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Formulation and Characterization of Irbesatan Solid Dispersions Prepared Using Poly Ethylene Glycols

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ABSTRACT

The purpose of the present study was to enhance the solubility and dissolution rate of a poorly water soluble drug by solid dispersion technique. Irbesartan was used as a model drug to evaluate its release characteristics from the formulations. Solid dispersions of Irbesartan with PEG 4000 and PEG 6000 were prepared by physical mixing, solvent evaporation and melting techniques in w/w ratios (drug: carrier). Characterization of the solid dispersions was carried out by Differential Scanning Calorimetry (DSC) and Fourier Transform Infra-Red spectroscopy (FTIR). The dissolution profiles of solid dispersions were compared with those of the pure drug. Solid dispersions of Irbesartan with PEG 4000 prepared by solvent evaporation technique at 1:1 ratio showed greater dissolution compared to other formulations. FTIR and DSC studies showed no significant interaction between Irbesartan and the hydrophilic carriers.

Keywords: dissolution, solid dispersions, melting technique, solvent evaporation, Irbesartan

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INTRODUCTION

Most of the new chemical entities under development are intended to be used as solid dosage forms due to their greater stability, smaller bulk and easy production [1]. In drug discovery, more than 40% of the new drug candidates show poor aqueous solubility that leads to poor bioavailability, thus hindering the oral delivery of numerous drugs [2].Drugs which show low aqueous solubility require high doses in order to reach therapeutic plasma concentrations after oral administration [3]. Poor solubility in water is the major problem encountered with formulation development of new chemical entities. For absorption, any drug should be present in the form of an aqueous solution at the site of absorption. Dissolution is the rate limiting step in most cases and thus increasing absorption and hence oral bioavailability of such drug molecules by formulation design approach proves promising. Hence producing a suitable formulation is important to improve solubility and bioavailability of such drugs [4].

Many techniques have been developed to improve solubility and to enhance the dissolution rate of poorly soluble drugs which includes both modifications to the drug substance itself and the creation of new formulations[5]. Among various techniques available to improve the rate of dissolution for poorly aqueous soluble drugs, the preparation of solid dispersions has been more effective in enhancing the rate of dissolution and the oral bioavailability[6]. Several investigations demonstrated that the formation of solid dispersions of relatively water insoluble drugs with various carriers can significantly increase their *in vitro* dissolution rates[7]. Chio and Riegelman defined the term solid dispersion as "a dispersion of one or more active ingredients in an inert carrier or a matrix of solid state which is prepared by melting (fusion), solvent method or melting solvent method"[8]. Numerous preparation methods for solid dispersions have been reported according to the literature and they deal with the challenge of mixing the polymer and the drug on a molecular level, while the polymer and the drug are generally poorly miscible[9].

Irbesartan is chemically denoted as 2-butyl-3-({4-[2-(2H-1,2,3,4-tetrazol-5-yl)phenylphenyl}methyl)-1,3 diazaspiro [4.4 non-1-en-4-one].It is generally classified as an anti hypertensive drug. The drug may also delay the progression of diabetic nephropathy and is also indicated for the reduction of progression of renal disease in patients who suffer from type 2 diabetes. Irbesartan is also used in the treatment of congestive heart failure as a second line drug. Irbesartan is practically insoluble in water. Being a BCS class II drug, its rate of absorption and extent of bioavailability are controlled by rate of dissolution in the gastrointestinal fluids. Hence, improvement in its solubility and dissolution rate may lead to an enhancement in bioavailability.

In this study, solid dispersions of Irbesartan were prepared by melting and solvent evaporation techniques. PEG 4000 and PEG 6000 were used as hydrophilic carriers to enhance dissolution rates and thus bioavailability. Solubility and dissolution rate of the solid dispersions were compared with Irbesartan. The physical properties of the prepared solid dispersions were characterized by FTIR and DSC studies.

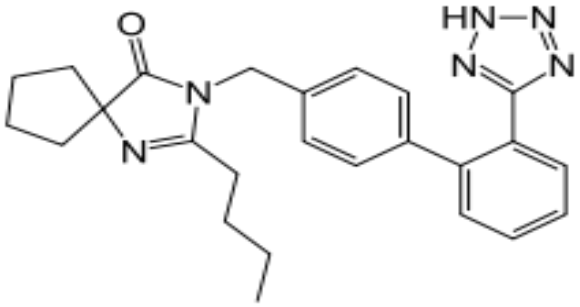

Figure 1:Structure of Irbesartan

MATERIALS AND METHOD

Materials

Irbesartan was received as a gift sample from Alembic Ltd, Baroda, India. All the other materials used in the present work were commercial samples. Polyethylene glycols (Yarrow Chem Products, Mumbai), Hydrochloric acid (Yarrow Chem Products, Mumbai), Methanol (Merck Limited, Mumbai). All the reagents used were of analytical grade. Freshly prepared distilled water was used in the work.

METHODS

Identification of drug

The drug was identified by Infrared spectroscopy (IR), melting point determination and Ultraviolet spectroscopy (UV).

Infrared Spectroscopy

Infrared (IR) spectra of drug was performed in the range of 4000cm^{-1} to 400cm^{-1} by using KBr pellet technique (Shimadzu, Japan.) and studied for the presence of characteristic peaks.

Ultraviolet Spectroscopy

The samples were subjected to UV spectrophotometric analysis and were scanned for absorption maxima ($\lambda_{max.}$) in the range of 200 to 400nm using UV-Visible Spectrophotometer in an appropriate medium. The obtained data was compared with that of reference values in literature.

Melting point determination

Melting point of Irbesartan was determined by capillary tube method. Fine powder of the drug was filled into a glass capillary tube which was previously sealed at one end. The capillary tube tied to a thermometer was subjected to increasing temperatures and the temperature at which Irbesartan melts was recorded [10].

Preparation of solid dispersions

Solid dispersions of Irbesartan with different polymers like PEG 4000, PEG 6000 were prepared using the following methods:

Physical mixtures (PM)

Required amounts of Irbesartan and the carriers (PEG 4000 and PEG 6000) in the ratios of % w/w (drug: carrier) were thoroughly mixed in a mortar and pestle in order to obtain a homogenous mixture. The resulting mixture was passed through 60 mesh sieve. The powder was stored in a screw cap vial at room temperature until use.

Solvent Evaporation (SE)

Different ratios of drug and carrier (PEG 4000 or PEG 6000) were prepared using methanol as solvent. Required quantities of drug and polymer were dissolved in methanol to get a clear solution. Solvent was removed by continuous titration which was carried out until a dry mass was obtained. This was further dried at 50 ^{0}C for 4hours in an oven. The product was powdered in a mortar, sieved through 60 mesh screen.

Melting Technique (MT)

Solid dispersions of Irbesartan with PEG 4000 and PEG 6000 were prepared by this method in the ratios of 1:1, 1:2 and 1:3. Required amounts of drug and the carrier were melted in a glass container in a heating mantle with vigorous stirring using a glass rod till it liquefies. The molten mixture was rapidly cooled on an ice bath. The product was pulverized and shifted through 60 mesh sieve.

Table 1: Composition of Solid dispersion formulations of Irbesartan

Formulation Code	Polymers used	Drug to Polymer ratio	Method of preparation
I 1		1:0.125	Physical Mixing
I 2	PEG 4000	1:0.5	
I 3		1:1	
I 4		1:0.125	Solvent Evaporation
I 5	PEG 4000	1:0.5	
I 6		1:1	
I 7		1:1	Melting Technique
I 8	PEG 4000	1:2	
I 9		1:3	
I 10		1:0.125	Physical mixing

I 11	PEG 6000	1:0.5	
I 12		1:1	
I 13		1:0.125	Solvent Evaporation
I 14	PEG 6000	1:0.5	
I 15		1:1	
I 16		1:1	Melting Technique
I 17	PEG 6000	1:2	
I 18		1:3	

***In vitro* dissolution studies**

Dissolution studies of Irbesartan in powder form and from its solid dispersions was studied using Electro lab which is an 8 station dissolution rate test apparatus with a paddle stirrer. These studies were conducted in 900 ml of simulated gastric medium (0.1N HCl of pH≈1.2) maintained at a temperature of 37±0.5 ^{0}C at 50rpm speed. 50mg of Irbesartan or its solid dispersion equivalent to 50mg of Irbesartan was added to the dissolution medium. At predetermined sampling intervals, 5ml of dissolution medium was withdrawn, filtered through Whatman filter paper. The withdrawn volume was replenished immediately with the same volume of the pre-warmed (37 ^{0}C) dissolution medium in order to maintain a constant volume throughout the test. The filtered samples were analyzed spectrophotometrically at 230 nm. Dissolution experiments were conducted in triplicate (n=3).

Dissolution studies of the drug in powder form, solid dispersions of drug and carrier can be carried out using dissolution apparatus. Thus obtained dissolution profiles are compared by analysis of variance (ANOVA) based, model-independent and model dependent approaches [11]. ANOVA methods detect statistically significant differences between dissolution profiles. Model-independent approaches are based on the ratio of area under the dissolution curve (dissolution efficiency) or on mean dissolution time [12, 13]. Relative performance of different concentrations of carriers in solid dispersions can be found by computing percent Dissolution Efficiency (%DE).

$$\% DE = \frac{\int_0^t Y\, dt}{Y_{100}\, t} \quad (1)$$

Where, y is the drug percent dissolved at time t

In model-dependent approaches, release data can be fitted to different kinetic models including zero order (Eq. 2), first order (Eq. 3), Higuchi matrix (Eq.4), Peppas-Korsmeyer (Eq .5) and Hixson Crowell (Eq. 6)

$$R = k_1\, t \quad (2)$$

$$\log UR = \frac{k_2\ t}{2.303} \quad (3)$$

$$R = k_3 \sqrt{t} \quad (4)$$

$$\log R = \log k_4 + n \log t \quad (5)$$

$$(UR)^{\frac{1}{3}} = k_5 t \quad (6)$$

Where, R and UR are the released and unreleased percentages, respectively, at time t; k_1, k_2, k_3, k_4 and k_5 are the rate constants of zero order, first order, Higuchi matrix, Peppas-Korsmeyer, and Hixson- Crowell model, respectively [14].

Characterization of Solid Dispersions

Fourier-transform infrared spectroscopy

The FTIR spectra were obtained by using an FTIR spectrometer (Shimazdu, Japan). The samples were previously ground and mixed thoroughly with potassium bromide, an infrared transparent matrix. The KBr discs were prepared by compressing the powders at a pressure of 5 tons for 5 min in a hydraulic press. Scans were obtained at a resolution of 2 cm^{-1}, from 4000 to 400 cm^{-1}.

It is used to detect the interaction between drug and polymer used for solid dispersion.

Differential scanning calorimetry (DSC)

Measurements were performed on a DSC- 6100 (Seiko Instruments, Japan) with a thermal analyzer. All accurately weighed samples (about 2 mg of Irbesartan or its equivalent) were placed in sealed aluminum pans, before heating under nitrogen flow (20 ml/min) at a scanning rate of 10 $^0C\ min^{-1}$ from 50 to 300 ^0C. An empty aluminum pan was used as reference [15].

RESULTS AND DISCUSSION

Identification of drug

Irbesartan was received as a gift sample and was identified by Infrared (IR) spectroscopy, Ultraviolet (UV) spectroscopy and melting point determination.

Infrared (IR) spectra:

TheIR spectrum of the drug was recorded using KBr disc technique. The spectrum showed peaks corresponding to the functional groups present in the drug structure of Irbesartan.

Ultraviolet (UV) spectroscopy:

Maximum absorption (λ_{max}) of Irbesartan was found to be 230nm which corresponds to the value given in the literature.

Melting point:

The melting point of the drug was found to be 165 ^0C which complies with the value for melting point of the drug.

***In vitro* dissolution studies:**

According to the results obtained on dissolution studies, all the solid dispersions exhibited higher rate of dissolution than the pure drug. This might be due to the change in the state of the drug from crystalline to amorphous, reduction of particle size, increase in wettability and prevention of aggregation of the drug particles by carriers. Simple physical mixing of the drug with the hydrophilic polymers increased the solubility of drug to some extent but formulation of solid dispersions by kneading, solvent evaporation and melting technique further improved the dissolution rate of the drug.

Pure drug showed around 53% dissolution over a period of 60minutes, while its solid dispersions enhanced the dissolution rate up to 89%. Irbesartan: PEG 4000 (1:1) ratio prepared by solvent evaporation technique showed highest dissolution rate. In vitro release data of drug best fitted to Korsemeyer-Peppas model with n value of 0.729 and hence exhibits non fickian diffusion.

Table 2: Dissolution study of formulations

Formulation Code	Method	Cumulative % drug release				
		10min	15min	30min	45min	60min
Pure drug		15.21±1.56	26.08±1.82	41.50±0.74	50.53±2.65	55.32±0.85
I 1	Physical	34.23±2.61	45.40±2.38	49.95±2.44	52.53±1.72	54.40±2.59
I 2	mixing	37.29±2.41	48.73±1.63	54.30±1.76	56.24±1.23	58.40±2.13
I 3		42.07±2.06	52.13±0.53	59.02±0.72	63.10±1.88	65.51±1.64
I 4	Solvent	47.48±0.92	53.75±0.74	58.70±1.53	63.09±0.79	66.58±1.67
I 5	Evaporation	56.73±0.59	62.36±2.73	68.02±2.08	75.43±2.60	79.30±0.85
I 6		63.25±1.45	74.39±1.72	81.13±2.87	86.81±0.91	89.14±1.63
I 7	Melting	55.52±0.85	62.28±1.20	69.24±1.77	76.64±1.36	78.74±1.82
I 8	Technique	57.82±1.03	66.18±1.47	71.02±1.21	79.66±1.96	83.16±0.84
I 9		64.20±0.73	71.04±1.18	76.27±1.67	82.74±1.62	85.47±1.84
I 10	Physical	29.81±2.76	39.46±2.38	46.80±2.06	50.43±1.88	53.59±2.64
I 11	mixing	34.67±0.70	46.05±1.66	52.40±1.82	54.71±2.73	57.22±1.49
I 12		35.52±2.84	45.84±2.33	54.06±0.61	56.10±2.50	58.14±0.89
I 13	Solvent	42.23±3.25	50.27±2.82	56.45±2.41	61.89±2.09	63.50±1.73
I 14	Evaporation	54.63±1.63	59.28±2.91	63.96±2.47	67.84±1.87	71.44±2.73
I 15		63.96±1.18	71.90±1.49	76.90±2.83	81.16±1.97	83.84±0.33
I 16	Melting	52.89±0.77	58.85±0.48	64.48±1.72	67.10±0.79	70.00±1.36
I 17	Technique	56.97±0.81	62.40±2.40	69.34±2.07	74.38±1.72	78.96±2.55
I 18		59.65±1.77	64.37±1.24	70.28±0.75	77.80±1.61	80.58±1.09

Table 3:Statistical parameters of various formulations of Irbesartan with different polymers after fitting drug release data to various release kinetics models

Formula-tions	Zero order model		First order model		H-M model		P-K model		H-C model	
	R	k_1	R	k_2	R	k_3	R	k_4	R	k_5
I 1	0.753	0.336	0.795	-0.004	0.826	3.836	0.850	0.229	0.781	-0.007
I 2	0.778	0.369	0.826	-0.006	0.846	4.197	0.868	0.230	0.810	-0.009
I 3	0.847	0.419	0.895	-0.009	0.910	4.733	0.931	0.231	0.880	-0.011
I 4	0.936	0.351	0.963	-0.006	0.971	3.905	0.980	0.177	0.955	-0.009
I 5	0.970	0.437	0.989	-0.013	0.988	4.812	0.988	0.181	0.985	-0.015
I 6	0.858	0.465	0.952	-0.023	0.917	5.250	0.940	0.179	0.926	-0.020
I 7	0.933	0.452	0.966	-0.013	0.973	5.032	0.986	0.193	0.957	-0.015
I 8	0.940	0.476	0.975	-0.016	0.966	5.270	0.970	0.192	0.967	-0.017
I 9	0.906	0.427	0.965	-0.016	0.949	4.773	0.963	0.167	0.949	-0.017
I 10	0.862	0.425	0.899	-0.006	0.921	4.794	0.931	0.304	0.887	-0.009
I 11	0.779	0.383	0.825	-0.006	0.852	4.367	0.874	0.252	0.810	-0.009
I 12	0.789	0.397	0.829	-0.006	0.866	4.542	0.896	0.257	0.816	-0.009
I 13	0.885	0.396	0.920	-0.006	0.940	4.454	0.959	0.219	0.909	-0.010
I 14	0.960	0.314	0.980	-0.006	0.986	3.477	0.990	0.142	0.975	-0.009
I 15	0.888	0.358	0.949	-0.013	0.938	4.011	0.959	0.141	0.931	-0.014
I 16	0.899	0.311	0.934	-0.006	0.950	3.492	0.972	0.148	0.923	-0.009
I 17	0.965	0.419	0.990	-0.013	0.991	4.629	0.996	0.175	0.984	-0.014
I 18	0.967	0.416	0.985	-0.013	0.988	4.589	0.989	0.167	0.981	-0.014

H-M Higuchi matrix, P-K Peppas- Korsmeyer, H-C Hixson Crowell, R correlation coefficient, k_1-k_5 constants of release kinetics.

Drug-polymer compatibility study by Fourier Transform Infrared Spectroscopy

IR spectrum of Irbesartan was characterized by presence of absorption bands at 3055cm^{-1} (N-H stretch), 2960cm^{-1} (C-H stretch), 1732cm^{-1} (C=O stretch), 1616 cm^{-1} (C-N stretch). All the solid dispersions showed characteristic peaks of Irbesartan and the carriers. No significant shift in the characteristic peaks for the drug and carrier indicated less significant interaction between them.

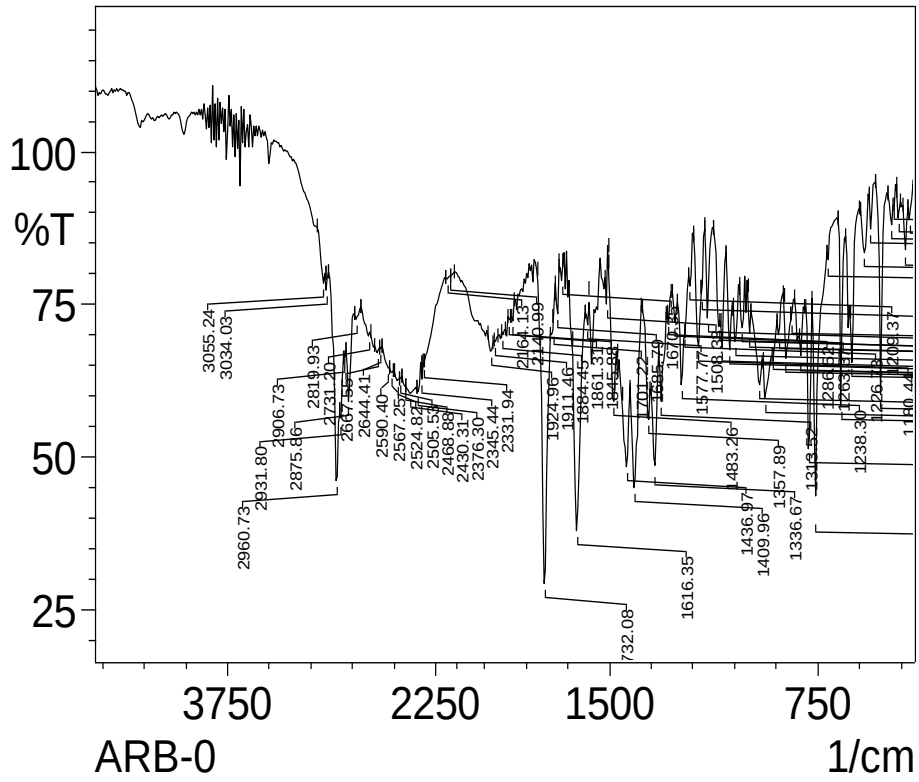

Figure 4: FTIR spectrum of Irbesartan

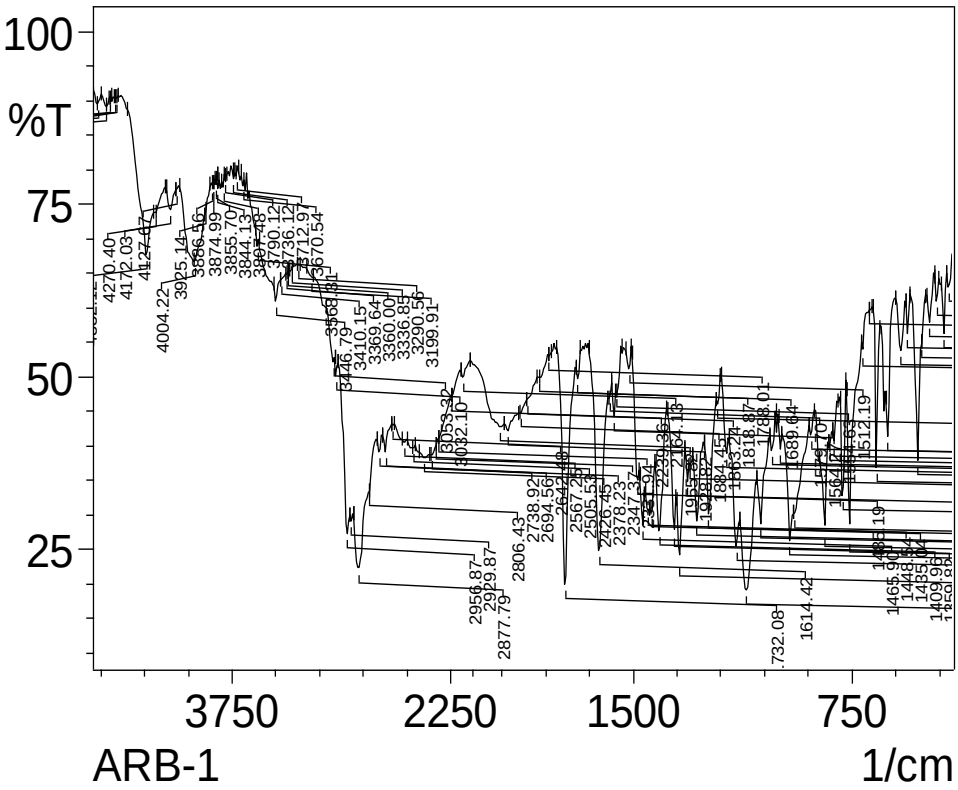

Figure 5: FTIR spectrum of Irbesartan SD with PEG 6000 (1:3 w/w)

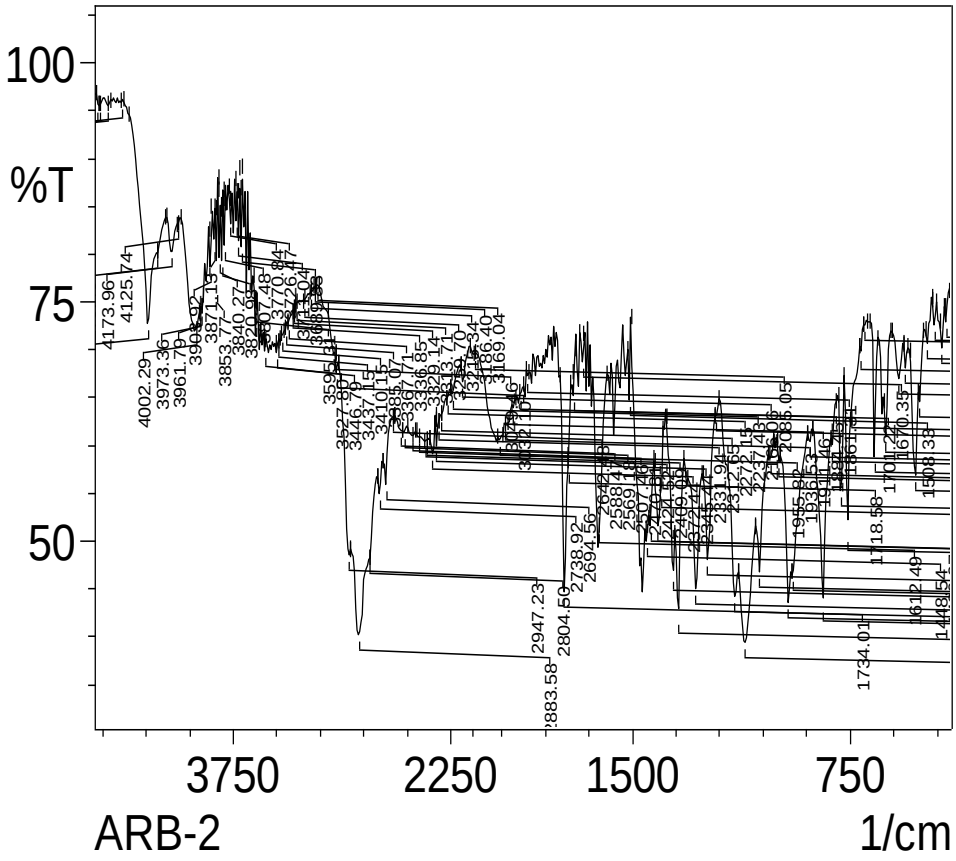

Figure 6: FTIR spectrum of Irbesartan SD with PEG 4000 (1:1 w/w)

Differential Scanning Calorimetry

The DSC thermogram of Irbesartan showed presence of a sharp endothermic peak at 184.9^{0}C indicating melting point of the drug. The onset of melting was observed at 179.58 ^{0}C. Absence of a sharp peak in the DSC thermogram for the SD formulations of drug with various grades of PEGs indicated the presence of the drug in amorphous form and no significant interaction between the drug and carrier.

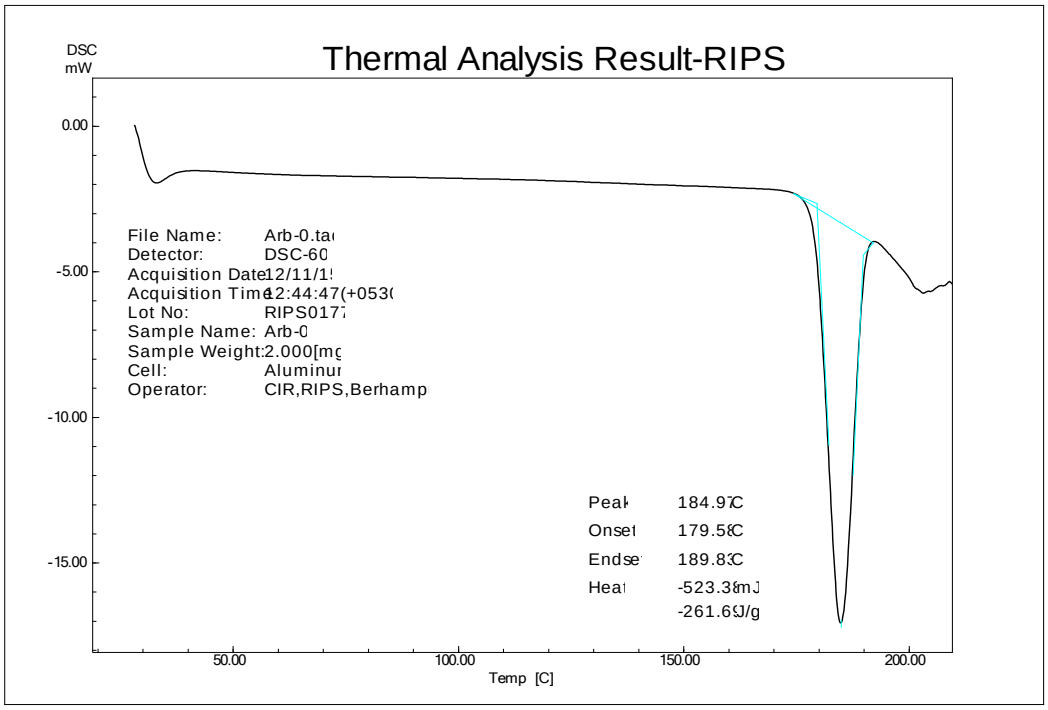

Figure 7: DSC thermogram of Irbesartan

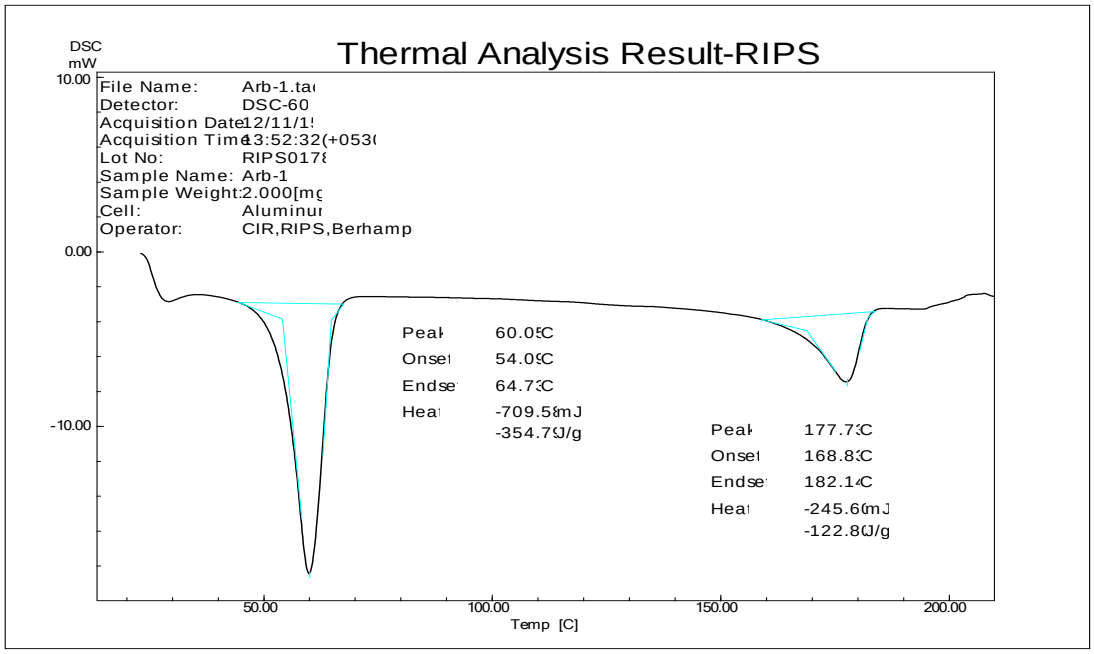

Figure 8: DSC thermogram of Irbesartan SD with PEG 6000 (1:3w/w)

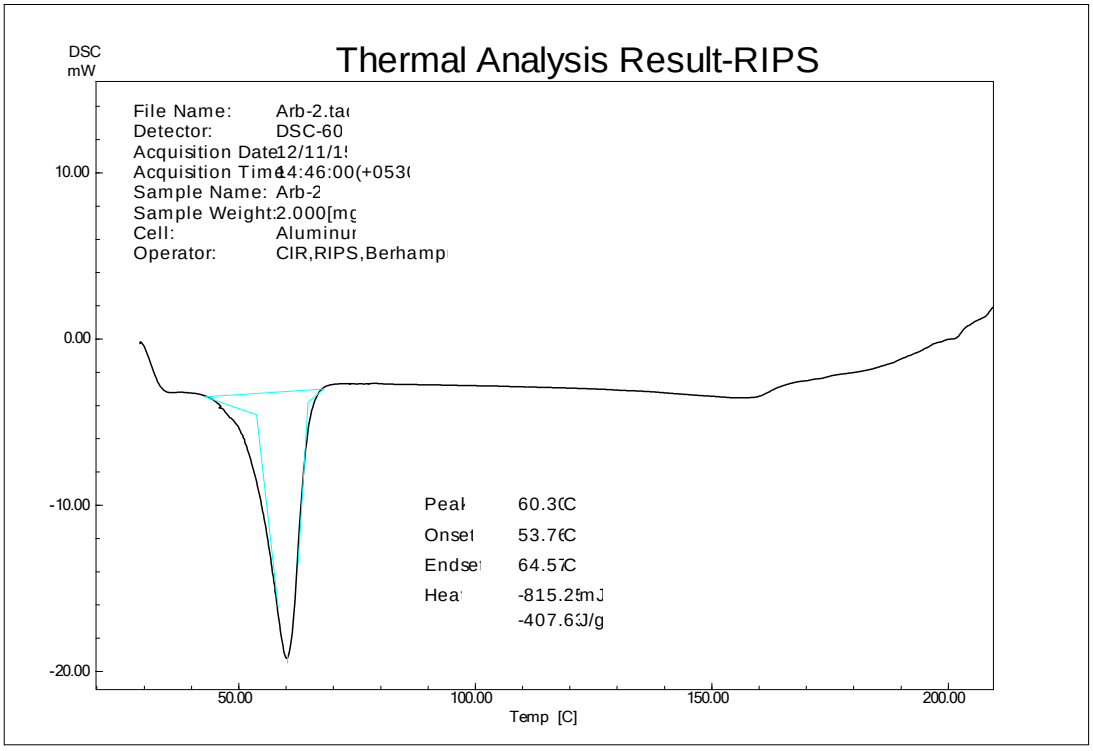

Figure 9: DSC thermogram of Irbesartan SD with PEG 4000 (1:1w/w)

CONCLUSION

The solubility and dissolution rate of Irbesartan can be enhanced by the formulation of solid dispersions with hydrophilic carriers like PEG 4000 and PEG 6000. The increase in solubility may be contributed due to reduction of particle aggregation of the drug, absence of crystallinity, increased wettability and alteration of surface properties of the drug from its solid dispersions. Simple physical mixing of the drug with the hydrophilic polymers increased the solubility of drug to some extent but formulation of solid dispersions by solvent evaporation and melting technique further improved the dissolution rate of the drug. Solid dispersions were prepared by solvent evaporation and melting techniques using PEG4000 and PEG 6000. Higher dissolution rates were obtained using PEG 4000 when compared to PEG 6000 as a hydrophilic carrier. Improved solubility was obtained at lower drug to polymer ratio using solvent evaporation technique. Solid dispersions prepared by solvent evaporation exhibited higher dissolution rates when compared to those prepared by melting technique. 1:1 w/w ratio of drug and PEG 4000 showed dissolution of about 89% by solvent evaporation technique. Solvent evaporation technique was found to be more advantageous when compared to the other techniques as it yielded higher dissolution rates at lower drug: carrier ratio.

From FTIR spectroscopy studies, it was concluded that there were no significant chemical interactions between Irbesartan and the different polymers used in the preparation of solid dispersions. DSC studies showed uniform distribution of drug in carrier matrix and partial conversion of crystalline form of the drug to amorphous form.

Thus the polymers and the techniques used in this study can be used successfully to obtain enhanced solubility and dissolution rates. This could potentially lead to an increase in the bioavailability that is so great that the dose administered could be lowered. The work can be carried out with available laboratory facilities without the requirement of any sophisticated equipments or instruments. The approach is economical and time saving.

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