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Research Article

DEVELOPMENT, EVALUATION AND CHARECTERIZATION OF SOLID DISPERSION FOR SOLUBILITY AND DISSOLUTION ENHANCEMENT OF IRBESARTAN

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ABSTRACT

The objective of the present study was to formulate Solid dispersions (SD) of Irbesartan to improve the solubility and dissolution rate to facilitate faster onset of action. Irbesartan is a BCS-II drug having low solubility and low availability. In the present study, SD's of Irbesartan with three different polymers (PEG-4000, PEG-6000 and PVP-K30) with five different drug-carrier ratios were prepared by solvent evaporation method. SD's were characterized by assay & content uniformity, FT-IR studies, PXRD (Powder X- ray diffractometry, DSC (differential scanning calorimetry), Gas chromatography and in vitro dissolution studies. The dissolution profile of prepared dispersion of Irbesartan: PEG 4000 in 1:9 ratio were faster compared to other carriers, DSC studies revealed that there was no interaction between drug: carrier where as the P-XRD demonstrated that there was a significant decrease in crystallinity of pure drug present in the solid dispersions, which resulted in an increased dissolution rate of Irbesartan.

Keywords: Irbesartan, PEG-4000, PEG-6000, PVP-k30, Solid dispersion.

1. INTRODUCTION

Poorly water soluble compounds have solubility, dissolution related bioavailability problems. Enhancement of solubility and dissolution rate is a challenging task in drug development. Nearly 40% of New Chemical Entities (NCE) currently being discovered are poorly water soluble[1]. The absorption rate of a poorly water-soluble drug, formulated as an orally administered solid dosage form, is controlled by its dissolution rate in the fluid at the absorption site. The dissolution rate is often the rate-determining step in drug absorption[2]. Therefore, the solubility and dissolution behavior of a drug are the key determinants of the oral bioavailability[3].

To improve the dissolution and bioavailability of poorly water-soluble drugs, researchers have employed various techniques such as Micronization[4], solubilization[5], salt formation, complexation with polymers, change in physical form, use of pro-drug and drug derivitization, pH alteration, addition of surfactants and others[6,7].

Chiou and serajuadin used the solid-dispersion technique for dissolution enhancement of poorly water-soluble drugs[8,9]. A solid dispersion can be defined as "The dispersion of one or more active ingredients in an inert carrier matrix in solid-state prepared by a melting (fusion), solvent, or melting – solvent method" Among various approaches, The solid-dispersion technique has often proved to be the most successful in improving the dissolution and bioavailability of poorly soluble, active pharmaceutical ingredients because it is simple, economical and advantageous.

The aim of the present study was to prepare solid dispersions in order to achieve increased dissolution rates.

Therefore, in the present study, solid dispersions of irbesartan were prepared by solvent evaporation technique using acetone as solvent for dissolving the drug. Acetone was selected as a solvent of choice since the drug has highest solubility in this solvent and acetone could be easily evaporated and recovered because of its low boiling point. Acetone as per ICH guidelines is categorized under class II solvents thus rendering it to be less toxic than other chlorinated solvents.

2. MATERIALS AND METHOD

Irbesartan (gift sample procured from Dr. Reddy's Laboratories, Hyderabad), PVP-K30 (ISP, Hyderabad) Polethyleneglycol-4000, Polyethyleneglycol-6000, Acetone (Ranchem) and all the reagents used were analytical grade.

2.1. Preparation of solid dispersions: Solvent Evaporation method

Solid dispersions of irbesartan in carriers PVP k 30, PEG 4000, PEG6000 were prepared by required amount of irbesartan was dissolved in 10 ml of acetone. Accurately weighed carrier corresponding to different drug**:** carrier ratio by weight was dispersed in drug solution. The solvent was allowed to evaporate on water bath under occasional stirring at temperature of 40-42^{o}C in a protected environmental condition containing an exhaust system. The dried mass was pulverized and was passed through a #100-mesh sieve. The powder was subsequently dried at 40°C for 3 hours in a tray drier. The powder was stored in desiccator for further studies.

2.2 Percent yield

Percent yield was determined by following formula

$$Yield = \left(\frac{a}{b+c}\right) \times 100$$

where, a is the weight of solid dispersion sifted through a # 60 sieve, b is the weight of irbesartan taken for solid dispersion preparation, and c is the weight of polymer taken for solid dispersion preparation.

Table 1: Coding formulations for SD of Irbesartan

DRUG	CARRIER	CODE	DRUG: CARRIER
Irbesartan (SD)	PVP K 30	SD-PVP1	1:1
		SD-PVP3	1:3
		SD-PVP5	1:5
		SD-PVP7	1:7
		SD-PVP9	1:9
	PEG 4000	SD-P4 1	1:1
		SD-P4 3	1:3
		SD-P4 5	1:5
		SD-P4 7	1:7
		SD-P4 9	1:9
	PEG 6000	SD-P6 1	1:1
		SD-P6 3	1:3
		SD-P6 5	1:5
		SD-P6 7	1:7
		SD-P6 9	1:9

2.3 Characterization of Solid Dispersions

2.3.1. Percent yield

Percent yield was determined by following formula:

$$Yield = \left(\frac{a}{b+c}\right) \times 100$$

where, a is the weight of solid dispersion sifted through a # 60 sieve, b is the weight of irbesartan taken for solid dispersion preparation, and c is the weight of polymer taken for solid dispersion preparation.

2.3.2. Assay

Accurately weighed samples equivalent to 75mg of drug was taken in a 100ml volumetric flask; 10ml methanol was added and sonicated for 20min to dissolve the drug. The volume was made to 100ml with 0.1N HCl. The dispersion was filtered using Whatmann filter paper. A 10ml aliquot of the above solution was taken and diluted to 100ml with 0.1N HCl. The absorbance of sample solution was determined at 245nm against acid blank.

2.3.3. In vitro dissolution studies

Irbesartan a pure drug & solid dispersions of irbesartan were subjected to dissolution test using in-vitro dissolution rate apparatus-I of USP XXIV. (Basket method). This test was performed using 1000ml of dissolution medium (0.1N HCL) at 37±2C.Accurately weighed samples (plain drug and surface solid dispersions) of drug were filled in '00' size hard gelatin capsule by hand filling method and placed in basket of dissolution apparatus which was rotated at 50rpm.A 5ml aliquot of dissolution medium was withdrawn at appropriate time intervals. An equal volume of fresh dissolution medium was immediately replaced. It was suitably diluted and analyzed spectrophotometrically by measuring absorbance at 245nm.The experiments were performed in triplicate. With the help of standard curve equation concentration were found using absorbance values.

2.3.4. Dissolution of Plain drug

The weighed quantity of drug was filled into the empty gelatin capsule. Capsule was placed in basket of dissolution vessel containing the pre-warmed media (37 ± 0.5°C). Dissolution studies of plain drug was conducted in 1000ml 0.1N HCL at 37± 0.5°C at 50 rpm.

2.3.5. Dissolution of surface solid dispersions

The weighed quantity of SSD was filled into the empty gelatin capsule. Capsule was placed in basket of dissolution vessel containing the pre-warmed media (37 ± 0.5°C). Dissolution studies of plain drug was conducted in 1000ml 0.1N HCL at 37± 0.5°C at 50 rpm.

2.3.6. Data treatment of dissolution studies

1. Dissolution profiles of % DR Vs time were obtained. Amount of drug released at 5,10, 15, 20,30,45,60,75,90 minutes were calculated and tabulated as $t_5,t_{10},t_{15},t_{20},t_{30},t_{45},t_{60},t_{75},t_{90}$ respectively.
2. Model independent parameter, the dissolution efficiency (DE_T) was employed to compare dissolution profiles of different samples. DE_T was calculated according to the following equation[13].

$$DE_T = \frac{\int_0^T y_t . dt}{y_{100} . T}$$

Where y_t is % of drug dissolved at any time t, denotes y_{100} 100% dissolution, the integral represents the area under dissolution curve between time zero and T.

2.3.7. Mechanism of drug release

Mechanism of drug release was obtained by applying the release data to various models like zero order, first order, Higuchi.

Table 2: Mechanism of drug release[14]

Model	Equation	Plot of graph	parameters
Zero order	$F= K_o t$	% drug release Vs time	K_o- release rate constant
First order	Log (100-F)=Kt	log % drug remaining Vs time	K- release rate constant
Higuchi release	$F= K_1 t^{1/2}$	% drug release Vs square root of time	K_1- release rate constant

Common key words: F- drug release; T –release time

The optimized SSD of irbesartan: SSG (1:7 ratio) was characterized for assay& content uniformity, FT IR studies, XRD, DSC, Gas chromatography and in vitro dissolution studies.

2.3.8. Powder X-Ray diffraction analysis

X- ray diffraction of drug (IRB), SSG, Drug: SSG (1:7) formulation was recorded by using "PAN alytical X'pert pro". The cross section of the samples was exposed to X-ray radiation with scanning range of 0-50θ.

2.3.9. Differential Scanning Calorimeter

Thermo grams of IRB, and Drug: SSG formulation was recorded by using "Perkin-Elmer differential scanning calorimeter with a pyris6 workstation". The accurately weighed sample was placed on aluminium pan and an empty aluminium pan was used as reference. Thermal behavior of the samples was investigated under a scanning rate of 10° C/ min, covering a temperature range of 0- 300°.

2.3.10. Gas chromatography

The determination of acetone was performed by gas chromatography on a Agilent GC 6890N with 7694E Head space sampler, fitted with flame ionization detector. Carrier gas was nitrogen. Headspace GC is used to detect solvent residues. The packed column was BD-624 capillary column. Temperature of oven was 60^0C injection port 140^0C and detector 250^0 C. Oven was programmed at 5^0 C/min for 10min, 15^0 C/min up to 250^0 C with a hold time of 7min.

3.0. RESULTS AND DICUSSION

3.1. Assay

The drug content was determined for irbesartan solid dispersions and they are given in Table 3.

Table 3: Assay of various formulations of solid dispersions (n=3)

DRUG	CARRIER	CODE	DRUG: CARRIER RATIO	ASSAY
Irbesartan (SD)	PVP K 30	SD-PVP1	1:1	97.64±0.55
		SD-PVP3	1:3	96.16±0.63
		SD-PVP5	1:5	91.50±0.78
		SD-PVP7	1:7	94.79±0.80
		SD-PVP9	1:9	97.85±0.40
	PEG 4000	SD-P4 1	1:1	101.35±1.16
		SD-P4 3	1:3	96.42±1.18
		SD-P4 5	1:5	102.01±0.55
		SD-P4 7	1:7	98.60±0.62
		SD-P4 9	1:9	101.33±0.92
	PEG 6000	SD-P6 1	1:1	98.72±0.49
		SD-P63	1:3	96.01±0.59
		SD-P6 5	1:5	97.03±0.58
		SD-P6 7	1:7	92.66±0.86
		SD-P6 9	1:9	94.31±2.6

3.2. Percentage yield

Percentage yield was calculated according to the formula and results are given in Table 4.

Table 4: Percentage yield of various formulations of solid dispersions

CODE	CARRIER	CODE	DRUG: CARRIER RATIO	% YIELD
Irbesartan (SD)	PVP K 30	SD-PVP1	1:1	96.87
		SD-PVP3	1:3	96.17
		SD-PVP5	1:5	97.35
		SD-PVP7	1:7	95.70
		SD-PVP9	1:9	95.74
	PEG 4000	SD-P4 1	1:1	91.70
		SD-P4 3	1:3	95.37
		SD-P4 5	1:5	97.06
		SD-P4 7	1:7	97.68
		SD-P4 9	1:9	96.98
	PEG 6000	SD-P6 1	1:1	95.34
		SD-P6 3	1:3	96.94
		SD-P6 5	1:5	95.74
		SD-P6 7	1:7	95.35
		SD-P6 9	1:9	97.14

3.3. In vitro dissolution

Dissolution data of solid dispersions on excipients are reported in Fig.1, Fig.2, and Fig.3. From the given data, it can be seen that all the prepared solid dispersion showed an enhancement in the dissolution rate of the drug compared to plain drug. Solid dispersions prepared by using PEG 4000 (1:9) showed enhanced dissolution when compared to other carriers. Solid dispersions of irbesartan were prepared with various carrier concentrations and the effect of increasing carrier concentration on dissolution rate was determined. This is because of as soluble carrier dissolves; the insoluble drug gets exposed to dissolution medium in the form of very fine particles for quick dissolution. The rank order of dissolution rate improvement for various carriers are; PEG 4000>PEG 6000>PVP K 30. The result was more

significant for PEG 4000 (1:9 drug: carrier ratio). 100% of drug release was seen within 45 min compared to 180 min for plain drug.

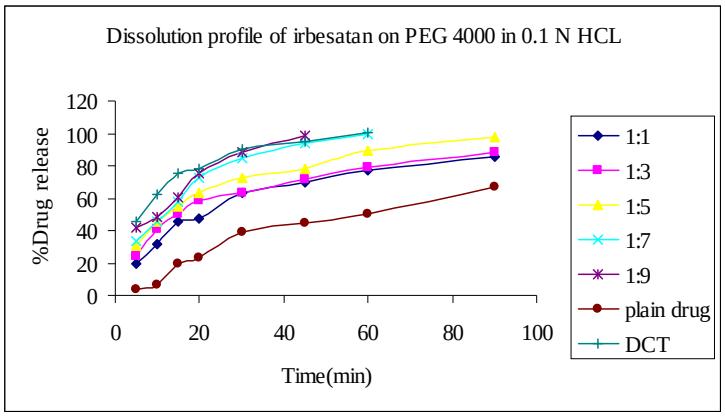

Fig. 1: Dissolution profile of Irbesartan on PEG 4000 in 0.1 N HCl

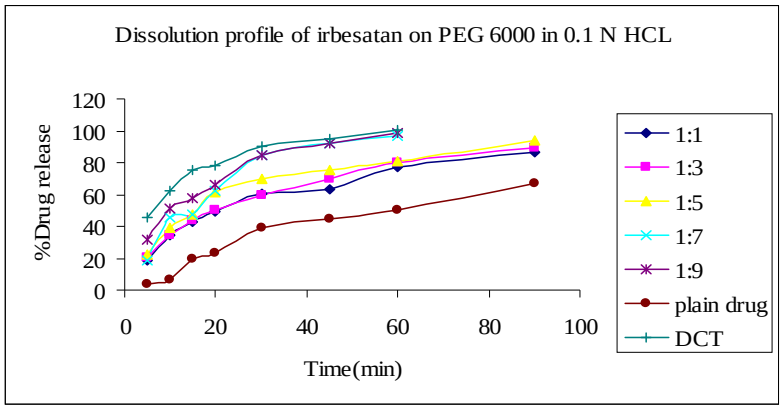

Fig 2: Dissolution profile of Irbesartan on PEG 6000 in 0.1 N HCl

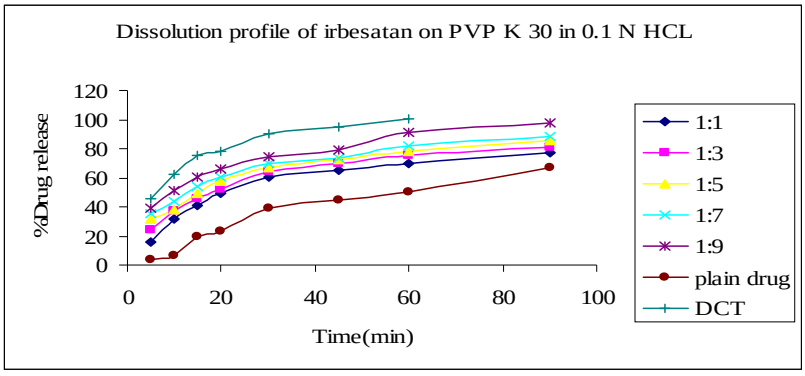

Fig. 3: Dissolution profile of Irbesartan on PVP K 30 in 0.1 N HCl

Table 5: Comparision studies of Dissolution profiles of different SDs in 0.1 N HCL

CODE	DRUG: CARRIER RATIO	T5	T15	T30	T45	T60	T90
SD-PVP1	1:1	15.38	49.60	60.41	65.23	69.98	76.91
SD-PVP3	1:3	23.83	52.11	64.43	69.73	75.22	81.00
SD-PVP5	1:5	31.95	57.61	67.09	72.25	78.19	85.81
SD-PVP7	1:7	35.59	60.69	69.74	73.85	81.90	88.72
SD-PVP9	1:9	38.61	66.05	74.82	78.81	91.37	97.30
SD-P4 1	1:1	19.30	45.20	62.85	69.80	77.11	85.91
SD-P4 3	1:3	23.83	50.54	63.15	71.30	78.77	88.79
SD-P4 5	1:5	30.46	54.97	72.60	78.54	89.00	98.07
SD-P4 7	1:7	33.93	57.55	84.74	94.21	99.52	-
SD-P4 9	**1:9**	**41.97**	**60.61**	**88.53**	**99.83**	-	-
SD-P6 1	1:1	18.85	42.64	60.74	63.63	77.25	86.48
SD-P6 3	1:3	20.51	44.16	59.71	69.81	80.00	88.95
SD-P6 5	1:5	21.87	47.51	69.47	75.39	80.87	94.26
SD-P6 7	1:7	18.85	47.07	84.57	91.93	96.93	-
SD-P6 9	1:9	31.67	57.42	84.73	92.09	98.45	-

3.4. Mechanism of drug release

To determine the kinetics of release, the drug release data was treated and rate constants for zero order, first order and Higuchi model was obtained and reported in Table4.12. The release of drug from solid dispersion followed Higuchi model kinetics as seen from the R^2 value.

Table 4: Release rate constants for solid dispersions

Code	Parameter	Zero order	First order	Higuchi model
SD P4 9	K	1.4751	-0.038	13.683
	r^2	0.9347	0.9649	0.9725

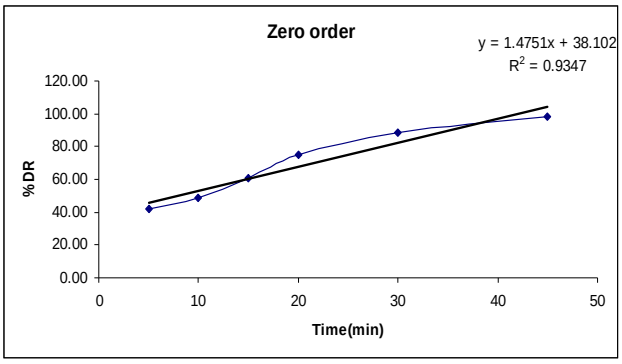

Fig. 4: PEG 4000 solid dispersions (1:9) Zero order

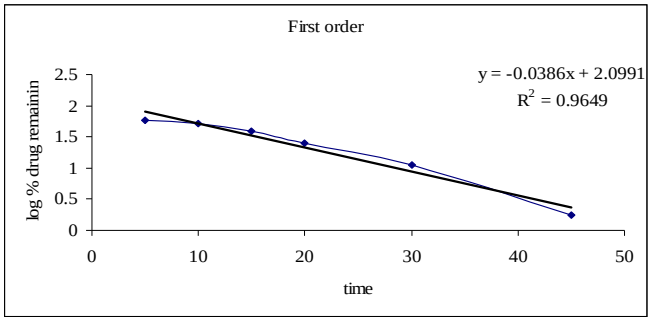

Fig 5: PEG 4000 solid dispersions (1:9) First order

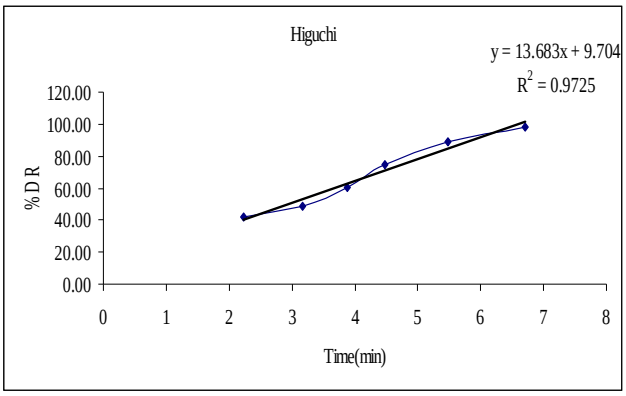

Fig. 6: PEG 4000 solid dispersions (1:9) Higuchi model

3.5. X-Ray diffraction studies

X-ray diffraction patterns revealed that pure irbesartan was in crystalline state (Fig 4.28), as it showed sharp distinct peaks notably at 2θ diffraction angles of 4.75°, 12.49°, 19.45°, 23.18°. PEG4000 was crystalline in nature and gives two characteristic peaks, one at 19.2° and the other broader one at 23.43°. The reflections (specific peaks) corresponding to the drug and other excipients were found in the formulation diffractogram with reduced intensity as compared to drug alone. And some characteristic drug peaks (23.18°) were disappearing in formulation diffractogram; this suggested destruction of crystalline nature of drug and drug might be converted from crystalline to amorphous form.

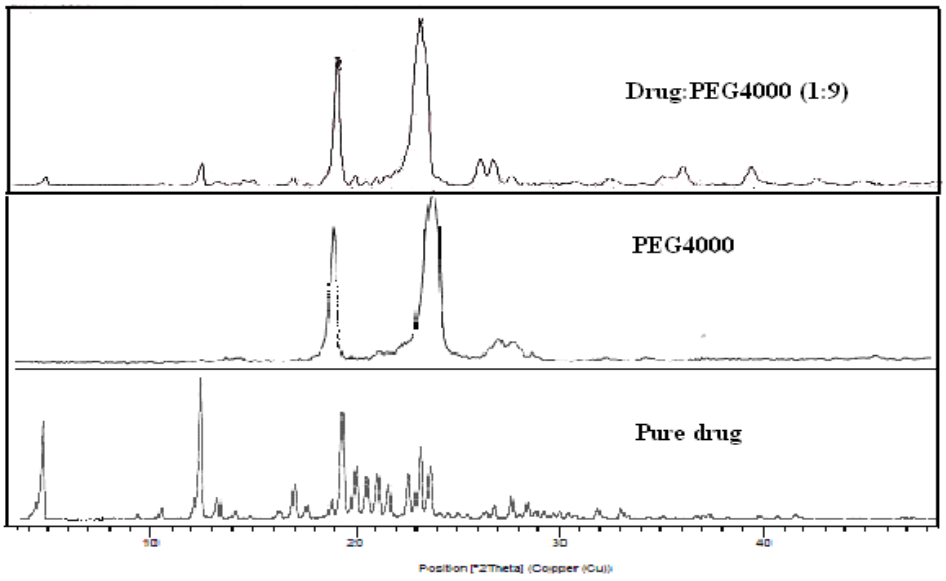

Fig. 7: X-RD spectrums of SD of irbesartan (SD P4 9)

3.6. Differential Scanning Calorimeter

The thermogram of pure irbesartan showed a sharp peak at 185°C (Fig.8), which corresponds to the melting temperature of irbesartan, sharpness of the peak indicating crystalline nature of the drug. The thermogram of PEG 4000 showed a peak at 50°C, which corresponds to the melting temperature of the carrier. In the optimized formulation (SD P4 9) 2 peaks were observed one at 61.2°C, another

one at 183.16°C, which corresponds for PEG4000 and irbesartan respectively (Fig.8). And the area and sharpness of the peaks were decreased, it indicated that the crystallinity of the drug was reduced and might be converted to amorphous form. There was no change in the peak temperature of the optimized formulation (SD P4 9) when compared to the pure drug, which indicates no interaction between drug and excipients.

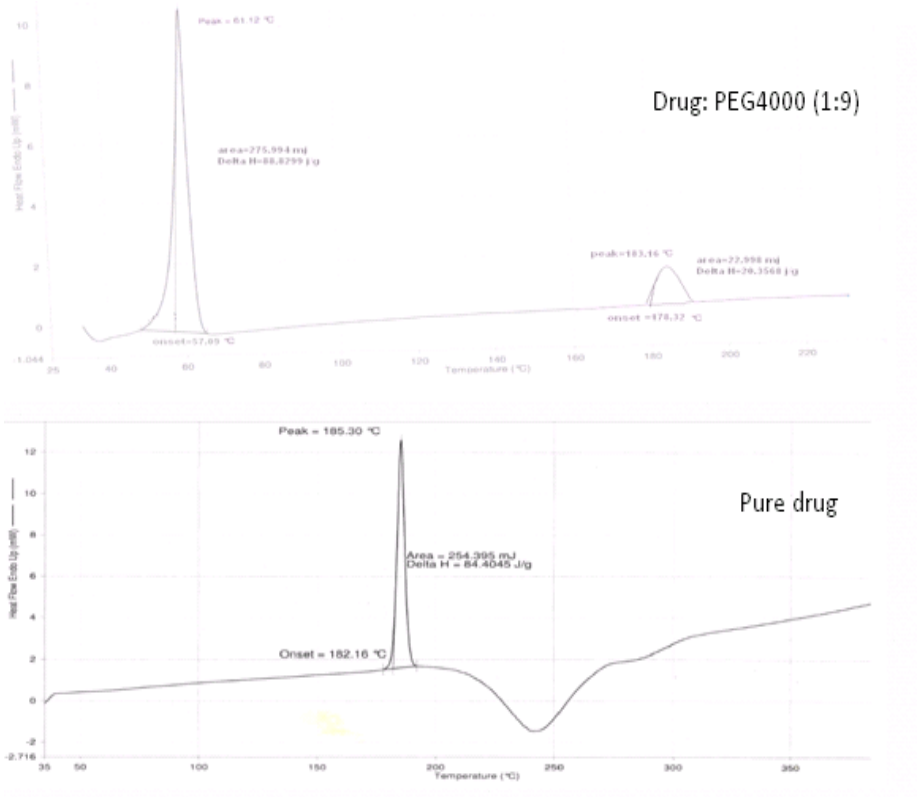

Fig. 8: DSC Thermogram of SD of Irbesartan (SD P4 9)

3.7 Residual solvents

Residual solvent concentration in surface solid dispersion of irbesartan prepared using acetone was performed by gas chromatography. The levels of acetone were below detectable limits. Hence, can be concluded that solvent deposition method was efficient in removal of solvents from SD well below permissible levels. Figure.9 shows a standard chromatogram for residual solvent obtained during the study. Figure.10 shows the chromatogram obtained after residual analysis

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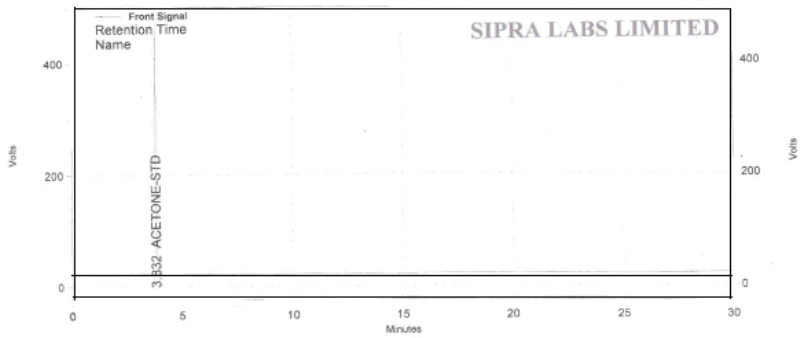

Fig. 9: Standard GAS chromatogram of Acetone

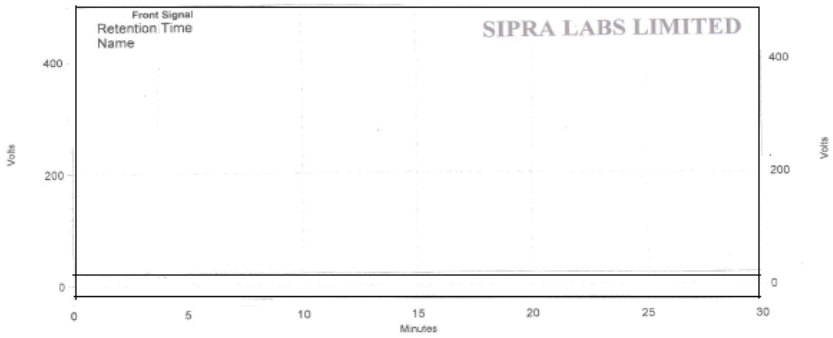

Fig. 10: Gas chromatogram of SD formulation (SD P4 9)

CONCLUSION

The enhancement of dissolution rate and oral bioavailability of poorly soluble drugs remains one of the most challenging aspects of the drug development. Among the different methods of dissolution enhancement, Solid dispersion technology was found to be more successful with number of drugs.

SD's of Irbesartan with three different polymers prepared by solvent evaporation method showed significantly higher drug dissolution in comparison with pure drug. FTIR and DSC showed no evidence of interaction between the drug and carrier. Among the polymers used tested PEG-4000 gave highest enhancement of dissolution rate and efficiency of Irbesartan (1:9 ratio). In each case the dissolution rate and DE 45% were increased as the concentration of carriers in the solid dispersions were increased. The order of increase in dissolution rate with various polymers is; PEG 4000>PEG 6000>PVP K 30.

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