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Development, Evaluation and Characterization of surface solid dispersion for solubility and dissolution enhancement of Irbesartan

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Abstract

The objective of the present study was to formulate Surface solid dispersions (SSD) 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, SSD's of Irbesartan with four different superdisintegrants (Crospovidone, Croscarmellose sodium, Sodium starch glycolate, Pre-gelatinized starch) with five different drug-carrier ratios were prepared by solvent evaporation method. SSD'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: SSG in 1:7 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 surface solid dispersions, which resulted in an increased dissolution rate of Irbesartan.

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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.

Preparation of SSD's is a technique that provides deposition of the drug on the surface of certain materials that can alter the dissolution characteristics of the drug. Deposition of drug on the surface of an inert carrier leads to a reduction in the particle size of the drug, thereby providing a faster dissolution rate. Various hydrophilic materials with high surface area can be utilized for deposition of the drug on their surfaces [10]

The drug irbesartan was selected for enhancement of solubility and dissolution rate as it is a poorly water soluble (BCS-II) anti hypertensive drug. One of the major problems in this drug is low solubility in biological fluids, which results into poor bioavailability (26%) after oral administration.

Results of literature survey revealed that till date, only 2 techniques have been employed, to improve solubility and dissolution rate of irbesartan, one study reported, an improvement of solubility by complexation with Beta Cyclodextrin's & compared the effect of various complexation methods (co-grinding, kneading, co-evaporation) on drug dissolution profiles[11]. In another study an improved dissolution of a poorly water soluble drug in solid dispersions with carriers like urea, mannitol, PVP, tartaric acid by using quench cooling technique. These solid dispersions of IRB showed an improvement in solubility and dissolution rates [12].

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

Therefore, in the present study, Surface 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.

Different tablet excipients like Sodium starch glycollate, Croscarmellose sodium, Crospovidone, Pre gelatinized starch, were selected for this study. Suitability of these excipients as carrier for irbesartan to form surface solid dispersion was determined from dissolution study.

2. Materials and Method:

Irbesartan (gift sample procured from Dr. Reddy's Laboratories, Hyderabad), Crospovidone (Polyplasdone XL-ISP, Hyderabad), Croscarmellose sodium (Ac-Di-sol, Colorcon), Pre-gelatinized starch (Shin-Etsu, Japan) Sodium starch glycolate type-B (Colorcon), Acetone (Ranchem) and all the reagents used were analytical grade.

3. Preparation of SSD of irbesartan:

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°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 desiccators for further studies.

Table 1: Coding formulations for SSD of Irbesartan

DRUG	CARRIER	CODE	DRUG:CARIIER RATIO
Irebesartan (SSD)	SSG	SSD-S1	1:1
		SSD-S3	1:3
		SSD-S5	1:5
		SSD-S7	1:7
		SSD-S9	1:9
	PGS	SSD-P1	1:1
		SSD-P3	1:3
		SSD-P5	1:5
		SSD-P7	1:7
		SSD-P9	1:9
	CCS	SSD-C1	1:1
		SSD-C3	1:3
		SSD-C5	1:5
		SSD-C7	1:7
		SSD-C9	1:9
	CP	SSD-CP1	1:1
		SSD-CP3	1:3
		SSD-CP5	1:5
		SSD-CP7	1:7
		SSD-CP9	1:9

3.1. Characterization of Surface Solid Dispersions:

3.1.1.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.

3.1.2. 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.

3.1.3. 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.

3.1.4. 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.

3.1.5. 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.

3.2. 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.

3.3. 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.

3.3. 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.

3.4. Differential Scanning Calorimeter:

Thermograms 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°.

3.5. 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°C injection port 140°C and detector 250° C. Oven was programmed at 5° C/min for 10min, 15° C/min up to 250° C with a hold time of 7min.

Table 3: % Yield & Assay of various formulations of Surface solid dispersions

Drug	Carrier	Code	Drug: carrier ratio	%Yield	Assay
Irebesartan (SSD)	SSG	SSD-S1	1:1	94.79	97.64±0.55
		SSD-S3	1:3	95.46	96.16±0.63
		SSD-S5	1:5	96.68	91.50±0.78
		SSD-S7	1:7	88.20	94.79±0.80
		SSD-S9	1:9	95.58	98.85±0.40
	PGS	SSD-P1	1:1	96.90	101.35±1.16
		SSD-P3	1:3	95.26	96.42±1.1
		SSD-P5	1:5	93.12	102.01±0.55
		SSD-P7	1:7	87.55	98.60±0.62
		SSD-P9	1:9	94.22	101.33±0.92
	CCS	SSD-C1	1:1	95.58	98.72±0.49
		SSD-C3	1:3	93.48	91.26±1.07
		SSD-C5	1:5	88.57	97.03±0.58
		SSD-C7	1:7	96.65	92.66±0.86
		SSD-C9	1:9	86.49	94.31±2.6
	CP	SSD-CP1	1:1	95.36	95.76±0.65
		SSD-CP3	1:3	93.62	102.06±0.68
		SSD-CP5	1:5	97.80	98.23±0.69
		SSD-CP7	1:7	92.51	96.62±0.89
		SSD-CP9	1:9	91.56	90.39±0.88

Percentage yield:

Percentage yield was calculated according to the formula and results are given in Table 3.

In vitro dissolution studies:

Dissolution data of surface solid dispersions on excipients were reported in Fig 1, Fig 2, Fig 3, and Fig 4. All the prepared surface solid dispersion showed an enhancement in the dissolution rate of the drug compared to plain drug. Surface solid dispersions prepared by using sodium starch glycolate (1:7, 1:9 ratios) showed enhanced dissolution rate when compared to other carriers. Surface solid dispersions of irbesartan were prepared with various carrier concentrations and the effect of increasing carrier concentration on dissolution rate was determined. The rank order of dissolution rate improvement for various carriers are; SSG>CCS>PGS>CP. The D: SSG 1:7, 1:9 ratios, both showed 100% drug release in 20 min. So Drug: SSG 1:7 selected as optimized formulation.

Table 4: Comparison studies of Dissolution profiles of different SSD in 0.1 N HCL (n=6)

CODE	D:C RATIO	T5	T20	T30	T45	T60	T90
SSD-S1	1:1	33.93	71.37	78.06	86.13	91.9	99.38
SSD-S3	1:3	43.13	74.78	81.94	90.49	99.27	-
SSD-S5	1:5	34.38	91.32	95.09	99.78	-	-
SSD-S7	**1:7**	**34.84**	**100.14**	-	-	-	-
SSD-S9	1:9	39.96	99.85	-	-	-	-
SSD-P1	1:1	15.23	33.64	45.57	49.11	53.76	66.97
SSD-P3	1:3	16.59	38.48	45.91	53.53	59.23	69.48
SSD-P5	1:5	18.85	40.94	49.74	56.77	62.76	73.80
SSD-P7	1:7	23.83	54.72	60.12	66.75	76.03	81.03
SSD-P9	1:9	26.99	62.97	69.76	75.99	81.93	92.30
SSD-C1	1:1	25.33	47.54	59.54	64.51	75.00	78.63
SSD-C3	1:3	29.86	49.50	57.43	63.75	78.49	83.61
SSD-C5	1:5	34.53	63.25	72.16	80.51	87.20	92.80
SSD-C7	1:7	43.89	69.40	75.33	81.58	91.58	97.51
SSD-C9	1:9	32.73	77.77	86.00	97.44	-	-
SSD-CP1	1:1	20.36	44.36	47.89	59.29	68.61	79.38
SSD-CP3	1:3	23.52	54.19	62.60	72.26	78.22	83.41
SSD-CP5	1:5	19.60	57.22	65.80	74.42	79.77	89.51
SSD-CP7	1:7	30.01	60.61	65.89	75.42	83.93	94.00
SSD-CP9	1:9	32.88	63.23	76.21	81.72	91.26	97.96
Pure Drug	1:0	3.77	19.18	23.68	44.35	50.22	66.99

Fig 1: Dissolution profiles of irbesartan on CCS in 0.1 N HCL

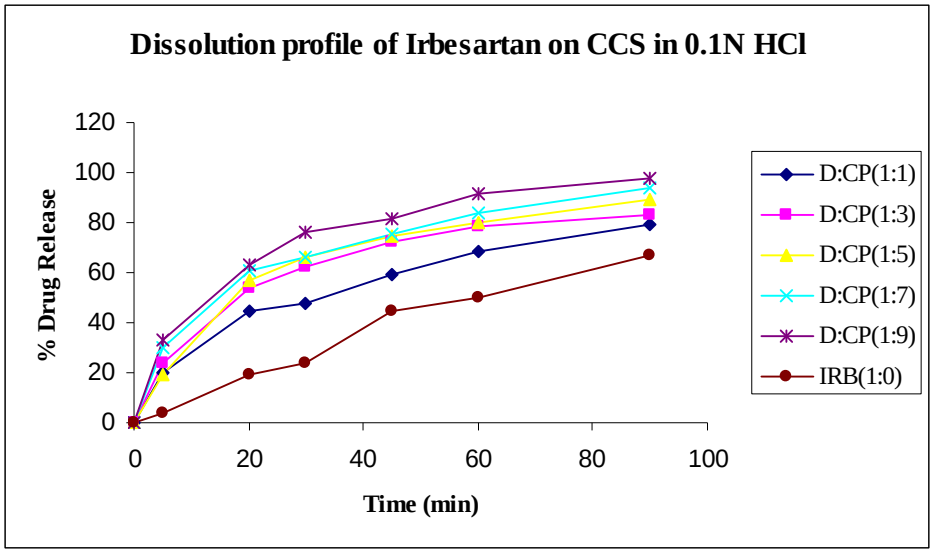


Fig 2: Dissolution profiles of irbesartan on SSG in 0.1 N HCL

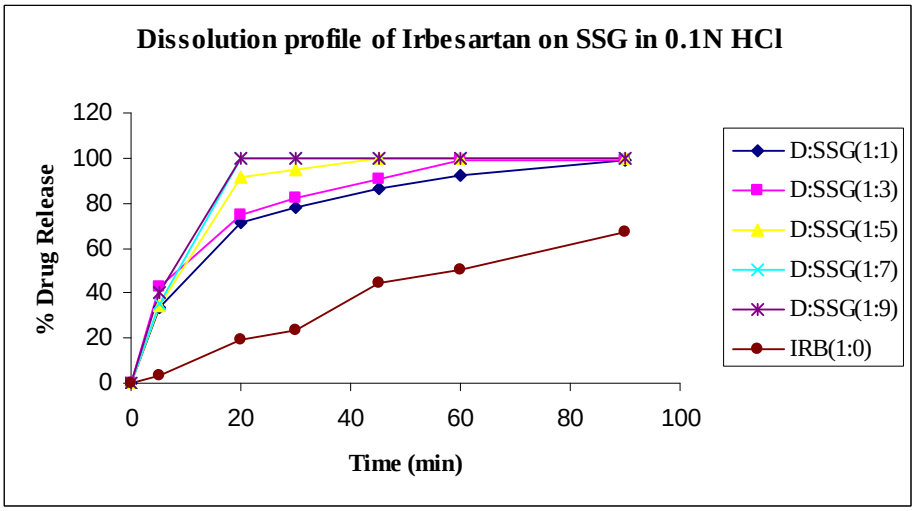


Fig 3: Dissolution profiles of irbesartan in PGS in 0.1 N HCL

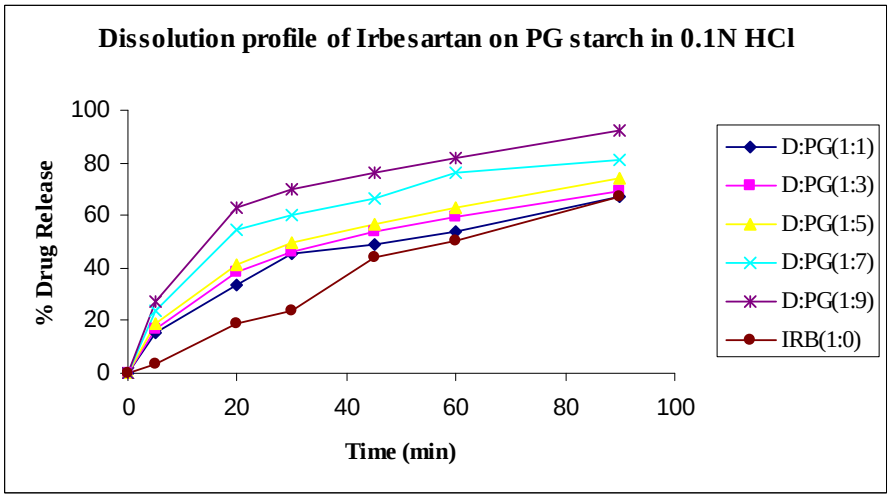
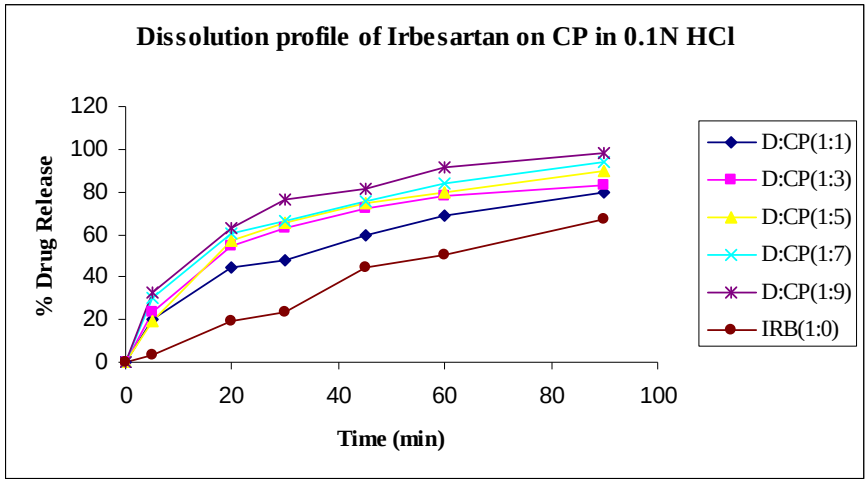


Fig 4: Dissolution profiles of irbesartan in CP in 0.1 N HCL



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 Table 5. The release of drug from surface solid dispersion followed first order kinetics as seen from R^2 value

Table 5: Release rate constants for surface solid dispersions:

Code	Parameter	Zero order	First order	Higuchi model
SSD S7	K	3.93	-0.098	27.61
	r^2	0.781	0.9731	0.8537

Fig 5: SSG surface solid dispersions (1:7) Zero order

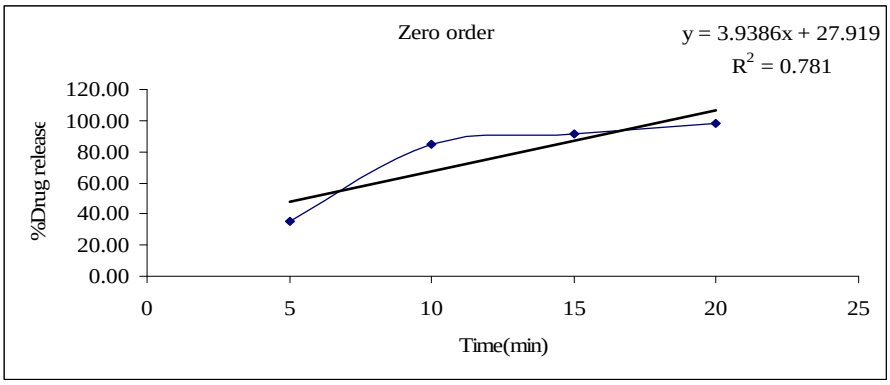


Fig 6: SSG surface solid dispersions (1:7) First order

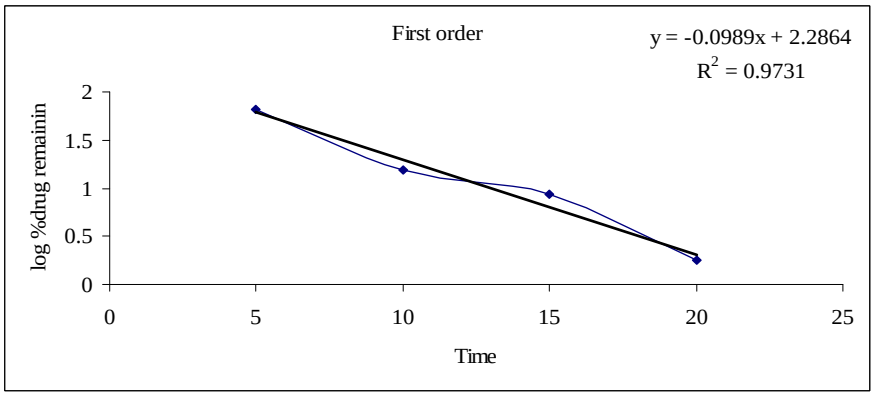
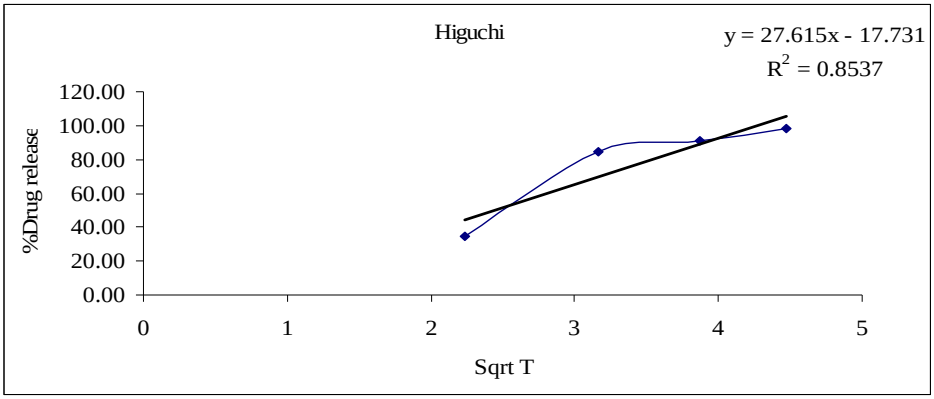


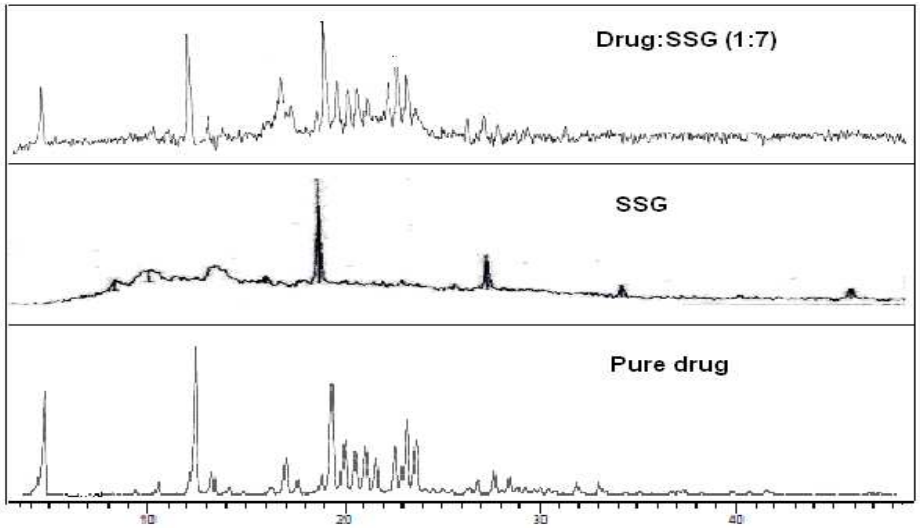
Fig 7: SSG surface solid dispersions (1:7) Higuchi model



X-Ray diffraction studies:

X-ray diffraction patterns revealed that pure irbesartan was in crystalline state (Fig 8), as it showed sharp distinct peaks notably at 2θ diffraction angles of 4.75°, 12.49°, 19.45°, 23.18°. The reflections (specific peaks) corresponding to the drug and SSG were also found in the formulation diffractogram with reduced intensity as compared to drug alone. The reduction in intensity and number of typical diffraction peaks in formulation diffractogram suggests reduction in crystalline nature of drug and may be converted from crystalline to amorphous form.

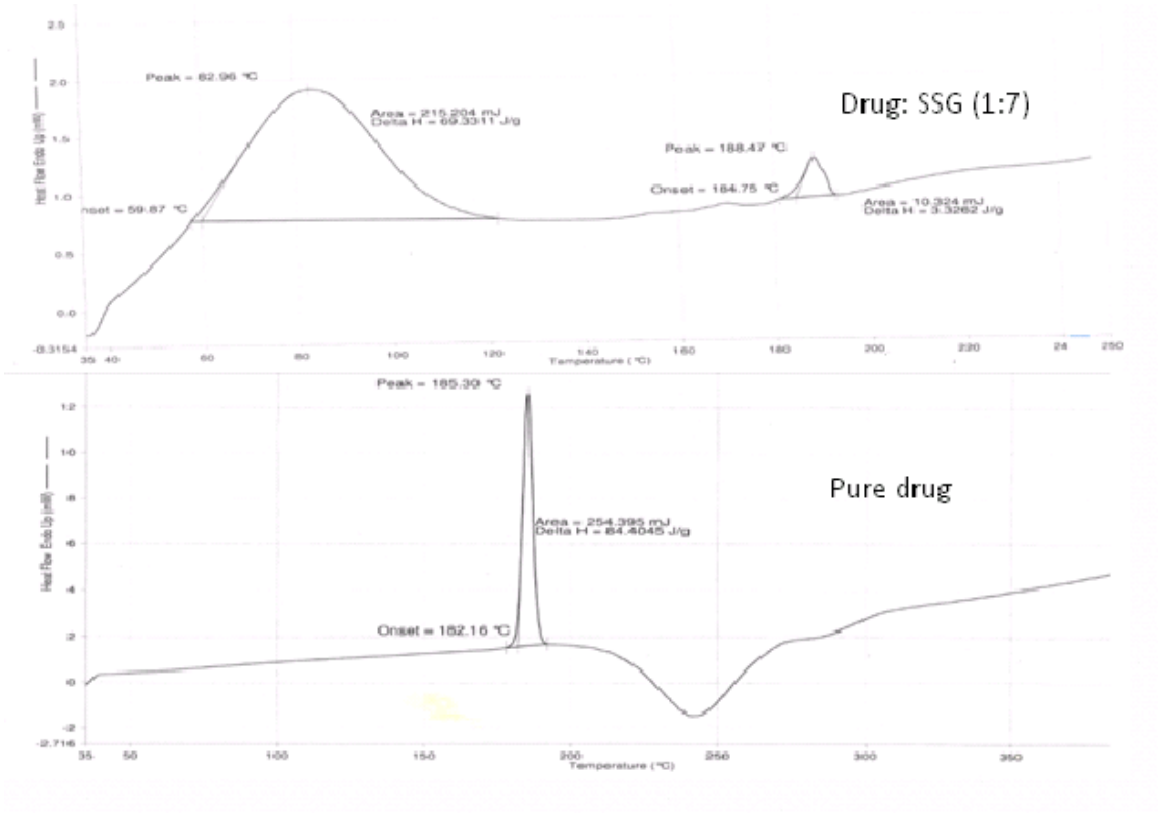
Fig 8: X-RD spectrums of SSD of irbesartan (SSD S7)



Differential scanning calorimeter:

The thermogram of pure Irbesartan showed a sharp peak at 185°C (Fig 9), which corresponds to the melting temperature of irbesartan, sharpness of the peak indicating crystalline nature of the drug. The thermogram of sodium starch glycollate (SSG) showed a peak at 82°C, which corresponds to the melting temperature. In the optimized formulation Drug: SSG (1:7) 2 peaks were observed one at 82.36°C, another one at 188.47°C, which corresponds for SSG and irbesartan respectively. And the area and sharpness of the peaks were decreased, which 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 (SSD S7) when compared to the pure drug, which indicates no interaction between drug and excipients.

Fig 9: DSC thermogram of SSD of irbesartan (SSD S7)



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 SSD well below permissible levels. Figure 10 shows a standard chromatogram for residual solvent obtained during the study. Figure 11 shows the chromatogram (SSD S7) obtained after residual analysis.

Fig 10: Standard Gas chromatogram of acetone

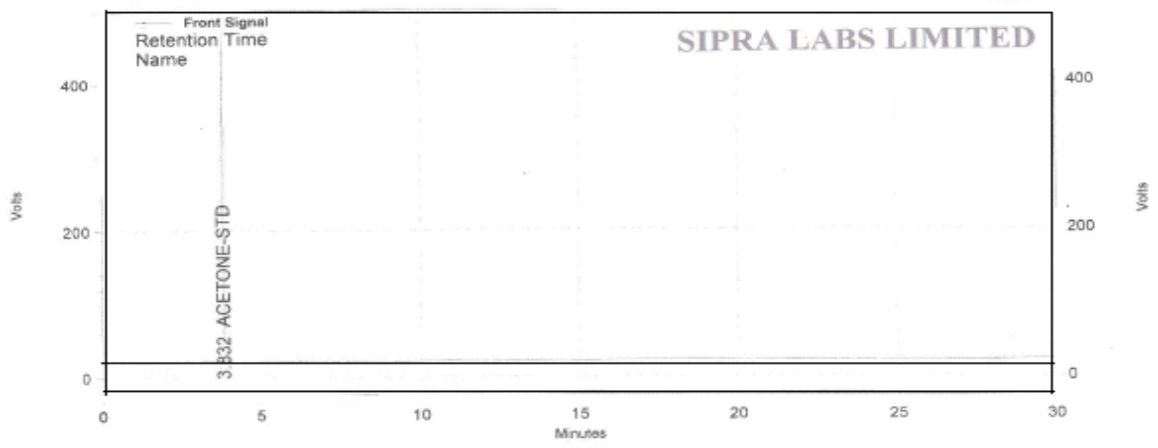
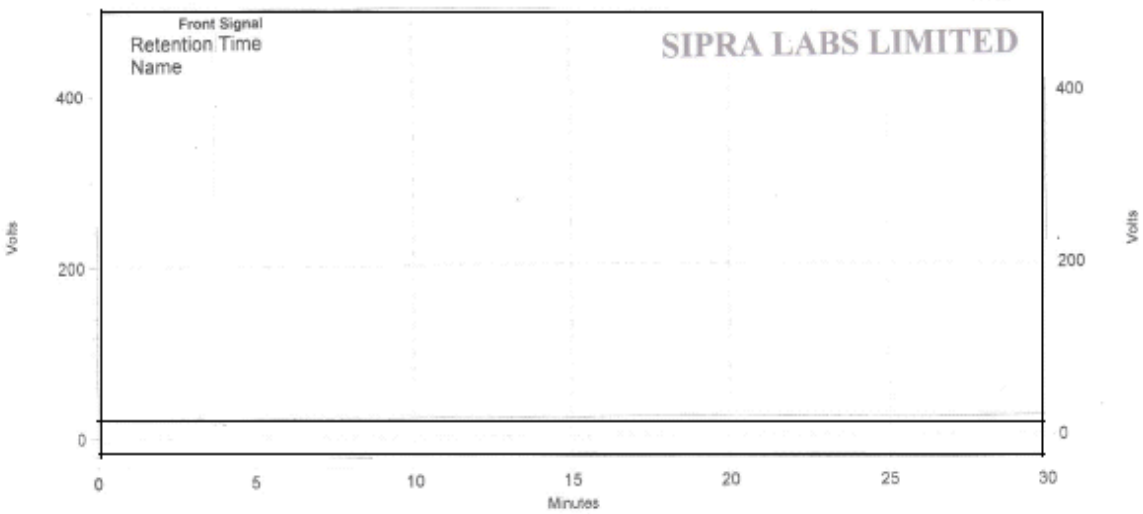


Fig: 11 Gas chromatogram of SSD of irbesartan (SSD S7)



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, Surface solid dispersion technology was found to be more successful with number of drugs.

SSD's of Irbesartan with four different super disintegrant 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 super disintegrant tested SSG gave highest enhancement of dissolution rate and efficiency of Irbesartan (1:7 ratio). In each case the dissolution rate and DE 30% were increased as the concentration of carriers in the surface solid dispersions were increased. The order of increase in dissolution rate with various super disintegrant is SSG>CCS>PGS>CP.

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