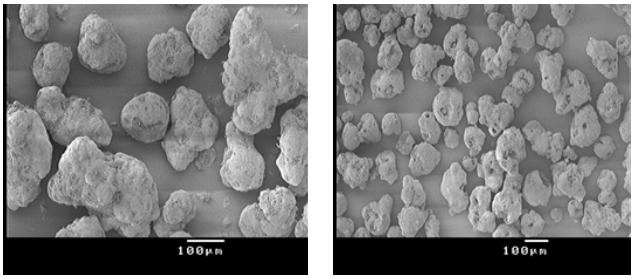

Figure 12: SEM photographs of EPL and ASD (EPL-004) manufactured.

%Yield Calculation

The % yields for the ASD prepared by spray drying technique were found in the ranged of 80.56 to 84.99% (as depicted in Table 4). This lower % yield was attributed to the lower batch size at lab level and this % yield can be increased in the large batches at plant level.

Saturation Solubility Study

Based on the solubility study performed in water and 0.1N HCl, solubility was increased as compared to the EPL when formulated in SD prepared by the spray drying technique. This increased solubility in SD is due to the amorphous nature of EPL in polymer SOL, which is confirmed by PXRD data and DSC thermogram. Comparative solubility of EPL, PM and SD were shown in the graph (Figure 4).

FT-IR Spectroscopy

The principal peaks for EPL were observed at wavenumbers 2960.73 cm^{-1} (C-H stretching), 1776.44 cm^{-1} (anhydride O-C=O stretching), 1728.22 cm^{-1} (C=O ester stretching), and 1660.71 cm^{-1} (C-O stretching) in the FTIR spectra obtained for the drug (shown in Figure 5), and a selected ASD (batch no. EPL-004) (shown in Figure 6). This elucidates that the SOL polymer utilized in the ASD produced by the spray drying process did not undergo any chemical interaction with the medication EPL.

Differential Scanning Calorimetry (DSC) Study

The main purpose of the DSC study is to assess the thermal melting properties of the pure drug substance EPL and the manufactured ASD by spray drying technique. Based on the thermogram obtained, drug EPL (shown in Figure 7) depicted melting endotherm at 238.54°C. Also thermogram of the physical mixture (PM) of EPL: SOL (1:4) (shown in Figure 8) presents two endotherms, one at 80.21° of SOL polymer and consequently at 238.16°C of drug EPL. As per the thermogram of ASD (EPL-004) (shown in Figure 9), showed only one endothermic peak at 80.62°C and the disappearance of drug EPL endothermic peak, which indicates that the drug EPL homogeneously disperses as an amorphous state in the polymer SOL.

PXRD Evaluation

As explained in the above section of DSC study of EPL-004 (shown in Figure 9), there was a disappearance of the endothermic peak of EPL which indicated that EPL was in an amorphous state in the ASD. Based on the PXRD diffractogram

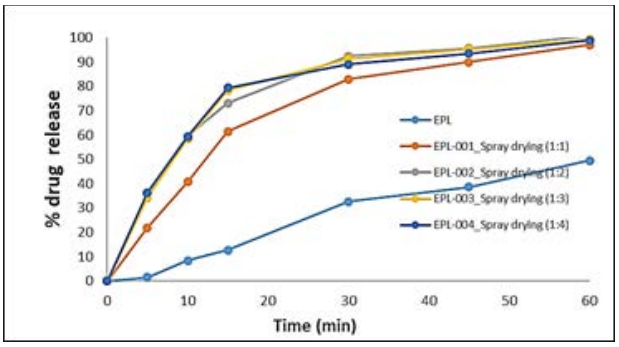

Figure 13: Dissolution profile of ASDs prepared and EPL in 0.1N HCL.

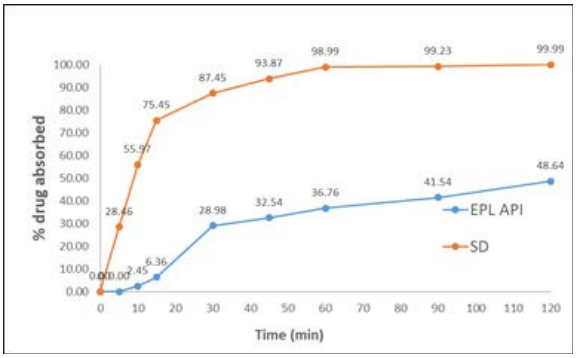

Figure 14: Ex-vivo intestinal absorption study: Drug EPL and ASD (EPL-004) absorption study

(as shown in Figure 10) for the drug EPL, polymer SOL, physical mixture of EPL: SOL (1:4) ratio and the selected ASD (EPL-004), shows that the drug EPL was appears to be in the crystalline state indicating distinctive peaks at 2θ values of 14.51°, 15.50°, 17.62°, 20.57°. However, the polymer SOL indicates amorphous diffractogram exhibiting non-sharp peaks while the PM showed EPL's distinctive peaks, which specifies the crystal-like nature of EPL in PM. Distinct peaks of the drug EPL disappeared in the diffractogram of ASD (EPL-004), suggesting that the crystalline form of EPL had been transformed into an amorphous form. The solubility and dissolution of EPL in ASD made through the spray-drying method were found to be improved after the substance was transformed from its crystalline to its amorphous state.

Powder Flow Investigation

Powder flow properties were determined, including bulk density, tribodynamic diameter, compressibility index, and Hausner ratio. The data from the experiments are listed in Table 5. The compressibility index and Hausner ratio indicated that the prepared ASD flowed well enough to mix with other excipients to form a solid dosage form, like tablets or capsules. D_{90} value of power spectral density (PSD) was calculated to be 12.177 µm (Figure 11).

Scanning Electron Microscopy Analysis

Based on the photographs of SEM obtained (as shown in Figure 12), EPL has large crystals shape with having specific morphology, while the SD prepared by spray drying having round particles with reduced crystal shapes which is may be due to the solid dispersion of EPL formed with polymer SOL.

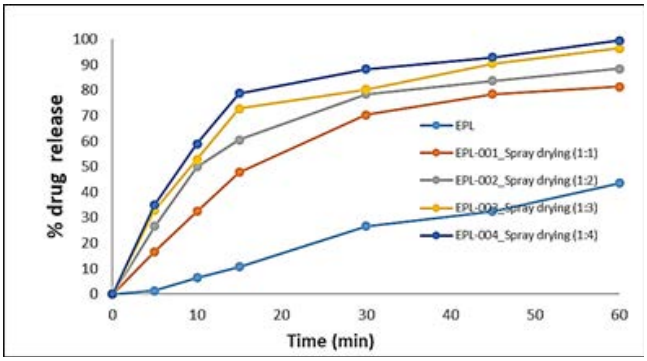

Figure 15: 1-month Dissolution profile of ASDs (at 40°/75% RH)

Dissolution Profile Study

Eplerenone is strongly acidic in nature as it shows a pKa value of 15.11; hence, it exhibits the highest in the stomach region.[8-9] The comparative dissolution profile of EPL and different ASDs prepared as shown in Figure 13. All ASDs showing enhancement in the % drug release of EPL. As per results obtained for dissolution profile, pure drug EPL shows lowest dissolution of about 33% in 30 minutes due to its low solubility whereas the all ASD manufactured by spray drying technique showed significant enhancement in the dissolution rate (about 82 to about 93%) in the 0.1N HCL medium as compared to pure drug EPL in 30 minutes. This enhancement in the dissolution rate of EPL in all ASD was due to the presence of amorphous form of EPL and it was also shown in the DSC thermogram and PXRD diffractogram in the above sections. Rapid dissolution was traced to the uniform distribution of the medication EPL across the water-soluble polymer. After the SOL polymer dissolves in the dissolution media, the fine drug particles are made accessible in the ASD, where they dissolve very quickly. By breaking down the medication into smaller pieces, the ASD enhances the drug's surface area and speeds up its breakdown.[10,11]

Intestinal Drug EPL (*Ex-vivo)* Absorption Study

The disintegration rate was predicted using data from an *ex-vivo* duodenal drug absorption research (Figure 14) rate of absorption pure drug EPL and the particular ASD (EPL-004) through the everted goat intestine using modified apparatus. EPL drug indicated 28.98 and 36.76% drug absorption at 30 and 60 minutes, respectively, while the selected SD (EPL-004) showed 87.45 and 98.99% drug absorption in 30 and 60 minutes, respectively. As shown in the results the rate of absorption through goat intestine of EPL in ASD (EPL-004) was considerably enhanced as matched to pure EPL drug substance. The drug EPL in the ASD (EPL-004) shows improved drug dissolving rate due to its amorphous form, smaller particle size, and large surface area.[12,13]

Stability Study

All the ASDs prepared by spray drying technique were loaded for stability study was continued for EPL-004 for 3 months. EPL-004 was selected as the final ASD for evaluation, as there was a significant decrease in the dissolution profile of

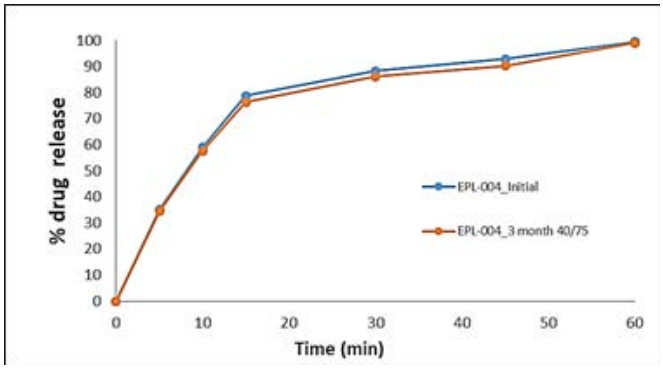

Figure 16: 3-month stability Dissolution profile of ASD EPL-004 (at 40°/75% RH)

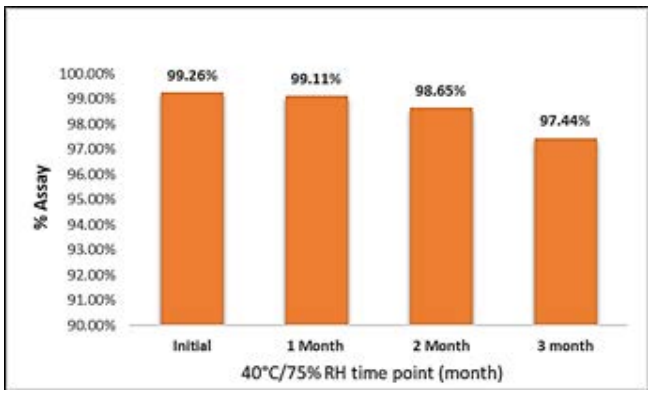

Figure 17: Stability assay analysis: EPL-004 other ASD prepared

other ASD prepared. A significant drop in % drug release was observed in EPL, EPL-001, EPL-002 and EPL-003 which is may be due to the recrystallization of EPL in SD, whereas no drop in dissolution is observed in EPL-004 (as shown in Figure 15 and 16) as compared to initial dissolution, which is attributed to the intact amorphous EPL in ASD prepared by spray drying technique. There is no substantial decline in the assay value of the prepared SD (EPL-004) compared with the initial assay test value. The stability assay values were well within the pharmacopoeial limits, i.e., for initial assay value was 99.26% and 3 months assay value was 97.44% (as shown in Figure 17).[14,15]

CONCLUSION

The aforementioned research demonstrated that EPL ASD could be produced using water-soluble polymer SOL and an industrially viable spray drying process. ASDs made with the water-soluble polymer SOL have a dissolving rate and intestinal absorption rate that are many times higher than those of the pure drug EPL. The amorphous state for EPL in ASD EPL-004 was confirmed with the DSC and XRD study. Enhancement of dissolution rate was associated with the amorphous state of EPL, homogenous solid dispersion of EPL in Water soluble SOL. This enhancement in dissolution rate exhibits rapid absorption through goat intestine, which was demonstrated in the *ex-vivo* intestinal *a*bsorption study. Suitable for manufacturing, poorly soluble pharmaceuticals like EPL can have their dissolution rates and absorption boosted by employing water-soluble polymers like SOL, and spray drying is the technique to use. This ASD is useful for making tablets, capsules, and other solid oral dosage forms.

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