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DISSOLUTION ENHANCEMENT OF POORLY WATER SOLUBLE EPROSARTAN BY HOT MELT EXTRUSION TECHNIQUE

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Keywords:

Melt extrusion, Solubility, Bioavailability, Eprosartan, Plasticizer, Glass transition temperature

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ABSTRACT: Objective: The prodigious challenge in the pharmaceutical industries was to enhance the solubility and the permeability of those drugs as key factors to improve their bioavailability. Various techniques have been used to improve the drug water solubility and release profile, and solid dispersions are considered to be the most successful techniques. The aim of the present study was to improve the solubility and bioavailability of a poorly water-soluble antihypertensive drug (Eprosartan) in the human body, using a solid dispersion technique (hot melt extrusion) and comparison with other methods. **Methods:** The development of solid dispersions as a practically viable method to enhance the bioavailability of poorly water-soluble drugs to overcome the limitations of previous approaches such as salt formation, solubilization by co-solvents and particle size reduction studies revealed that drugs in solid dispersion need not necessarily exist in the micronized state. Solid solution was prepared by solvent evaporation, fusion method, hot melt extrusion technique at 1:1.1, 1:2 (Eprosartan: Soluplus) and 1:1.5:0.5 (Eprosartan:Soluplus: Kollidan/Plasdone) ratios respectively. Solid Solution was evaluated for saturation solubility, dissolution rate, XRD, FTIR, and DSC. **Results:** From the studies, it was concluded that the solubility of Eprosartan was increased by the solid dispersion approach. Among the three techniques, the solubility of the drug increased by hot melt extrusion technique when compared to solvent evaporation and fusion methods. Therefore, the carrier surplus was suitable for enhancement of solubility of Eprosartan than other carriers used in this investigation such as kollidon VA64 and plasdone K29/32 and DSC, XRD data concluded that hot melt extrusion process devastates the edge peaks of Eprosartan which indicate the complete conversion of the crystal form of Eprosartan to amorphous form. Dissolution and solubility studies also showed enhancement in the release rate of hot melt extrusion complex. Stability studies at 40 º C / 75% RH were studied, and it shows that the sample is stable even after 90 days of study. Hot melt extrusion is commensurate method to improve dissolution and permeability of poorly water-soluble Eprosartan. **Conclusion:** In the present study, an attempt was made to formulate and evaluate the Eprosartan solid dispersions using soluplus, kollidon VA64 and plasdone K29/32 as carriers, prepared by using solvent evaporation, fusion, and hot melt extrusion methods. From the studies, it was concluded that the solubility of Eprosartan was increased by the solid dispersion approach. Among the three techniques, the solubility of the drug increased by hot melt extrusion technique when compared to solvent evaporation and fusion methods. Therefore, the carrier soluplus was suitable for enhancement of solubility of Eprosartan than other carriers used in this investigation, such as kollidon VA64 and plasdone K29/32. The low hygroscopicity and low glass transition temperature of soluplus make it particularly suitable for hot melt extrusion.

INTRODUCTION: Oral drug delivery is the most widely utilized route of administration among all the routes of administration that has been explored for systemic delivery of drugs *via* pharmaceutical products of the different dosage form. The oral route is considered most natural, uncomplicated, convenient, and safe due to its ease of administration, patient compliance, and cost-effective manufacturing process. Many drugs are either incompletely or ineffectively absorbed after oral administration due to their poor bioavailability. More than 45% of the new chemically synthesized drug being generated through drug discovery

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programs are poorly water-soluble compounds BCS in class II and IV. The bioavailability is mainly controlled by the delivery of the drug as determined by its pharmaceutical formulation, the solubility, and the permeability through the gut wall. The poorly soluble drugs cannot be completed within the time at absorption site due to slow dissolution rate and procreation of a low concentration gradient across the GIT governing to the possibilities of gastric decomposition of the drug to longer gastrointestinal residence time and squatty bioavailability by the formation of non-absorbable complexes, by metabolization or by premature elimination.

The enhancement of oral bioavailability of such poorly water-soluble drugs remains one of the most challenging aspects of drug development. The development of solid dispersions as a practically viable method to enhance the bioavailability of poorly water-soluble drugs to overcome the limitations of previous approaches such as salt formation, solubilization by co-solvents and particle size reduction studies revealed that drugs in solid dispersion need not necessarily exist in the micronized state. Eprosartan mesylate, chemically (E)- 4-({2-Butyl-5-2-carboxy-2-(thiophene-2-ylmethyl) eth-1-en-1-yl-1H-imidazol-1-yl} methyl) benzoic acid is an anti-hypertensive drug which prevents the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT1 receptor in vascular smooth muscle [1].

Eprosartan has poor solubility, and low dissolution rate in the aqueous gastrointestinal fluids often cause insufficient bioavailability belonging to class II drug. Bioavailability is 15%. T_{max} is 1-2 h, and approximately 98% is protein bound. Vd is 308 lit (at steady state), metabolized to inactive ingredients and terminal elimination half-life is 5-9 h [2, 3]. After oral dosing, approximately 90% is recovered in feces and approximately 7% in urine [4, 5, 6]. Among various techniques in improving the dissolution and bioavailability of the poorly soluble drug, solid dispersions are considered to be the most successful techniques. There are two main solid dispersion manufacturing methods: the melting method, such as hot melt extrusion (HME) and solvent evaporation methods, such as spray drying[7]. HME is the process of embedding drug in a polymeric carrier. Specifically, HME dosage forms are complex mixtures of API, functional excipients, and processing aids, which are blended using industry-standard equipment [8]. The mixture is processed at elevated temperature and pressure, which disperses the drug in the matrix at a molecular level through the formation of a solid solution [9, 10]. Hot-melt extrusion can be used to improve the rate of dissolution of poorly soluble drugs [11].

HME can be simply defined as the process of forming a new material (the extrudate) by forcing it through an orifice or die under controlled conditions, such as temperature, mixing, feed-rate, and pressure. Hot melt extrusion (HME) is the process of applying heat and pressure to melt a polymer and force it through an orifice in a continuous process. HME is a well-known process, developed to produce polymer products of uniform shape and density and this technology shows numerous benefits over traditional methods, including shorter processing times, environmental advantages due to the elimination of solvents and the more efficient delivery of drugs to patients.

Solubilizers also play an important role in influencing the permeation of drugs across the membranes from solid dispersions. Soluplus (polyvinyl caprolactam- polyvinyl acetate-poly-ethylene glycol graft copolymer (PCL-PVAc-PEG)) is a new pharmaceutical excipient designed originally for preparing solid solutions of poorly water-soluble drugs by hot melt extrusion technology [12]. Soluplus is a water-soluble copolymer with the average molecular weight ranging from 90,000 to 140,000 g/mol, and it is capable of solubilizing poorly water-soluble drugs [13]. Kollidon VA 64, plasdone k29/32 are used as solubilizer as well as a stabilizer and plasticizer. Thus, the objective of the present investigation was to improve the dissolution rate of poorly water-soluble Eprosartan by preparing its solid dispersion by hot melt extrusion.

MATERIALS AND METHODS:

Materials: Eprosartan was obtained as a generous gift from Mylan Laboratories Ltd., Nashik, India. Soluplus, kollidon VA64 and plasdone K29/32 were provided by BASF, Mumbai. All other chemicals used were of analytical grade.

Methodology:

Pre-Formulation Studies: Pre-formulation involves the application of biopharmaceutical principles to the physicochemical parameters of drug substance are characterized to design optimum drug delivery system [14].

Characterization of EM (Eprosartan Mesylate):

EM was Characterized by Following Test:

Description: [15] Eprosartan was studied for its color and physical appearance.

Saturation Solubility: [16] Solubility of Eprosartan mesylate in different buffers was determined by shake flask method. Briefly, an excess amount of model drug was added to each volumetric flask containing the selected vehicle and mixed thoroughly. The volumetric flasks were then fixed onto a water bath shaker and shaken for 24 h at 25ºC. Samples were removed after the specified time and filtered through 0.45 µm PVDF syringe is driven membrane filter unit, the absorbance of filtered solutions was determined, and the amount of drug solubilized was calculated.

TABLE 1: SATURATION SOLUBILITY

Saturation Solubility of Model drug (API)	
S. no.	**Medium**
1	Water
2	pH 1.2
3	pH 4.5
4	pH 6.8
5	pH 7.5

Melting Point: [17] Eprosartan melting point was determined by the instrumental method. This method involves the insertion of the capillary in the paraffin bath, and the melting temperature was recorded electronically (Melting point apparatus VEEGO).

Polymer-Drug Interaction Study:

XRD: [18] Eprosartan was subjected to XRD (P.W. 1729, X-ray generator, Philips, Netherland). To study XRD pattern, the drug sample was placed into the aluminum holder, and the instrument was operated between the initial and final 2θ angle of 5-500, respectively.

FT-IR Spectroscopic Analysis: [18] Eprosartan, was subjected to Fourier Transform Infra-Red (FT-IR 8400s spectrophotometer Shimadzu) studies to check the characteristic sharp peaks of drug and its functional groups. The potassium bromide (KBr) disk method was used for the preparation of the sample. The samples were ground gently with anhydrous KBr and compressed to form a pellet. The scanning range was 400-4000 cm^{-1}.

Differential Scanning Calorimetry (DSC): [18] Eprosartan was subjected to DSC study using (Mettler TA 4000) DSC apparatus. First 5-10 mg of sample was weighed into the aluminum crucible. This powder was analyzed by heating at a scanning rate of 100ºC / min over a temperature range 50 to 2000 ºC with a nitrogen flow of 50 ml/min.

Analytical Method Development for Eprosartan Mesylate: Determination of absorption maxima A spectrum of the working standards was obtained by scanning from 200-400 nm against the reagent blank to fix absorption maxima. The λ_{max} was found to be 234 nm. Hence, all further investigations were carried out at the same wavelength.

TABLE 2: CALIBRATION CURVE OF EPROSARTAN IN 4.5 pH SODIUM ACETATE BUFFER

Concentration (µg/mL)	Absorbance
0	0
2	0.094
4	0.172
6	0.254
8	0.330
10	0.410

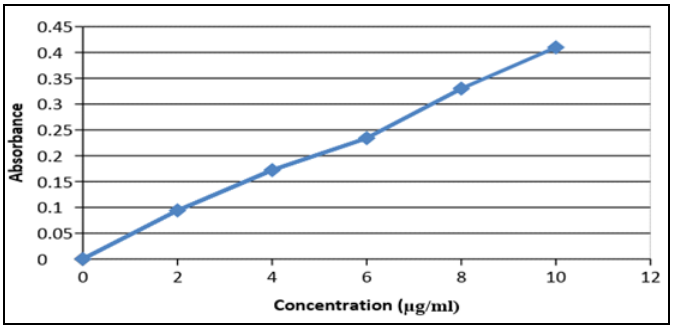

FIG. 1: STANDARD PLOT OF EPROSARTAN IN 4.5 pH BUFFER

Preparation of Calibration Curve: [19] 100 mg of Eprosartan mesylate was dissolved in methanol 5 ml, volumetric flask make up to 100 ml of phosphate buffer of pH 7.4, from this primary stock 10 ml was transferred to another volumetric flask made up to 100 ml with phosphate buffer of pH 7.4, from this secondary stock was taken separately and made up to 10 ml with phosphate buffer of pH 7.4, to produce 10, 20, 30, 40 and 50 µg/mL

respectively. The absorbance was measured at 234 nm by using a UV spectrophotometer.

Formulation Development:

Method for Preparation by Solvent Evaporation Method (F1-F9): Solid dispersions were prepared by the solvent evaporation method. Methanol was used as a solvent. Eprosartan mesylate dose was taken as 200 mg. Water-soluble polymers such as surplus, kollidon VA64, and plasdone K29/32 were selected as carriers. Drug and polymers were taken in different ratios stated in the formulation chart **Table 3**. The prepared solid dispersions were passed through the sieve no. 20 to get uniform sized particles. The solid dispersions were mixed with required quantities of diluent, lubricant, and glidant. The blend was evaluated for pre-compression parameters and tablets prepared by direct compression machine.

TABLE 3: COMPOSITION OF EPROSARTAN FORMULATIONS FOR SOLID DISPERSION BY SOLVENT EVAPORATION

Ingredients (mg)	Formulation code	
	SD1	SD2
Model drug	400	400
Soluplus	400	-
Kollidon VA 64	-	400
Plasdone K 29/32	-	-
Methanol (ml)	20	20

Preparation of Eprosartan Tablets by Direct Compression Technique: To the sieved solid dispersion, mannitol SD 200, avicel pH 102, crospovidone and magnesium stearate were added as extra-granular part and blended thoroughly. This final lubricated blend was compressed into tablets using 10.00 mm standard rectangular concave punches.

TABLE 4: COMPOSITION OF EPROSARTAN SOLID DISPERSION FOR TABLETS USING SOLUPLUS

Ingredients (mg)	Formulation code	
	F1	F2
Solid dispersion using soluplus	800	800
Mannitol SD 200	160	-
Avicel PH 102	-	160
Crospovidone	56	56
Magnesium stearate	4	4
Total	1020	1020

Preparation of Solid Dispersion by Fusion Method (F10-F13): Eprosartan and carriers to be used in formulations were dispensed separately. The carriers (soluplus and kollidon VA 64) were melted separately using a hot plate. The drug was added to the melted carriers in the ratios 1:1; 1:0.5 and mixed thoroughly. The resultant solid dispersions were collected and milled. The milled material was passed through sieve no. 40 and stored for further studies in **Table 5**. To the sieved solid dispersion, mannitol SD 200, avicel pH 102, crospovidone and magnesium stearate were added as extra-granular part and blended thoroughly. This final lubricated blend was compressed into tablets using 10.00 mm standard rectangular concave punches.

TABLE 5: COMPOSITION OF EPROSARTAN SOLID DISPERSION FOR TABLETS USING KOLLIDON VA64

Ingredients (mg)	Formulation code	
	F4	F5
Solid dispersion using Kollidon VA 64	800	800
Mannitol SD 200	160	-
Avicel pH 102	-	160
Crospovidone	56	56
Magnesium stearate	4	4
Total	1020	1020

TABLE 6: COMPOSITION OF EPROSARTAN SOLID DISPERSION FOR TABLETS USING PLASDONE K29/32

Ingredients (mg)	Formulation code	
	F7	F8
Solid dispersion using Plasdone K 29/32	800	800
Mannitol SD 200	160	-
Avicel pH 102	-	160
Crospovidone	56	56
Magnesium stearate	4	4
Total	1020	1020

TABLE 7: COMPOSITION OF EPROSARTAN FORMULATIONS FOR SOLID DISPERSION BY FUSION METHOD

Formulation code	Ingredients (mg)	
	Drug	Soluplus
SD4	400	200
SD5	400	400
SD6	400	-
SD7	400	-

TABLE 8: COMPOSITION FOR TABLETS OF EPROSARTAN SOLID DISPERSION

Ingredients	Quantity (mg)		
	F10	F11	F12
Solid dispersion with soluplus	600	800	-
Solid dispersion with kollidon VA64	-	-	600
Mannitol SD 200	80	80	80
Avicel pH 102	80	80	80
Crospovidone	56	56	56
Magnesium stearate	4	4	4
Total	820	1020	820

Preparation of Solid Dispersion by Hot Melt Extrusion (F14 - F19): Eprosartan mesylate kollidon® VA64, plasdone, and soluplus were mixed (The drug and carrier were mixed properly in the ratios 1:1, 1:0.5, 1:0.4, 1:0.3, 1:0.2 and 1:0.1) using a V-shell blender (Patrtreson-Kelley Twin Shell Dry Blender) for 10 min. The resulting physical mixture blends were extruded using a twin-screw extruder (Process 11 Twin Screw Extruder, Thermo Fisher Scientific) at the screw speed of 150 rpm, at a temperature range of 100-130 °C. All extrudates were milled and sieved through an ASTM #35 mesh to obtain a uniform particle size and stored for further studies **Table 20**.

TABLE 9: COMPOSITION OF EPROSARTAN FORMULATIONS FOR SOLID DISPERSION BY HOT MELT EXTRUSION METHOD

Formulation code (Drug: Soluplus)	Ingredients (mg) Drug
SD8 (1:0.1)	400
SD9 (1:0.2)	400
SD10 (1:0.3)	400
SD11 (1:0.4)	400
SD12 (1:0.5)	400
SD13 (1:1)	400

TABLE 10: COMPOSITION OF EPROSARTAN FORMULATIONS FOR TABLETS

Ingredients	Quantity (mg)					
	F14	F15	F16	F17	F18	F19
Solid dispersion		440	480	520	560	600
Mannitol SD 200		80	80	80	80	80
Avicel PH 102		80	80	80	80	80
Crospovidone		56	56	56	56	56
Magnesium stearate		4	4	4	4	4
Total		660	700	740	780	820

Physicochemical Evaluation of Tablets:

Micrometric Properties of Pre-compressed Powder: The flow properties of the pre-compressed powders of various batches were determined by the simple angle of repose using fixed-base cone method. A glass funnel was cinched with its tip positioned at a fixed height (h) above graph paper placed on a horizontal surface. The sample was poured through the funnel until the apex of the conical pile touched to the tip of the pipe. The height and radius of the heap were measured. The experiment was repeated in triplicate; the angle of repose (tan θ) was calculated using the following equation.

$$\text{Angle of repose} = \tan^{-1}(h / r)$$

Where, h- the height of the cone, r - circular base radius.

Density Measurements: The bulk density apparatus was used to evaluate the bulk and tapped densities of the pre-compressed powder. A previously measured quantity of the formulated granules was transferred to a 50cc graduated measuring cylinder. The filled cylinder fitted with bulk density apparatus and its timer knob adjusted for 500 tapings. Then, the bulk volume before and after the 500 tapings was noted. Tapped density was performed in the same way as the bulk density measurement. The experiment repeated for triplicate values 11. Following equations were used to measure the densities of the different batch granules.

$$\text{Bulk density (Db)} = \text{Sam. Wt. (g)} / \text{Apparent sam. Vol. (V0)}$$

$$\text{Tapped density (Dt)} = \text{Sam wt. (g)} / \text{Volume after tapping (Vf)}$$

Following equation was used to calculate the compressibility index or Carr's index value of pre-compressed powder;

$$\text{Carr's or compressibility Index (\%)} = Dt - Db / Dt \times 100$$

Hausner's ratio of pre-compressed powder determined by comparing the tapped density to the bulk density by using the equation;

$$\text{Hausner's proportion (H)} = Dt / Db$$

Weight Variation, Hardness, and Friability: Around 20 tablets were weighed individually and calculated its average weight for weight variation parameter. For each formulation, the hardness of 10 randomly selected tablets was examined using a Pfizer hardness tester (A-101 Secor, India) by measuring in kg/cm^2. The Roche friabilator (USP EF-2, Electro Lab.) was used to evaluate the percent friability. From each batch, ten tablets were weighed and placed in the plastic chamber.

The friabilator rotated for 4 min or 100 revolutions. After 100 revolutions tablets were removed from the chamber and re-weighed. The following formula was used to determine the percentage of weight loss or friability;

Friability (%) = Weight loss after friability / Weight before friability × 100

Content Uniformity and Assay: Ten tablets were weighed and powdered from each batch. The 10 mg powder equivalent of Eprosartan was suspended in 100 ml of water containing 10 ml of methanol. The resulting solution was transferred into a conical flask, closed and it was shaken for 12 h by using a mechanical shaker at room temperature. Next day it was stirred for 15 min. Filtered the solution and diluted suitably. Then the diluted filtrate was measured for absorbance at λ_{max} 234 nm using UV- Visible spectrophotometer (SHIMADZU, Mini-2140 series, Japan). The drug content in the tablet was determined by using the formula;

$$\text{Assay (\%)} = \frac{\text{Abs. of Sam}}{\text{Abs. of Std Std.}} \times \frac{\text{Std. wt Sam.}}{\text{Dilution}} \times \frac{\text{Dilution}}{\text{label quantity}} \times \frac{\text{Drug purity}}{100} \times 100$$

In-vitro drug release studies drug release estimation was performed with various batches of the compressed Eprosartan mesylate tablets by using citrate buffer with pH 4.5 for 60 min using dissolution test apparatus USP XIII paddle type (Model-TDT08L, Electrolab Mumbai, India), 75 rpm in 900 ml dissolution medium and temperature maintained at 37 ± 0.5 ºC. Samples (5 ml) were collected at 5, 10, 15, 30, 45, and 60 min period.

After each sampling, the equal volume of the medium was replaced with the same volume of the fresh medium. The sample was filtered through a 0.45µ membrane filter and diluted with appropriate dilution with the respective medium. Then estimate the Eprosartan concentration in the solution by using UV-Visible spectrophotometry measured at λ_{max} 234 nm. The absorbance measured at different time intervals; then, the concentration, amount of drug released, and the percentage of drug release was calculated.

Mechanism of Drug Release Kinetics Studies: The *in-vitro* dissolution data of Eprosartan subjected to kinetic treatment to get the order of release and best-fit model for the formulations. The various kinetic equations like zero-order (% release *vs.* time), first order (Log % retained *vs.* time), Higuchi matrix (cumulative % drug release *vs.* square root of time) and Korsmeyer and Peppas equation (Log cumulative percent drug released *vs.* log time). The coefficients of correlation (r) values were calculated for the linear curves obtained by regression analysis plots.

Zero-Order Kinetics: Following equation was used to determine the drug release followed by the zero-order kinetics;

$$\text{Concentration (C)} = \text{Initial concentration } (C_i) - K_0 t$$

Where C is the amount of drug dissolved in time t, C_i is the initial amount of drug in the solution (most times C = 0), and K_0 is the zero order release constant. When the data plotted as (%) cumulative drug release versus time; if the plot is linear, then the data obeys zero-order release kinetics with a slope equal to K_0.

First-Order Kinetics: Following equation was used to determine the drug release followed the first-order kinetics;

$$\text{Log concentration (C)} = \text{Log of } C_0 - K_t / 2.303$$

Where; C = remaining drug concentration at time (t), C_0 = Initial drug concentration, K = First-order rate constant (h^{-1})

When the calculated data were plotted as log cumulative percent drug remaining *vs.* time obtained a straight line that indicates that the release follows first order kinetics. The constant "K" can be obtained by multiplying 2.303 with slope values.

Stability Studies: [20, 21] Accelerated stability studies short-term accelerated stability studies for three months according to International Conference on Harmonization guidelines were performed on the optimized formulation. They were subjected to stability studies at 40 °C / 75% RH in a stability chamber for three months. Initial evaluation of the tablets was done, and at the end of 15 days, 45 days and 90 days, the tablets were again analyzed for physical appearance and *in-vitro* drug release profile.

RESULTS AND DISCUSSION:

Characterization of Eprosartan:

Description: White to slightly cream colored powder. Hence, confirms the description as per the certificate of analysis.

Saturation Solubility: The solubility studies have revealed that higher saturation solubility (mg/mL) at pH 4.5 than at pH 6.8. The hot melt method shows better saturation solubility of SDs prepared by using carrier soluplus in the ratio of 1:1.5 in pH 7.4 as compared to the fusion method and solvent evaporation method. The increase in the saturation solubility of drug can be explained by the improved dissolution of SDs.

Determination of λ_{max}: The prepared stock solution was scanned between 200-400 nm to determine the absorption maxima. It was found to be 234 nm.

Melting Point: Melting point by the capillary method and instrumental method observed was 246 ºC and 240 ºC respectively. (As per the literature 249-251ºC).

Differential Scanning Calorimetry (DSC): Thermal analysis of Eprosartan by differential scanning calorimetry showed a characteristic sharp endothermic peak at 250.35 ºC indicating the melting point of the drug. The DSC thermogram of the solid solution shows absences of characteristic melting endotherm of Eprosartan in all batches.

As a single glass transition of solid solution in case of Eprosartan-soluplus (1:1) solid solution indicating the perfect miscibility of ritonavir and soluplus. As a single glass transition temperature is characteristic of the thermoplastic system, the DSC thermogram shows complete amorphization of Eprosartan.

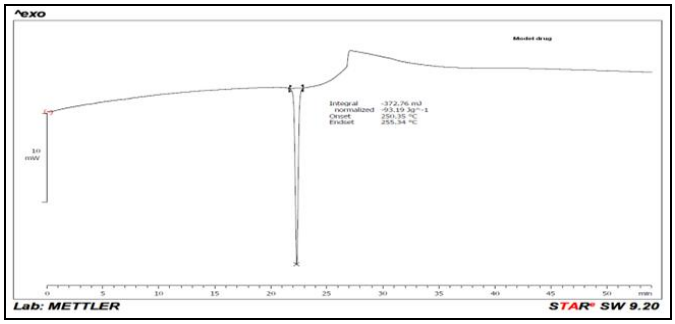

FIG. 2: DSC THERMOGRAPH OF EPROSARTAN

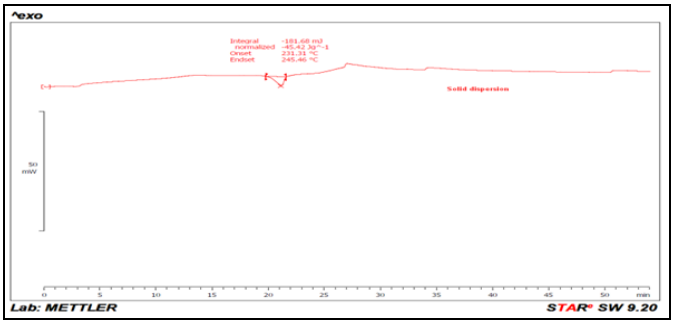

FIG. 3: DSC THERMOGRAPH OF SOLID DISPERSION

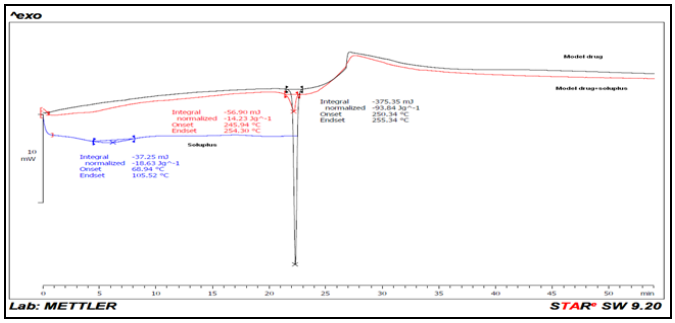

FIG. 4: DSC THERMOGRAM OF EPROSARTAN + SOLUPLUS

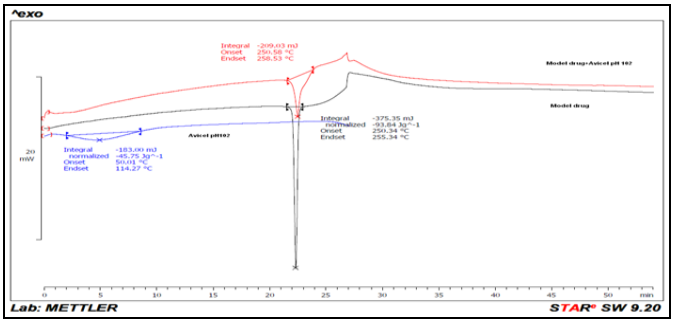

FIG. 5: DSC THERMOGRAM OF EPROSARTAN + AVICEL PH 102

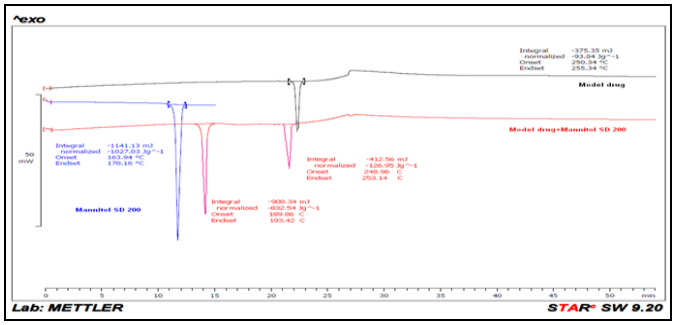

FIG. 6: DSC THERMOGRAM OF EPROSARTAN + MANNITOL (PEARLITOL SD 200)

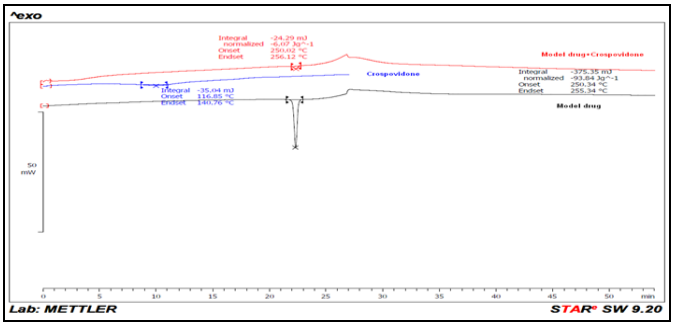

FIG. 7: DSC THERMOGRAM OF EPROSARTAN + CROSPOVIDONE (POLYPLASDONE XL 10)

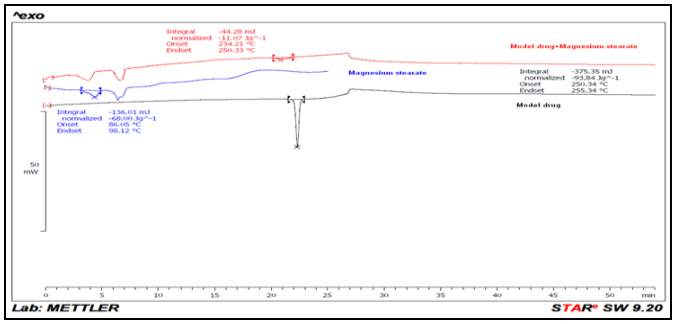

FIG. 8: DSC THERMOGRAM OF EPROSARTAN + MAGNESIUM STEARATE DISPERSION

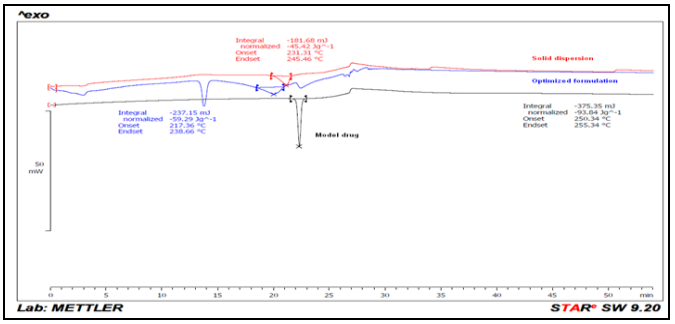

FIG. 9: DSC THERMOGRAM OF DRUG, SOLID AND OPTIMIZED FORMULATION

TABLE 11: COMPATIBILITY OF EPROSARTAN WITH DIFFERENT EXCIPIENTS WITH AID OF DSC

Sample	The appearance of new peaks	The fade of existing peaks	Shifting of peaks >15 °C
Drug + Soluplus	No	No	No
Drug + Microcrystalline cellulose (Avicel pH 102)	No	No	No
Drug + Mannitol (Pearlitol SD 200)	No	No	No
Drug + Crospovidone (Polyplasdone XL 10)	No	No	No
Drug + Magnesium stearate	No	No	No

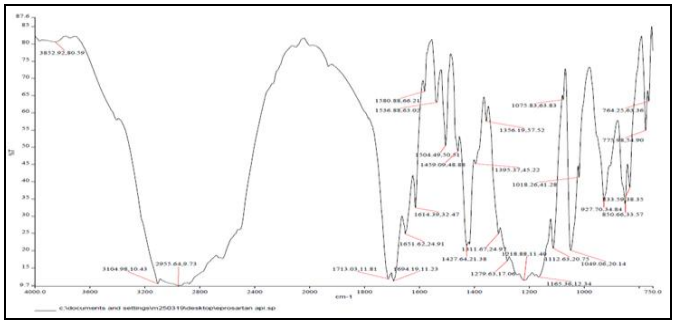

FIG. 10: FT–IR SPECTRA OF EPROSARTAN

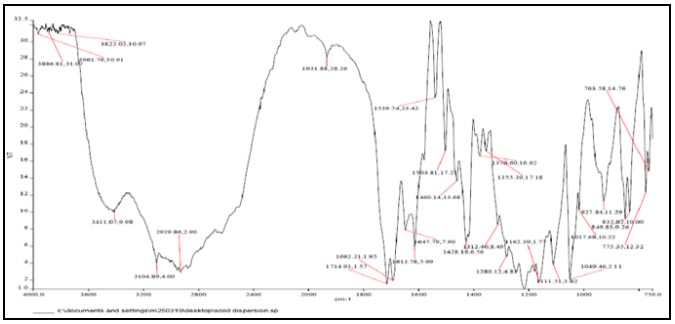

FIG. 11: FT –IR SPECTRA OF SOLID DISPERSION

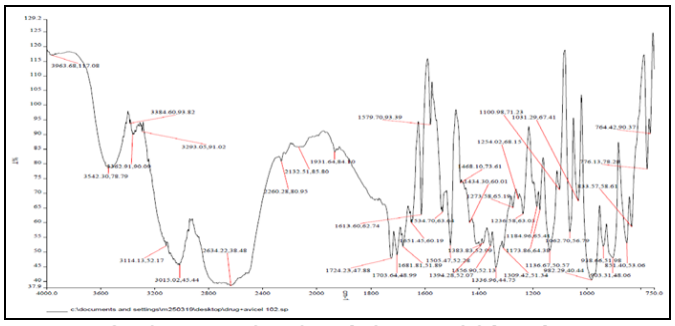

FIG. 12: FT–IR SPECTRA OF EPROSARTAN + AVICEL PH 102

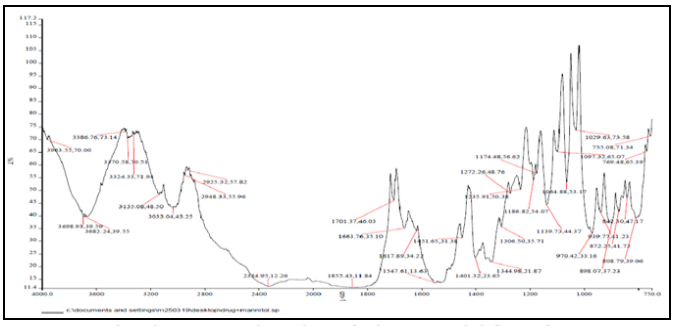

FIG. 13: FT–IR SPECTRA OF EPROSARTAN + MANNITOL SD 200

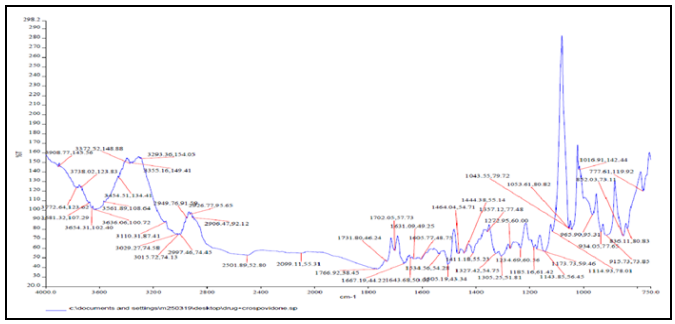

FIG. 14: FT–IR SPECTRA OF EPROSARTAN + CROSPOVIDONE

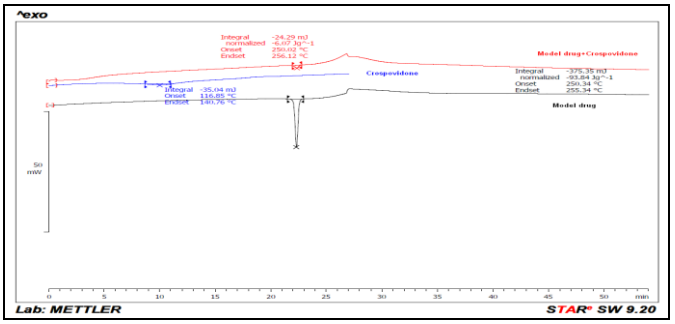

FIG. 15: FT –IR SPECTRA OF EPROSARTAN + MAGNESIUM STEARATE

FT-IR: The FTIR spectra showed that Eprosartan showed a band of alkyl group at 202 cm^{-1}, methyl substituted alkyl group at 208 cm^{-1}, acid or amine salt at 252 cm^{-1}, aromatic compound at 258 cm^{-1},

mono or di-substituted aromatic compound at 263 cm^{-1}, an ionized compound at 404 cm^{-1}, amine salt at 406cm^{-1}, tetrahydropyran compound at 616 cm^{-1}, aromatic or conjugated aliphatic carboxylic acid at 3302 cm^{-1}, phenyl substituted aliphatic carboxylic acid at 3304 cm^{-1}, substituted aryloxy carboxylic acid at 3307 cm^{-1}, amino or hydroxyl benzoate at 3824 cm^{-1}, carboxylic acid at 4923 cm^{-1}, and unsaturated conjugated carbonyl compound at 4927 cm^{-1} and with the combination of other excipients slight changes were observed. This concluded that there were no such drug-polymer interactions in the SDs.

X-ray Powder Diffraction (XRPD): XRPD was used to determine the crystallinity of the hot melt extrudes of a solid solution. The X-ray diffractograms of the solid solution were compared with those of crystalline drug. From the figure, it is observed that t semi-rigid peaks were absent from the diffract grams of the hot melt extrude of a solid solution. Hence, the absence of peaks of crystallinity of pure Eprosartan mesylate indicated complete amorphization of Eprosartan mesylate in solid solution. Thus, amorphization of Eprosartan mesylate due to processing with soluplus was the reason for the dissolution enhancement. The X-ray diffraction analysis also performed for an optimized formulation which revealed that there is a change in molecular form of the drug from crystalline to amorphous form during preparing as solid dispersion but no change in molecular form during the preparation of formulation from solid dispersion.

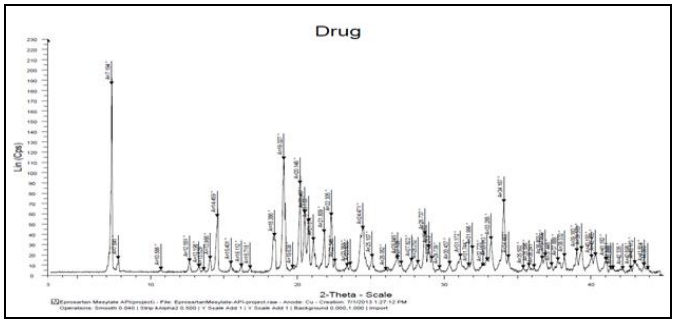

FIG. 16: XRD OF EPROSARTAN

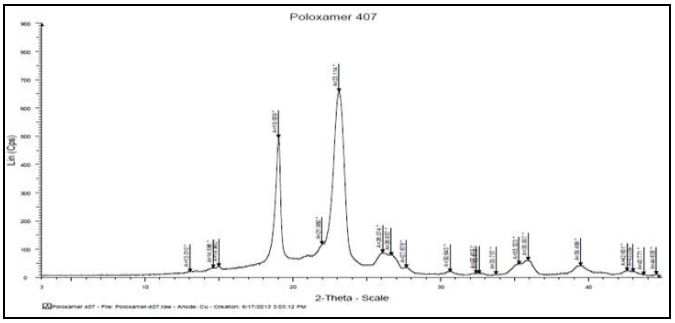

FIG. 17: XRD GRAPH OF OPTIMIZED FORMULATION

Calibration Curve of Eprosartan Mesylate: The standard curve of Eprosartan mesylate was obtained, and a good correlation was obtained with an R^2 value of 0.999. The medium selected was pH 4.5 phosphate buffer. The standard graph values of Eprosartan mesylate are shown in **Fig. 1**.

Evaluation:

Powder Characterisation of Solid Dispersion of Different Trial Batches: According to the results showed in **Table 12**, the solid dispersions prepared by solvent evaporation have compressibility index in the range of 20-29% and Hausner's ratio in the range of 1.3-1.4 which explains the solid dispersions prepared by solvent evaporation have poor flow.

The solid dispersions prepared by fusion method have compressibility index in the range of 19-23% and Hausner's ratio in the range of 1.4-1.9 which explains the solid dispersions prepared by fusion have passable flow.

TABLE 12: POWDER CHARACTERISATION OF SOLID DISPERSION OF DIFFERENT TRIAL BATCHES

Solid dispersion	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Compressibility Index (CI) (%)	Hausner's ratio (HR)
SD1	0.341	0.476	28.36	1.395
SD2	0.347	0.482	28.00	1.389
SD3	0.449	0.515	26.99	1.369
SD4	0.462	0.624	19.51	1.24
SD5	0.485	0.562	19.66	1.244
SD6	0.546	0.565	20.05	1.250
SD7	0.452	0.574	19.94	1.249
SD8	0.502	0.699	19.54	1.242
SD9	0.541	0.634	19.91	1.248
SD10	0.553	0.587	20.21	1.253
SD11	0.587	0.623	20.0	1.25

SD12	0.539	0.642	22.12	1.284
SD13	0.521	0.622	19.94	1.249
SD14	0.497	0.546	19.68	1.245
SD15	0.448	0.519	18.3	1.224
SD16	0.476	0.542	18.02	1.219
SD17	0.483	0.512	18.00	1.218
SD18	0.401	0.496	17.05	1.205
SD19	0.412	0.500	17.60	1.21

TABLE 13: POST COMPRESSION PARAMETERS OF TABLETS FROM SOLVENT EVAPORATION BATCH

Formulation	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Compressibility Index (CI) (%)	Hausner's ratio (HR)
F1	0.461	0.582	20.79	1.26
F2	0.472	0.594	20.53	1.258
F3	0.469	0.588	20.23	1.253
F4	0.562	0.705	20.28	1.254
F5	0.572	0.712	19.66	1.244
F6	0.566	0.708	20.05	1.250
F7	0.554	0.692	19.94	1.249
F8	0.564	0.701	19.54	1.242
F9	0.559	0.698	19.91	1.248

The solid dispersions prepared by hot melt extrusion have compressibility index in the range of 17-20% and Hausner's ratio in the range of 1.21-1.24 which explains the solid dispersions prepared by hot melt extrusion have fair flow property.

Physical Evaluation of Eprosartan Mesylate Solid Dispersion Tablets: All the tablets of different batches complied with the official requirement of weight variation as their weight variation passes the limits.

TABLE 14: PHYSICAL CHARACTERIZATION OF TABLETS

Formulation	The average weight of Tablet (mg)	Average thickness (mm)	Average hardness (kp)	Friability (%)	Disintegration time (sec)
F1	1020	8.40	5	0.12	130-135
F2	1021	8.40	5	0.14	140-150
F3	1020	8.39	5	0.11	145-150
F4	1019	8.41	5	0.14	155-160
F5	1021	8.42	5	0.13	165-170
F6	1020	8.43	5	0.12	175-180
F7	1020	8.39	5	0.11	180-185
F8	1021	8.40	5	0.13	185-190
F9	1020	8.41	5	0.12	195-200

TABLE 15: DISSOLUTION DATA OF FORMULATIONS PREPARED BY SOLVENT EVAPORATION

Formulation code	% Drug release ± SD							
	0 min	5 min	10 min	15 min	20 min	25 min	30 min	45 min
F1	0	7.4±0.16	8.28±0.12	9.89±0.11	11.77±0.13	18.28±0.12	21.87±0.10	24.36±0.14
F2	0	7.24 ±0.06	8.65±0.15	10.53±0.17	12.19±0.21	18.08±0.12	21.69±0.11	27.33±0.13
F3	0	8.59±0.11	9.89±0.08	11.52±0.08	13.66±0.14	21.55±0.15	26.79±0.21	30.64±0.14
F4	0	6.45±0.15	7.42±0.18	7.92 ±0.11	8.67 ±0.13	14.26±0.14	20.83±0.17	23.36±0.14
F5	0	6.82±0.18	7.72±0.08	8.48 ±0.12	9.21 ±0.09	14.11±0.19	20.96±0.04	23.85±0.15
F6	0	7.21±0.09	8.26±0.14	9.54 ±0.16	10.63±0.17	14.78±0.12	18.19±0.21	24.42±0.18
F7	0	5.74±0.16	6.02±0.08	6.72 ±0.12	7.94 ±0.17	14.86±0.14	17.32±0.18	20.86±0.14
F8	0	6.05±0.15	6.98±0.12	7.82 ±0.11	8.25 ±0.15	13.92±0.18	16.74±0.16	21.87±0.13
F9	0	6.43±0.17	7.02±0.18	8.12 ±0.08	8.98 ±0.12	15.79±0.21	19.58±0.12	22.28±0.12

The hardness of the tablets ranged from 5.6 to 5 $kg/cm^{2,}$ and the friability values were less than 0.11%, indicating that the tablets were compact and hard. The thickness of the tablets ranged from 8.44cm, and Carr's index of the tablets ranged from 19-25% all the formulations not satisfied the content of the drug as they contained 78-89% of Eprosartan mesylate not shown good uniformity in drug content was observed. *In-vitro* dissolution data presented in **Table 15** showed that formulations prepared from solid dispersion prepared by solvent evaporation have % drug release in the range of 22.89-31.72%. The amount of drug released was more in formulation F3 which

has soluplus as carrier and mannitol and avicel as carriers in the range of 1:1 when compared to other formulations. All the formulations follow first-order rate kinetics. Thus, all the physical attributes of the prepared tablets were found to be practically not in control limits.

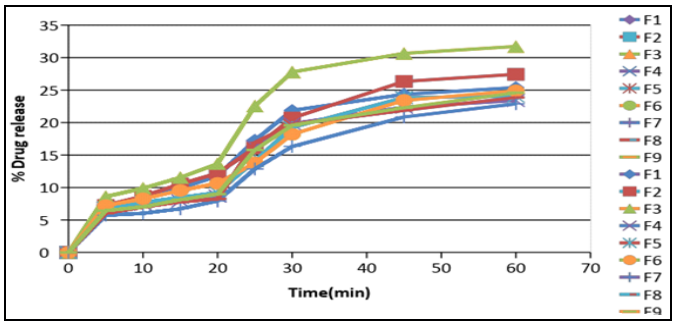

FIG. 18: *IN-VITRO* DRUG RELEASE PROFILE OF EPROSARTAN FORMULATIONS PREPARED BY SOLVENT EVAPORATION (F1-F9)

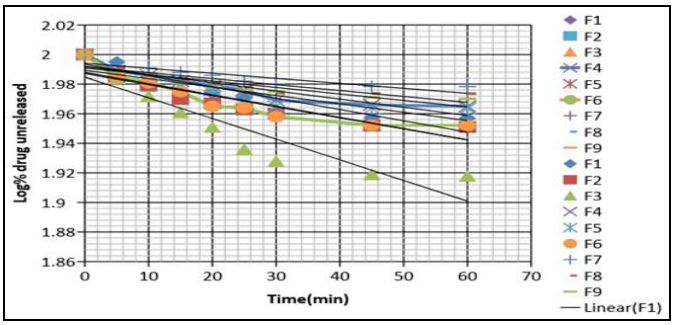

FIG. 19: FIRST ORDER PLOT OF EPROSARTAN FORMULATIONS PREPARED BY SOLVENT EVAPORATION

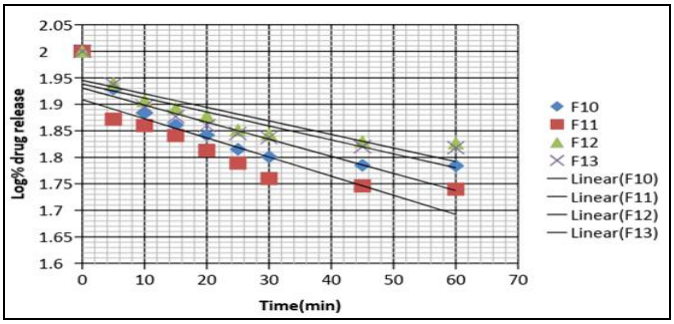

FIG 20: FIRST ORDER PLOT OF FORMULATIONS PREPARED BY FUSION METHOD

Evaluation Results of Tablets from Solid Dispersions Prepared by Fusion: The tablet blends prepared from solid dispersion prepared by fusion have compressibility index in the range of 20-23% and Hausner's ratio in the range of 1.24-1.28 resulting passable flow property. The tablets of formulations F10, F11 have an average weight of 1020 mg, an average thickness of 8.42 mm, average hardness of 5 kg/cm^2 and friability in the range of 0.10-0.11% according to the **Table 17**. *In-vitro* dissolution data presented in **Table 18** showed that formulations prepared from solid dispersion prepared by fusion have % drug release in the range of 39.14-45%. The amount of drug released was more in formulation F11 which has drug and soluplus in the ratio of 1:1 and mannitol and avicel as carriers in the range of 1:1 when compared to other formulations. All the formulations follow first-order rate kinetics.

TABLE 16: BLEND CHARACTERIZATION OF FORMULATIONS OF TRIAL BATCHES

Formulation	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Compressibility index (CI) (%)	Hausner's ratio (HR)
F10	0.454	0.569	20.21	1.253
F11	0.488	0.610	20.0	1.25
F12	0.542	0.696	22.12	1.284
F13	0.534	0.667	19.94	1.249

TABLE 17: PHYSICAL CHARACTERIZATION OF TABLETS

Formulation	The average weight of Tablet (mg)	Average thickness (mm)	Average hardness (kp)	Friability (%)	Disintegration time (sec)
F10	821	7.20	5	0.10	140-145
F11	1021	8.42	5	0.11	120-125
F12	821	7.19	5	0.11	150-155
F13	1020	8.42	5	0.10	130-140

TABLE 18: DISSOLUTION DATA OF FORMULATIONS PREPARED BY FUSION

Formulation code	% Drug release± SD							
	0 min	5 min	10 min	15 min	20 min	25 min	30 min	45 min
F10	0	14.96±0.21	23.6±0.14	27.38±0.12	30.36±0.14	34.54±0.16	36.72±0.18	38.96±0.14
F11	0	25.46±0.24	27.53±0.17	30.65±0.15	34.98±0.18	38.42±0.16	42.4±0.10	44.21±0.09
F12	0	12.86±0.14	19.24±0.16	21.7±0.13	24.42±0.18	28.76±0.14	30.12±0.18	32.24±0.16
F13	0	13.12±0.18	21.24±0.16	24.62±0.18	27.41±0.19	29.86±0.14	31.24±0.16	33.89±0.21

Evaluation Results of Tablets from Solid Dispersions Prepared by Hot Melt Extrusion: The tablet blends prepared from solid dispersion prepared by hot melt extrusion have compressibility index in the range of 17-20% and Hausner's ratio in the range of 1.20-1.245 resulting fair flow property. The tablets have an average hardness of 5 kg/cm^2 and friability in the range of 0.11-0.14%. *In-vitro* dissolution data presented in **Table 21** showed that formulations prepared from solid dispersion prepared by hot melt extrusion have % drug release in the range of 68.74-92.14%. The amount of drug released was more (92.14%) in formulation F19 which has soluplus as carrier and mannitol and avicel as carriers in the range of 1:1 when compared to other formulations so it is optimized for further studies. All the formulations follow first-order rate kinetics.

TABLE 19: BLEND CHARACTERIZATION OF FORMULATIONS OF TRIAL BATCHES

Formulation	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Compressibility index (CI) (%)	Hausner's ratio (HR)
F14	0.453	0.564	19.68	1.245
F15	0.428	0.524	18.3	1.224
F16	0.441	0.538	18.02	1.219
F17	0.446	0.544	18.00	1.218
F18	0.428	0.516	17.05	1.205
F19	0.432	0.522	17.24	1.208

TABLE 20: PHYSICAL CHARACTERIZATION OF TABLETS

Formulation	Average Weight of Tablet(mg)	Average thickness (mm)	Average hardness (kp)	Friability (%)	Disintegration time (sec)
F14	661	6.14	5	0.12	80-85
F15	701	6.35	5	0.11	70-75
F16	741	6.54	5	0.11	55-60
F17	780	6.80	5	0.12	40-45
F18	821	7.16	5	0.10	35-40
F19	1020	8.36	5	0.13	20-25

TABLE 21: DISSOLUTION DATA OF FORMULATIONS PREPARED BY HOT MELT EXTRUSION

Formulation code	% Drug release ± SD							
	0min	5 min	10 min	15 min	20 min	25 min	30 min	45 min
F14	0	47.98±0.02	50.64±0.06	54.84±0.03	58.98±0.12	61.83±0.07	64.27±0.06	68.62±0.08
F15	0	49.42±0.08	52.38±0.07	56.96±0.05	62.13±0.13	65.22±0.06	67.86±0.18	69.33±0.21
F16	0	50.02±0.18	54.42±0.02	58.28±0.06	61.29±0.11	64.12±0.08	69.32±0.08	71.46±0.04
F17	0	52.11±0.09	58.44±0.16	61.64±0.16	64.06±0.15	67.44±0.21	71.65±0.15	74.56±0.14
F18	0	60.98±0.22	65.42±0.18	68.35±0.15	71.62±0.18	73.22±0.11	75.63±0.07	77.33±0.17
F19	0	69.23±0.17	73.43±0.11	77.42±0.18	81.95±0.15	84.82±0.18	88.64±0.16	91.86±0.12

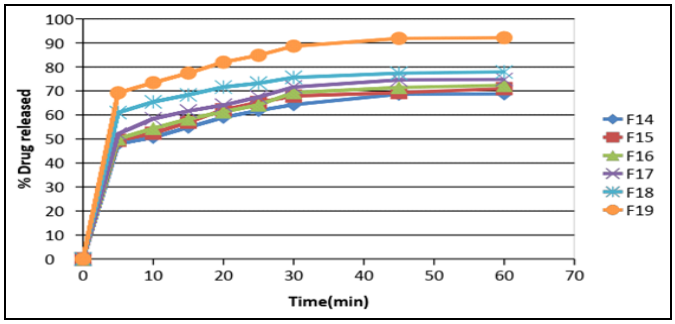

FIG. 21: *IN-VITRO* DRUG RELEASE OF FORMULATIONS PREPARED BY HOT MELT EXTRUSION METHOD

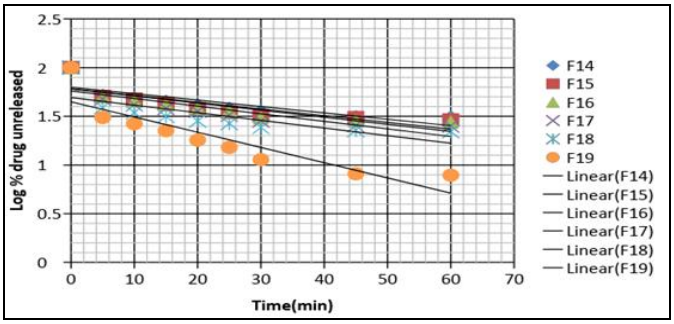

FIG. 22: FIRST ORDER PLOT OF FORMULATIONS PREPARED BY HOT MELT EXTRUSION

Evaluation of Drug Release Kinetics: All the batches from F- 1 to F-19 of Eprosartan mesylate tablet formulations were subjected to various release kinetics like zero-order kinetics and first-order kinetics models to determine the release pattern of the drug. The *in-vitro* dissolution patterns were shown in **Fig. 20** and **21** of the tablet formulations. The correlation coefficient (R^2) is given in **Table 22**. The R^2 values of first-order kinetic models are more than the zero order kinetic model values which determining that the drug is following the first order kinetics in the *in-vitro* release.

Stability Study: Stability study of the dosage form must include a section for product characterization, and another section to study the product stability during storage. Formulations are evaluated for their appearance, possible weight gain in drug content thickness, flatness, folding endurance, tensile strength, moisture content and moisture uptake, and *in-vitro* release study by keeping dosage form in different temperature and humidity condition after a specified time. The stability study indicates that the formulation is quite stable at different conditions of storage.

TABLE 22 PERCENTAGE DRUG RELEASE OF PURE DRUG

Time (min)	0	5	10	15	20	25	30	45	60
% Drug release	0	3.42	5.21	6.64	7.87	8.42	9.34	10.89	14.52

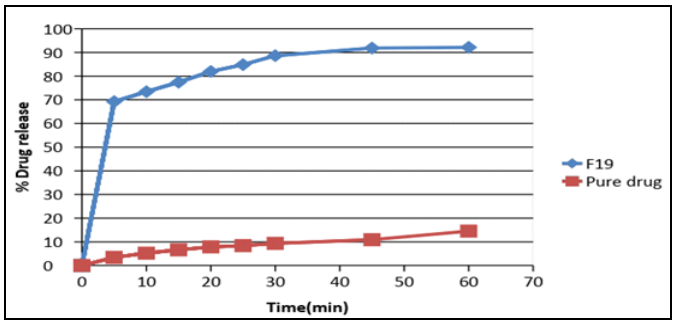

FIG. 23: COMPARISON OF % DRUG RELEASE DATA OF PURE DRUG AND OPTIMIZED FORMULATION

TABLE 23: *IN-VITRO* DISSOLUTION KINETICS OF EPROSARTAN FORMULATIONS USING DIFFERENT DILUENTS AND CARRIERS

S. no.	Formulation	Correlation coefficient		DE_{60} (%)	K (min)	T_{50} (hr)	T_{90} (hr)
		Zero order	First order				
1	F1	0.775	0.993	15.38	0.082	3.25	5.616
2	F2	0.723	0.986	17.42	0.0757	2.87	5.16
3	F3	0.782	0.984	21.72	0.088	2.30	4.14
4	F4	0.691	0.991	13.4	0.084	3.73	6.71
5	F5	0.676	0.989	14.05	0.0761	3.55	6.40
6	F6	0.672	0.988	14.89	0.104	3.35	6.04
7	F7	0.658	0.910	12.89	0.102	3.87	6.98
8	F8	0.651	0.964	13.88	0.092	3.60	6.48
9	F9	0.642	0.973	14.59	0.165	3.42	6.16
10	F10	0.863	0.933	39.14	0.105	1.27	2.29
11	F11	0.838	0.920	44.96	0.088	1.11	2.00
12	F12	0.828	0.982	32.85	0.139	1.522	2.73
13	F13	0.824	0.911	34.11	0.096	1.46	2.63
14	F14	0.836	0.932	68.74	0.112	0.727	1.30
15	F15	0.811	0.944	70.96	0.089	0.704	1.26
16	F16	0.799	0.939	72.32	0.096	0.610	1.24
17	F17	0.786	0.952	74.78	0.124	0.668	1.203
18	F18	0.769	0.961	77.94	0.108	0.641	1.15
19	F19	0.791	0.977	92.14	0.115	0.542	0.976

TABLE 24: ACCELERATED STABILITY STUDY OF F19 OPTIMIZED FORMULE

Formulation	Time	Parameters			
		Hardness kg/cm^3	Friability	Drug content	Disintegration time (Sec)
F19	15 days	5.5	0.009	99.3	24.2
F19	15 days	5.5	0.009	99.6	24.5
F19	15 days	5.5	0.009	99.7	24.3

CONCLUSION: Among the various formulations, the formulation F19 with the concentration of drug and soluplus, kollidon VA64, plasdone K29/32 and 10 mg of avicel was ideal enough to formulate it as solid dispersions by solvent evaporation, fusion and hot melt extrusion technique. Among the three techniques, the solubility of the drug increased by hot melt extrusion technique with concentration of drug and soluplus when compared to solvent evaporation and fusion methods. Therefore the carrier soluplus was suitable for enhancement of solubility of Eprosartan than other carriers used in this investigation such as kollidon VA64 and plasdone K29/32. The drug release of this immediate release formulation was not more than 60 min. From the above results, it was concluded that the improved drug dissolution could be achieved by formulating Eprosartan as a solid solution with the polymers such as soluplus. The low hygroscopicity and low glass transition temperature of soluplus make it particularly suitable for hot melt extrusion, and the addition of a plasticizer is not required in case of soluplus because of low glass transition temperature.

So, from the data reported, the proposed method of preparation can be ideal for preparing immediate release tablets of Eprosartan mesylate and the optimized formulations shows good stability over the period of 3 month at 40 ± 2 ºC / 75% ± 5% RH. With all the above information it was confirmed that the amount of drug release was more with F19 than with other formulations. So formulation F19 was optimized for further evaluations.

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