ENCHANCEMENT OF SOLUBILITY AND DISSOLUTION RATE OF ANTI-HYPERTENSION DRUG BY SOLID DISPERSION TECHNIQUE

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ABSTRACT

Irbesartan is an angiotensin II type, receptor antagonist. Angiotensin II is formed from angiotensin I in a reaction catalyzed by angiotensin converting enzyme (ACE, kininase II). Angiotensin II is the principal pressor agent of the renin-angiotensin system, with effects that include vasoconstriction, stimulation of synthesis and release of aldosterone, cardiac stimulation and renal reabsorption of sodium. Irbesartan blocks the vasoconstricting and aldosteron secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT_1 receptor in vascular smooth muscle. Irbesartan is used to treat high blood pressure (hypertension) and to help protect the kidneys from damage due to diabetes. Lowering high blood pressure helps prevent strokes, heart attacks, and kidney problems. This drug works by blocking the hormone angiotensin thereby relaxing blood vessels, causing them to widen. It is also used to treat congestive heart failure and to help protect the kidneys from damage due to diabetes.

The purpose of present work on enhancement of solubility and dissolution rate of Irbesartan by solid dispersion technology employing various water dispersible carriers. A new class of tablet excipients called 'super disintegrants' like sodium starch glycolate (SSG), crosspovidone (CP), croscarmellose sodium (CCS) and microcrystalline cellulose (MCC*)* were used by physical mixing and solvent evaporation methods. Various ratios of drug and carrier such as 1:1, 1:2 and 1:4 were used in the preparation.

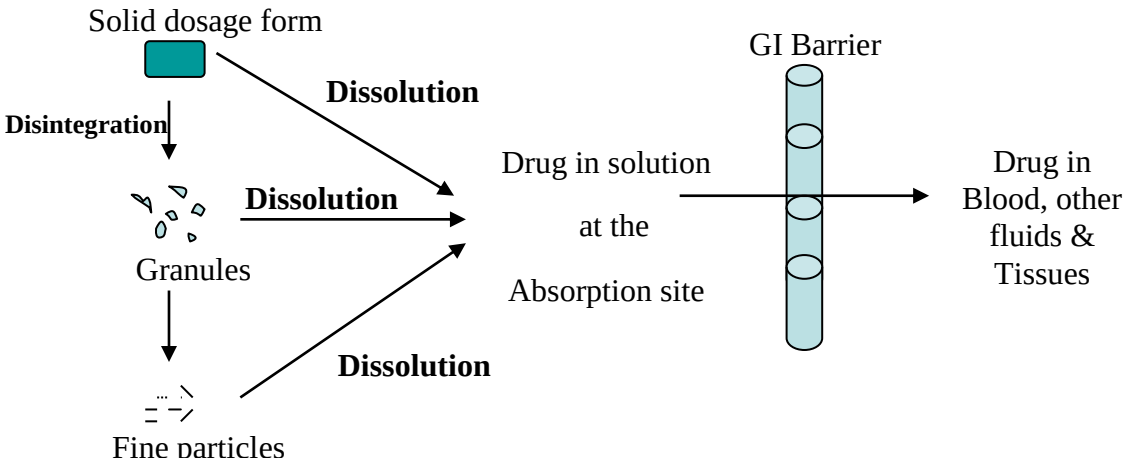
Key words: Solid dispersions, super disintegrants, hypertension, crossprovidone.

INTRODUCTION: UV Spectrophotometric method based on the measurement of absorbance at 244nm in 0.1N HCl (1.2 pH) was used in the present study for the estimation of Irbesartan. From the preformulation studies of the Irbesartan solid dispersions,The results indicated that there is no chemical interaction between drug and carrier when formed as solid dispersion and results are seen in table 1. From the physico-mechanical parameters of the formulated tablets, it is clear that all the tablets fulfilled the official requirements of the compressed tablets(direct compression). The results of the disintegration test revealed that F5 has faster disintegration and it disintegrates within two minutes (95sec).The are seen in table 2. All the solid dispersions prepared were found to be fine free flowing powders. The drug content was uniform in a batch of solid dispersions in all the cases. The dissolution of Irbesartan from all the solid dispersions was rapid and several times higher than the dissolution of the corresponding pure drug. Drug dissolution from all solid dispersions followed first order kinetics. All the dissolution parameters estimated i.e. $T_{50,}$ T_{90}, DE_{30}% and K_1 values indicated rapid and higher dissolution of the drug (Irbesartan) from solid dispersions than that of corresponding

pure drug. Among the superdisintegrants tested CP gave highest enhancement of dissolution rate and efficiency of Irbesartan. In each case the dissolution rate (K_1) and DE_{30}% were increased as the concentration of carriers (superdisintegrants) in the solid dispersions was increased. The order of increase in dissolution rate with various superdisintegrants CP > SSG > CCS > MCC with Irbesartan. Among all in-house formulations F5 showed maximum dissolution. A 4.25 and 6.15 fold increase in DE_{30}% and dissolution rate (K_1) were observed with formulation F5. From this, it is clear that instead of the pure drug Irbesartan, Irbe: CP (1:4) solid dispersion prepared by solvent evaporation method can be used to formulate tablets, so that there will be maximum dissolution of the drug from the formulation and in turn, it increases the bioavailability of the drug. The increasing order of dissolution rate F5 > F4 > F3 > F2 > F1.

The main goal of pharmaceutical formulation is to achieve better therapeutic activity in the shortest possible time by using smallest quantity of drug administered by the most suitable route[1].

Fig 1: Dissolution and Absorption of Drugs from Solid Dosage Forms[3]



When a drug is administered orally in a solid dosage form such as tablet, capsule it must be released from the dosage form and dissolved in the gastro intestinal fluid before it can be absorbed[2]. The bioavailability of many poorly water soluble drugs is limited by their dissolution rates, which are in turn controlled by the surface area that they present for dissolution[3]. Two consecutive transport processes can be identified to describe the oral absorption of drugs from solid dosage forms.

1. Dissolution of the drug in vivo to produce a solution
2. Transport of the dissolved drug across the gastrointestinal membrane.

Each process can be characterized by a rate constant. If the rate of dissolution of the drug is significantly slower than the rate of absorption, the dissolution of the drug becomes the rate-limiting step in the absorption process, and the particle size of the drug is of greater importance in the transport from the gastrointestinal (GI) tract to the site of action Most drugs are passively absorbed and their rates of absorption are dependent upon the concentration gradients in each case; by increasing the dissolution rate in GI tract, the absorption rate increases, so long as the dissolution rate is still the limiting step[4]. This commonly occurs for drugs with limited water solubility.

SOLID DISPERSION TECHNOLOGY

The enhancement of oral bioavailability of poorly soluble drugs remains one of the most challenging aspects of drug development. Although salt formation, solubilization and particle size reduction have commonly been used to increase dissolution rate and thereby oral absorption and bioavailability of such drugs,

there are some practical limitations of these techniques[5]. Incase of salts, the increased dissolution rate in the gastrointestinal tract may not be achieved because of the reconversion of salts into aggregates of their respective acid (or) base forms. Further solubilization of drugs in organic solvents or in aqueous media by the use of surfactants and co-solvents leads to liquid formulations that are usually undesirable from patient acceptability and commercialization. Particle size reduction is commonly used to increase the dissolution rate and there is a practical limit to how much size reduction can be achieved by such commonly used methods as controlled crystallization and grinding.

Polymers Used in Solid Dispersions

Various Suitable water-soluble carriers include polymers such as polyethylene glycol, poloxamers, polyoxyethylene stearates, poly-epsilon-caprolactone, polyvinylpyrrolidone (PVP), polyvinylpyrrolidone-polyvinylacetate copolymer PVP-PVA (Kollidon VA64), poly- methacrylic polymers (Eudragit RS, Eudragit RL, Eudragit NE, Eudragit E) and polyvinyl alcohol (PVA), hydroxypropyl cellulose (HPC), hydroxypropyl methyl cellulose (HPMC), methyl cellulose, and poly ethylene oxide (PEO). Further various molecular weight grades of these polymers have been used for the preparation of solid dispersion and solid solutions. Polymers and surface-active agent combinations are used. Superdisintegrants and Cyclo-dextrins are primarily used to enhance solubility, chemical protection, taste masking and improved handling by the conversion of liquids into solids by entrapment.

Polymers containing acidic functional groups may be suitable for solid dispersions, which release the active substance in a preferred pH range providing acceptable absorption in the intestines. Such polymers may be one ore more selected from the group comprising hydroxypropyl methylcellulose pthalate (HMPCP), polyvinyl acetate pthalate (PVAP), hydroxypropylmethylcellulose acetate succinate (HPMCAS), alginate, carbomer, carboxymethylcellulose.

The weight ratio of active substance to polymer may be in a range from about 3: 1 to about 1: 20. However, narrow ranges of from about 3: 1 to about 1: 5, such as, e.g., from about 1: 1 to about 1: 3 or above may also be used.

Characterization of solid dispersion:

Solid dispersions can be characterized by any of the following techniques.

1) Thermomicroscopical analysis
2) Differential Thermal analysis
3) Powder X-ray diffraction.

SCOPE OF WORK

The enhancement of oral bioavailability of poorly soluble drugs remains one of the most challenging aspects of drug development. Although salt formation solubilization and Size reduction have commonly been used to increase dissolution rate and there by oral absorption and bioavailability of such drugs. There are some practical limitations of these techniques. The solid dispersion approach has been widely and successfully applied to improve solubility, dissolution rate and consequently the bioavailability of poorly soluble drugs. Many hydrophilic excipients like PEG 4000, PEG 6000, Mannitol, PVP, and poloxamers can be used to enhance the dissolution of drug. In the present study, an attempt was made to increase solubility and dissolution of drugs by solid dispersion technique using sodium starch glycolate (SSG), crosspovidone (CP), croscarmellose sodium (CCS) and microcrystalline cellulose (MCC*)* by physical mixing and solvent evaporation methods.

The drug Irbesrtan was selected for enhancement of solubility and dissolution rate.

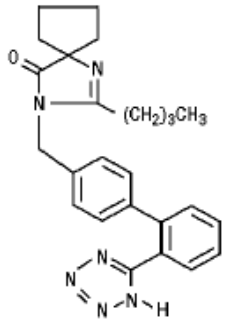
Irbesrtan is a poorly water soluble (BCS class II) anti hypertensive drug. One of the major problems of this drug is low solubility in biological fluids, which results into poor bioavailability after oral administration. Due to poor solubility of drug, its bioavailability rate (26%) is limited by drug dissolution. Therefore, in the present study, an attempt has been made to increase solubility of Irbesrtan by solid dispersion using physical mixing (PM) and solvent evaporation (SE) technique of Irbesrtan with SSG, CP, CCS and MCC and to improve the dissolution of drug.

DRUG PROFILE

IRBESARTAN

Chemical name: Chemically it is 2-butyl-3-[*p*-(-*0*-1*H*-tetrazol-5-ylphenyl)benzyl]-1,3-diazaspiro[4.4]non-1-en-4-one.

Structure:



ANALYTICAL METHODS

Determination of λmax of Irbesartan

Procedure:

10 mg of Irbesartan was dissolved in 5 ml of methanol and made upto 10 ml with distilled water (1000µg/ml) (Stock solution)

↓

1ml of stock solution was dissolved in 10 ml distilled water

↓ (100µg/ml)

Above solution was diluted to made series of dilutions containig 5ml, 10ml and 15ml

↓

Above solutions were scanned using systronics UV-visible double beam spectrophotometer

↓

The scanned value was 244nm

PREPARATION OF IRBESARTAN SOLID DISPERSIONS

The solid dispersions of Irbesartan were prepared in 1:1, 1:2 and 1:4 ratios by two methods as

1. Physical mixing method:

Irbesartan and each of surface active carriers MCC, CCS, SSG and CP were weighed accurately and mixed thoroughly in mortor and pestle with triturating for about 10 min. These mixtures were then passed through sieve number #60 and finally, stored in air tight containers till further use.

2. Solvent evaporation method :

Irbesartan and each of surface active carriers MCC, CCS, SSG and CP were weighed accurately in various ratios (1:1, 1:2 and 1:4) and transferred to china dish containing sufficient quantity of methanol to dissolve. Methanol was evaporated on heating mantle at 60^0C. The resulting solid dispersions were stored for 24 hrs in desiccator to congeal. The mass obtained was crushed, pulverized. Finally, dispersions were passed through sieve number #60 and were stored in air tight containers till further use.

3. Solubility studies:

Solubility study was performed according to method reported by Higuchi and Connors. Excess (usually more than1mg/ml concentration) of solid dispersions were added to 25ml distilled water taken in stopper conical flasks and mixture were shaken for 24hrs in rotary flask shaker. After shaking to achieve equilibrium, 2ml aliquots were withdrawn at 1hr intervals and filtered through Whatman filter paper. The filtrate was diluted if necessary and analyzed by UV- spectrophotometer at 244 nm. Shaking was continued until three consecutive readings were same. Results were given in table-3,4.

EVALUATION OF IRBESARTAN SOLID DISPERSIONS

All Irbesartan solid dispersions were evaluated for:

- Drug content estimation.
- *In-vitro* dissolution study.

Drug content Estimation

The percentage drug content in physical mixtures and solvent evaporative dispersions was estimated by dissolved 50 mg quantities of physical mixtures and solvent evaporative dispersions in methanol, mixed thoroughly by shaking and the volume was made up to the mark with solvent (0.1N HCl). The solution was filtered and the filtrate was diluted suitably with 0.1N HCl (1.2 pH) and absorbance was measured at 244 nm using UV/Visible spectrophotometer. The results are given in table 5,6.

***In-vitro* dissolution studies:**

In-vitro dissolution studies of pure drug, physical mixtures and solid dispersions were carried out for 60 minutes using *USP Dissolution test apparatus type II* (Lab India DISSO 2000, eight stages) at 50 rpm.

Physical mixture and solvent evaporation dispersions equivalent to 150 mg of pure drug (Irbesartan) used for dissolution study at 37±0.50^{0}C in 900ml of 0.1N HCl (1.2 pH) as dissolution medium. Aliquot equal to 5 ml was withdrawn at regular time intervals (10, 20, 30, 40, 50, 60 min), an equal volume of fresh dissolution medium was replaced to maintain the sink condition and aliquots were measured at 244 nm UV/Visible spectrophotometer. DE_{30}%, T_{50}, T_{90}, k_1 and R^2 values were calculated from dissolution data. The results are given in table-7,8.

PRE-FORMULATION STUDIES OF IRBESARTAN SOLID DISPERSIONS

Angle of Repose:

Flow ability of final blend is determined by calculating angle of repose by fixed height method. A funnel with 10mm upper diameter of stem is fixed at a height of 2cm over the platform. About 2gm of sample slowly passed along the wall of the funnel tip. The tip of the pile formed and touches the steam of the funnel. A rough circle is drawn around the pile base and the radius of the powder cone is required. The results are given in table 9.

Angle of repose is calculated by the following formula

$\tan\theta = h/r$

Where: **θ** = angle of repose

h = height of the pile

r = average radius of the powder cone.

Bulk Density and Taped Density:

Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. Quantities of 2 gm of solid dispersions were introduced in to 10 ml measuring cylinder. After that the initial volume was noted and the cylinder was allowed to fall under its own weight on to a hard surface from the height of 14mm ± 2 at second intervals. Tapping was continued until no further change in volume was noted. LBD and TBD were calculated using the following equations. The results are given in table 9.

LBD= Weight of the powder blend/Untapped Volume of the packing

TBD=Weight of the powder blend/Tapped Volume of the packing

Compressibility Index:

The Compressibility Index of the solid dispersions were determined by Carr's compressibility index. It is a simple test to evaluate the LBD and TBD of a powder and the rate at which it packed down. The results were given in table 9. The formula used for calculation of Carr's Index is as below:

Carr's Index (%) = [(TBD-LBD) x100]/TBD

Hausner's ratio:

The ratio of tapped density to the bulk density of solid dispersions is called as Hausner'ratio. Results are given in table 9.

Hausner's ratio = Tapped density/Bulk density

FORMULATION AND EVALUATION OF IRBESARTAN TABLETS

Formulation of Irbesartan tablets:

Tablets containing Irbesartan (150mg) and Irbesartan solid dispersions prepared by solvent evaporation method (equivalent to 150mg of pure Irbesartan) were formulated. The formula of Irbesartan tablets is given in table 21. Direct compression method was used for the preparation of tablets. In this, microcrystalline cellulose (MCC) was used as direct compressible vehicle, mannitol was used as diluent and talc, magnesium stearate as lubricant and glidants respectively.

Procedure for preparation of compressed tablets of Irbesartan:

Direct compression method:

All the ingredients were blended in a closed dry plastic container. The blend of powder was compressed into tablets to a hardness of 2-4 kg/cm^2 on a 'Cadmach' single punch tablet machine. In each case thirty tablets were prepared. The tablets were stored in a tightly closed container and evaluated for following characteristics in triplicate.

Evaluation of Irbesartan tablets:

Weight variation test[8]:

Twenty tablets from each batch were taken and weighed. The average weight was calculated, then each tablet was weighed individually and weight of each tablet was noted. The weights of individual tablets were then compared with the average weight. The results were given in table-10.

Friability:

Friability test was performed by using "Roche friabilator". Twenty tablets of each batch were weighed and placed in a friabilator chamber and it was allowed to rotate 100 revolutions. After completion of 100 revolutions, tablets were weighed and the loss in weight indicated the friability. The friability values were given in table- 10.

Hardness[5]:

Hardness of the tablet was measured by using "Monsanto type hardness tester". The results were expressed in kg/cm^2. The results were given in table- 10.

Disintegration test[6]:

One tablet was placed in each tube of disintegration apparatus (Thermonic model) and the test was carried out using distilled water as Disintegration medium at 25 ^{0}C. The time for Disintegration was noted in each test product for six tablets. The results are given in table- 10.

Content of active ingredient[7]:

For drug content analysis, twenty tablets were accurately weighed and finely powdered. The quantity of powder, equivalent to 150 mg of Irbesartan was taken in a 100ml volumetric flask and filtered the solution, 1ml

of the filtrate was dissolved in 10ml of 0.1N HCl (1.2 pH) and assayed for drug content at 244nm, using spectrophotometer. The results are given in table 10.

***In-vitro* dissolution study of Irbesartan tablets:**

In-vitro dissolution study of tablets was conducted using USP dissolution apparatus II (lab India DISSO 2000, eight stages) at 244nm, using 0.1 N HCl (1.2pH) maintained at 37±0.5 ^{0}C. Aliquot equal to 5 ml was withdrawn at regular time intervals (10, 20, 30, 40, 50, 60 min), an equal volume of fresh dissolution medium was replaced to maintain the sink condition and aliquots were measured at 244 nm UV/Visible spectrophotometer. The in-house formulations were taken for comparative study with market formulation to observe the dissolution characteristics of in-house formulations with market formulation. The results are shown in figure , & Table . The dissolution parameters are given in table 10.

Table 1: Calibration curve for the estimation of Irbesartan

Concentration (µg/ml)	Absorbance at 244nm
0	0.000
2	0.090
4	0.176
6	0.271
8	0.369
10	0.454

Fig 2: Calibration curve for the estimation of Irbesartan

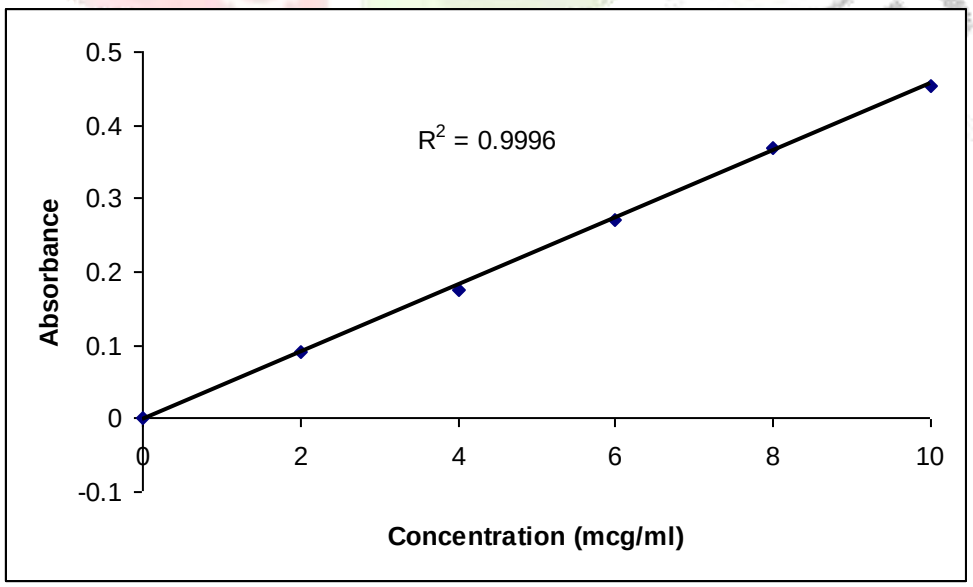


Table 2: Phase Solubility Studies of Irbesartan (Pure Drug)

Solvent	Amount soluble (Irbesartan) in mg/ml
0.1N HCl (1.2 pH)	1.71
pH 2.0	0.145
pH 3.0	0.091
pH 4.5	0.065
pH 6.8	0.181
pH 7.4	0.801
Distilled Water	0.005
Distilled Water + 0.5% SLS	1.03
Distilled Water + 1% SLS	1.45
Distilled Water + 2% SLS	0.50

Table 3: List of Irbesartan solid dispersions prepared and their compositions

DRUG	CARRIER	S.D CODE
Irbesartan (1)	MCC (1)	PM1(1:1)
Irbesartan (1)	MCC (2)	PM2 (1:2)
Irbesartan (1)	MCC (4)	PM3 (1:4)
Irbesartan (1)	MCC (1)	SE1 (1:1)
Irbesartan (1)	MCC (2)	SE2 (1:2)
Irbesartan (1)	MCC (4)	SE3 (1:4)
Irbesartan (1)	CCS (1)	PM4 (1:1)
Irbesartan (1)	CCS (2)	PM5 (1:2)
Irbesartan (1)	CCS (4)	PM6 (1:4)
Irbesartan (1)	CCS (1)	SE4 (1:1)
Irbesartan (1)	CCS (2)	SE5 (1:2)
Irbesartan (1)	CCS (4)	SE6 (1:4)
Irbesartan (1)	SSG (1)	PM7 (1:1)
Irbesartan (1)	SSG (2)	PM8 (1:2)
Irbesartan (1)	SSG (4)	PM9 (1:4)
Irbesartan (1)	SSG (1)	SE7 (1:1)
Irbesartan (1)	SSG (2)	SE8 (1:2)
Irbesartan (1)	SSG (4)	SE9 (1:4)
Irbesartan (1)	CP (1)	PM10 (1:1)
Irbesartan (1)	CP (2)	PM11 (1:2)
Irbesartan (1)	CP (2)	PM12 (1:4)
Irbesartan (1)	CP (1)	SE10 (1:1)
Irbesartan (1)	CP (2)	SE11 (1:2)
Irbesartan (1)	CP (4)	SE12 (1:4)

Note: PM1 to **PM3** and **SE1** to **SE3** correspond to preparations containing "**MCC**"; **PM4** to **PM6** and **SE4** to **SE6** correspond to preparations containing "**CCS**"; **PM7** to **PM9** and **SE7** to **SE9** correspond to preparations containing "**SSG**"; **PM10** to **PM12** and **SE10** to **SE12** correspond to preparations containing "**CP**".

Table 4: Solubility studies of Irbesartan solid dispersions prepared by physical mixing method

System	Solubility (mg/ml)
Pure drug	0.001
PM1(1:1)	0.0017
PM2 (1:2)	0.003
PM3 (1:4)	0.0041
PM4 (1:1)	0.002
PM5 (1:2)	0.0038
PM6 (1:4)	0.0072
PM7 (1:1)	0.0058
PM8 (1:2)	0.0115
PM9 (1:4)	0.0147
PM10 (1:1)	0.0094
PM11 (1:2)	0.024
PM12 (1:4)	0.0287

Table 5: Solubility studies of Irbesartan solid dispersions prepared by solvent evaporation method

System	Solubility (mg/ml)
Pure drug	0.001
SE1 (1:1)	0.0018
SE2 (1:2)	0.0027
SE3 (1:4)	0.0035
SE4 (1:1)	0.004
SE5 (1:2)	0.007
SE6 (1:4)	0.0098
SE7 (1:1)	0.0112
SE8 (1:2)	0.0124
SE9 (1:4)	0.026
SE10 (1:1)	0.0178
SE11 (1:2)	0.0264
SE12 (1:4)	0.0356

Table 6: Irbesartan content of various solid dispersions by physical mixing

System	% Drug content*
PM1(1:1)	98.70 ± 0.32
PM2 (1:2)	96.64 ± 0.87
PM3 (1:4)	95.12 ± 0.36
PM4 (1:1)	95.87 ± 0.54
PM5 (1:2)	96.35 ± 0.65
PM6 (1:4)	98.23 ± 0.23
PM7 (1:1)	94.74 ± 0.86
PM8 (1:2)	97.76 ± 0.45
PM9 (1:4)	96.67 ± 0.65
PM10 (1:1)	95.83 ± 0.34
PM11 (1:2)	96.29 ± 0.24
PM12 (1:4)	99.10 ± 0.18

* Indicates mean of three readings.

Table 7: Irbesartan content of various solid dispersions by solvent evaporation method

System	% Drug content*
SE1 (1:1)	96.44 ± 0.78
SE2 (1:2)	98.80 ± 0.35
SE3 (1:4)	97.56 ± 0.79
SE4 (1:1)	95.37 ± 0.34
SE5 (1:2)	97.65 ± 0.23
SE6 (1:4)	98.74 ± 0.73
SE7 (1:1)	98.34 ± 0.63
SE8 (1:2)	94.76 ± 0.37
SE9 (1:4)	99.36 ± 0.26
SE10 (1:1)	96.32 ± 0.65
SE11 (1:2)	97.98 ± 0.77
SE12 (1:4)	98.61 ± 0.90

* Indicates mean of three readings.

***In vitro* dissolution studies of Irbesartan solid dispersions:**

Drug release from solid dispersions (physical mixtures and solvent evaporation) was faster than pure drug (table 3 & 4). Drug release was found to be increase with increasing concentration of carriers (table 3 & 4). The dissolution rate of drug from solid dispersions (solvent evaporation method) were found to be faster than from physical mixture, this may be due to molecular and colloidal dispersion of drug in carrier matrix of MCC, CCS, SSG and CP. The dissolution of drug was found to be faster from solid dispersions with CP than from solid dispersions prepared with MCC, CCS and SSG. It was observed that 100% drug release was obtained from the solid dispersions (prepared by solvent evaporation method) of Irbesartan: CP and Irbesartan:

SSG in 30 and 50 minutes, respectively (table 10,11) (fig 3,4). The enhanced dissolution rate with crospovidone (CP) may be attributed to their surface activity, which facilitates wetting and subsequent solubilization of drug.

Table 8: Dissolution profiles of Irbesartan solid dispersions prepared by physical mixing method using MCC

Time (min)	% Drug dissolved* (mean ± s.d., n= 3)			
	Pure drug	PM1(1:1)	PM2 (1:2)	PM3 (1:4)
0	0	0	0	0
10	12.62±0.88	33.87±0.93	39.45±0.43	46.49±0.05
20	34.54±0.70	42.50±0.68	49.28±0.09	66.15±0.49
30	40.78±0.39	52.86±0.99	55.39±0.65	74.25±0.51
40	42.77±0.27	58.84±0.54	65.49±0.04	80.90±1.20
50	49.28±0.60	66.68±0.37	70.93±0.28	83.82±0.44
60	58.71±0.94	72.26±0.38	72.26±0.02	87.54±0.04

* Indicates mean of three readings.

Table 9: Dissolution profiles of Irbesartan solid dispersions prepared by solvent evaporation method using MCC

Time (min)	% Drug dissolved* (mean ± s.d., n= 3)			
	Pure drug	SE1(1:1)	SE2 (1:2)	SE3 (1:4)
0	0	0	0	0
10	12.62±0.88	37.32±0.71	48.08±0.08	60.30±0.44
20	34.54±0.70	52.73±0.22	63.23±0.97	75.51±0.09
30	40.78±0.39	62.56±0.11	71.36±1.24	79.30±0.77
40	42.77±0.27	70.14±0.09	79.30±0.43	83.42±0.28
50	49.28±0.60	75.58±0.04	82.76±0.11	89.93±0.07
60	58.71±0.94	79.97±0.88	85.15±0.78	91.92±0.63

* Indicates mean of three readings.

Table 10: Dissolution profiles of Irbesartan solid dispersions prepared by physical mixing method using CP

Time (min)	% Drug dissolved* (mean ± s.d., n= 3)			
	Pure drug	PM10 (1:1)	PM11 (1:2)	PM12 (1:4)
0	0	0	0	0
10	12.62±0.88	41.18±0.29	43.04±0.71	58.58±1.24
20	34.54±0.70	55.93±0.42	72.13±0.83	81.69±0.72
30	40.78±0.39	62.70±0.39	83.02±0.41	84.61±0.67

40	42.77±0.27	68.01±0.25	85.54±0.06	89.13±0.51
50	49.28±0.60	73.33±0.84	87.27±1.01	94.31±0.62
60	58.71±0.94	81.66±0.27	88.27±0.54	95.51±0.86

* Indicates mean of three readings.

Table 11: Dissolution profiles of Irbesartan solid dispersions prepared by solvent evaporation method using CP

Time (min)	**% Drug dissolved* (mean ± s.d., n= 3)**			
	Pure drug	**SE10 (1:1)**	**SE11 (1:2)**	**SE12 (1:4)**
0	0	0	0	0
10	12.62±0.88	42.24±0.91	55.26±0.11	69.87±0.02
20	34.54±0.70	67.74±0.38	69.21±0.45	96.57±0.70
30	40.78±0.39	78.77±0.33	81.43±0.86	100.02±0.69
40	42.77±0.27	83.82±0.53	88.73±0.09	-
50	49.28±0.60	86.61±0.89	95.38±0.42	-
60	58.71±0.94	89.53±0.61	96.8±0.33	-.

* Indicates mean of three readings.

Fig 3: Dissolution profiles of Irbesartan solid dispersions prepared by physical mixing method using CP

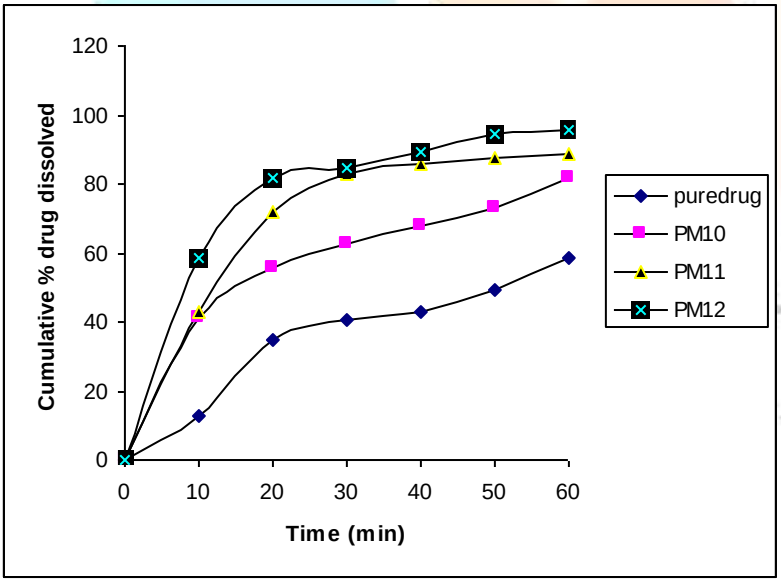


Fig 4: Dissolution profiles of Irbesartan solid dispersions prepared by solvent evaporation method using CP

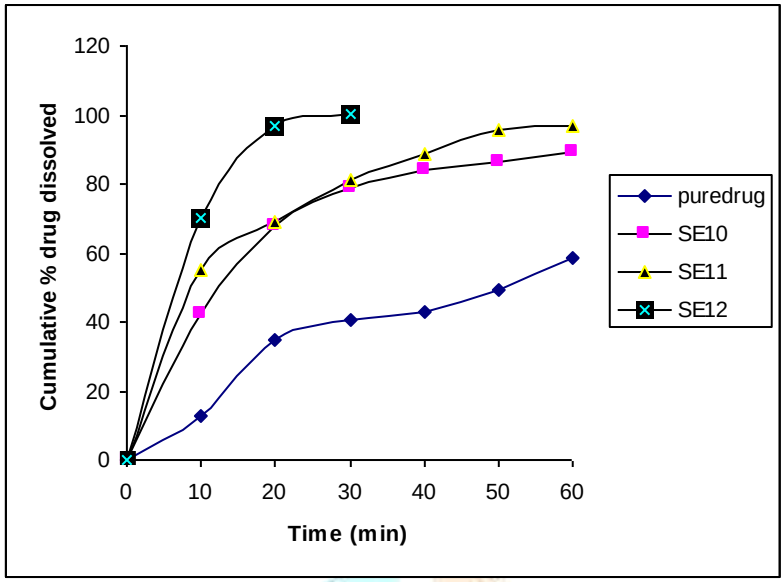


Fig 5: First order plots of Irbesartan solid dispersions prepared by physical mixing method using CP

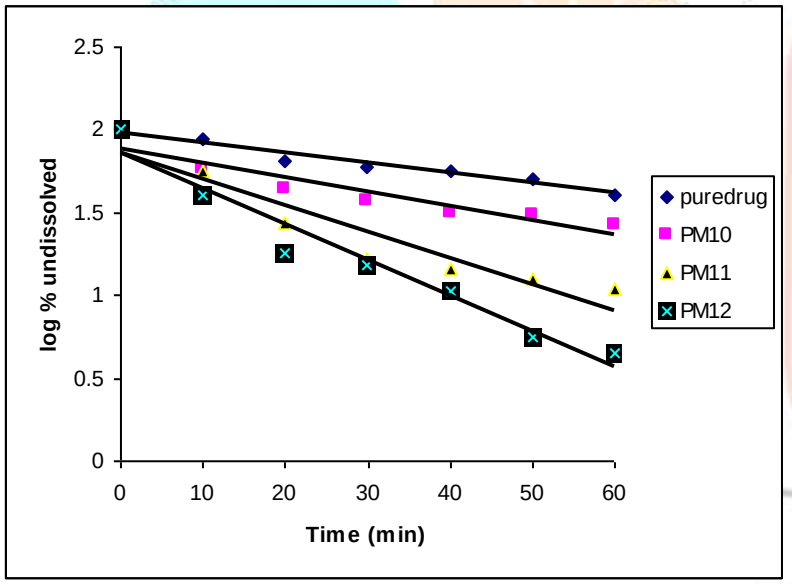


Fig 6: First order plots of Irbesartan solid dispersions prepared by solvent evaporation method using CP

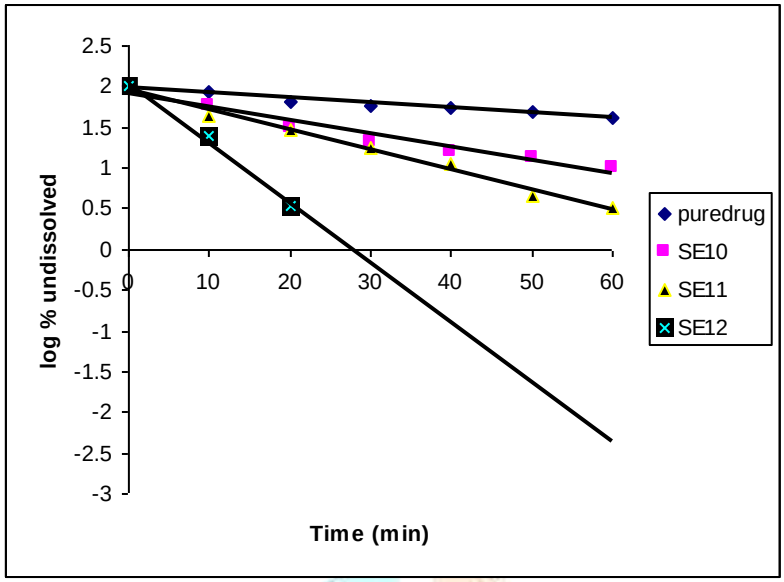


Table 12: Dissolution kinetics of Irbesartan solid dispersions prepared by physical mixing

System	T_{50} (min)	T_{90} (min)	DE_{30}%	K_1 (min^{-1})	R^2 Value
Pure drug	50	>60	20.41	0.0138	0.9658
PM1	28	>60	28.62	0.0162	0.9740
PM2	20	>60	32.23	0.0299	0.9687
PM3	18	>60	42.17	0.0461	0.9537
PM4	25	>60	30.29	0.0182	0.9783
PM5	20	>60	33.69	0.0301	0.9531
PM6	8	60	46.44	0.0512	0.9405
PM7	25	>60	32.18	0.0203	0.9445
PM8	15	>60	44.58	0.0423	0.9748
PM9	8	48	48.97	0.0713	0.9590
PM10	18	>60	3595	0.0276	0.9831
PM11	16	>60	45.05	0.0713	0.9964
PM12	8	42	51.09	0.0806	0.9559

Table 13: Dissolution kinetics of Irbesartan solid dispersions prepared by solvent evaporation

System	T_{50} (min)	T_{90} (min)	DE_{30}%	K_1 (min^{-1})	R^2 Value
Pure drug	50	>60	20.41	0.0138	0.9658
SE1	20	>60	34.22	0.0276	0.9734
SE2	12	>60	40.98	0.0344	0.9341
SE3	8	60	48.43	0.0484	0.9787
SE4	15	>60	36.44	0.0345	0.9787
SE5	10	58	42.99	0.0368	0.9767
SE6	8	28	54.01	0.0578	0.9972
SE7	15	>60	38.45	0.0391	0.9738
SE8	8	55	47.04	0.0506	0.9367
SE9	5	25	54.97	0.0599	0.9181
SE10	15	>60	42.74	0.0598	0.9543
SE11	8	45	45.85	0.0856	0.9898
SE12	5	15	60.50	0.2003	0.9889

Drug- Excipient compatibility studies:

Infrared spectroscopy

Infrared spectra were recorded on a Fourier transform Infrared (FTIR) spectrophotometer using KBr dispersion method. All samples were recorded in the range of 4000-400 cm^{-1}.

IR spectra of Irbesartan, carriers, solid dispersions prepared by solvent evaporation (1:4) method are illustrated in Figure 20.

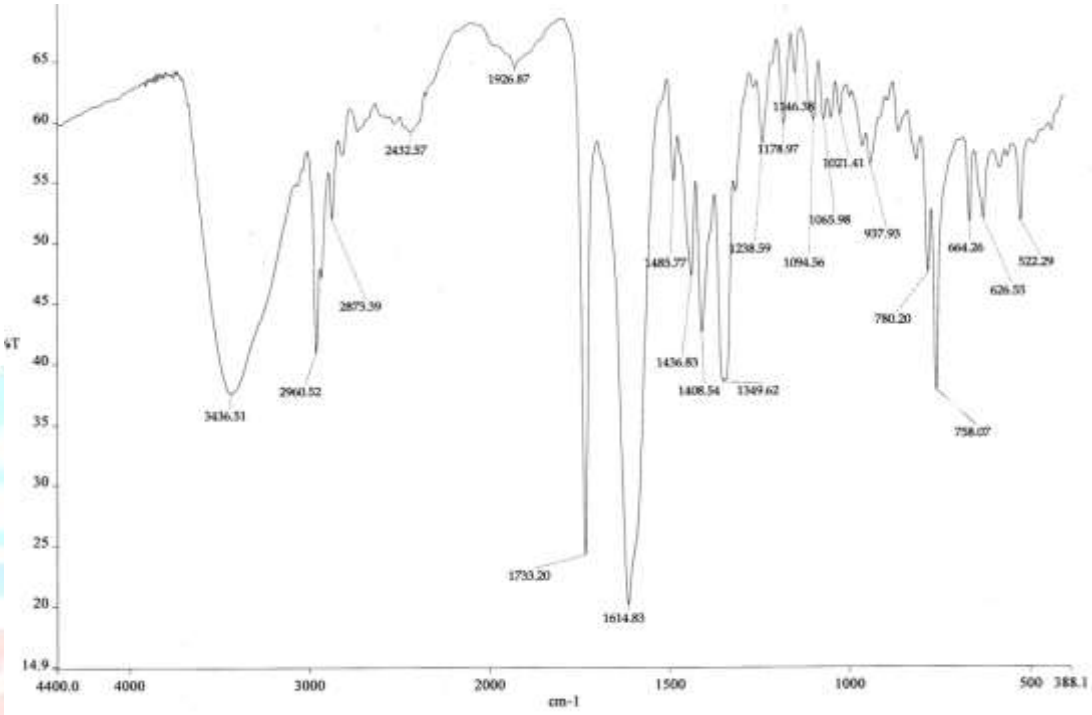
Characteristic peaks of irbesartan at 3436.51 cm^{-1} (N-H stretching), 2960.52 cm^{-1} (C-H stretching), 1733.30 cm^{-1} (C=O stretching), 1485.77 cm^{-1} (C=C stretching) and 1614.83 cm^{-1} (N-H bending) were observed.

SSG, CCS and MCC showed similar absorption bands due to the similarities of molecular structure, in which Characteristic peaks of O-H stretching (3371.85 cm^{-1}, 3349.79 cm^{-1}, 3348.32 cm^{-1} respectively), C-H stretching (2929.00 cm^{-1}, 2906.86 cm^{-1}, 2906.48 cm^{-1}), CH_2 bending (1422.56 cm^{-1}, 1430.66 cm^{-1}, 1430.07 cm^{-1}) and C-O stretching (1157.00 cm^{-1}, 1161.92 cm^{-1}, 1162.04 cm^{-1}) were observed.

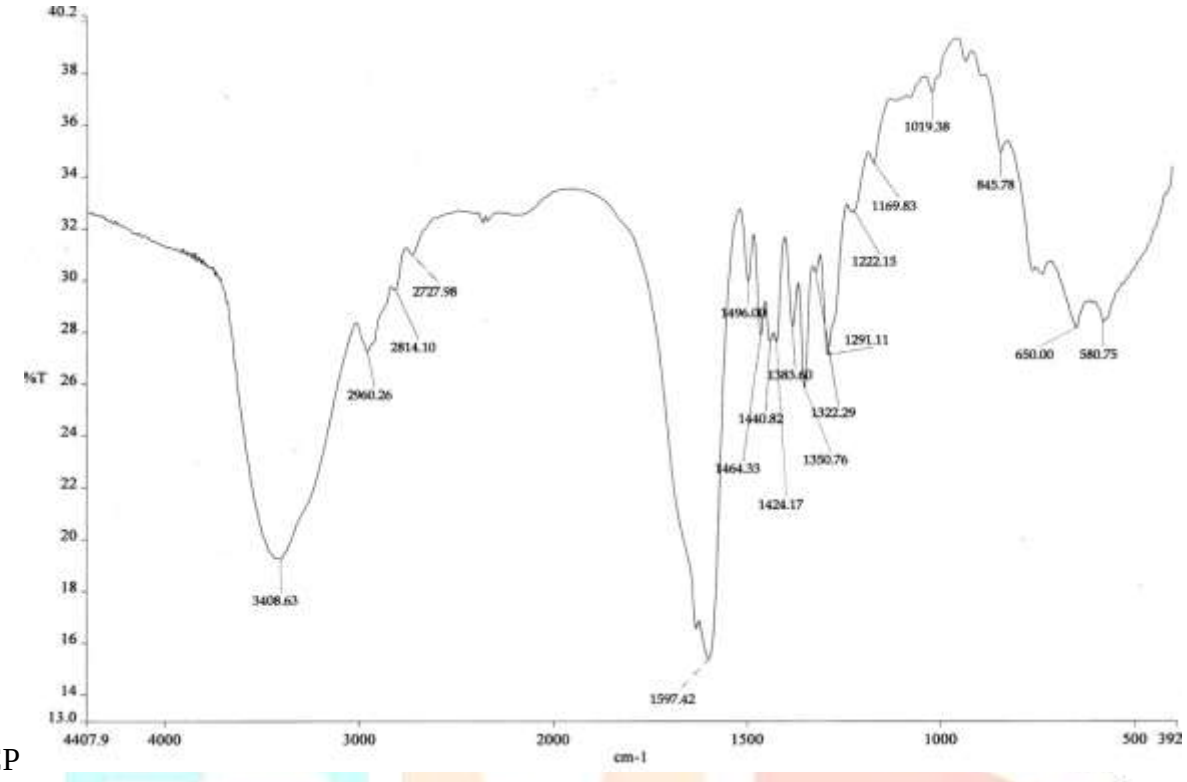
CP shows characteristic peaks of C-H stretching aliphatic (2814.10 cm^{-1}), CH_2 bending (1424.17 cm^{-1}) and aromatic C-N stretching (1383.60 – 1169.83 cm^{-1}).

All Physical mixtures and solvent evaporation dispersions showed peaks of irbesartan (pure) and carriers. These results indicated that there is no chemical interaction between drug and carrier when formed as solid dispersion.

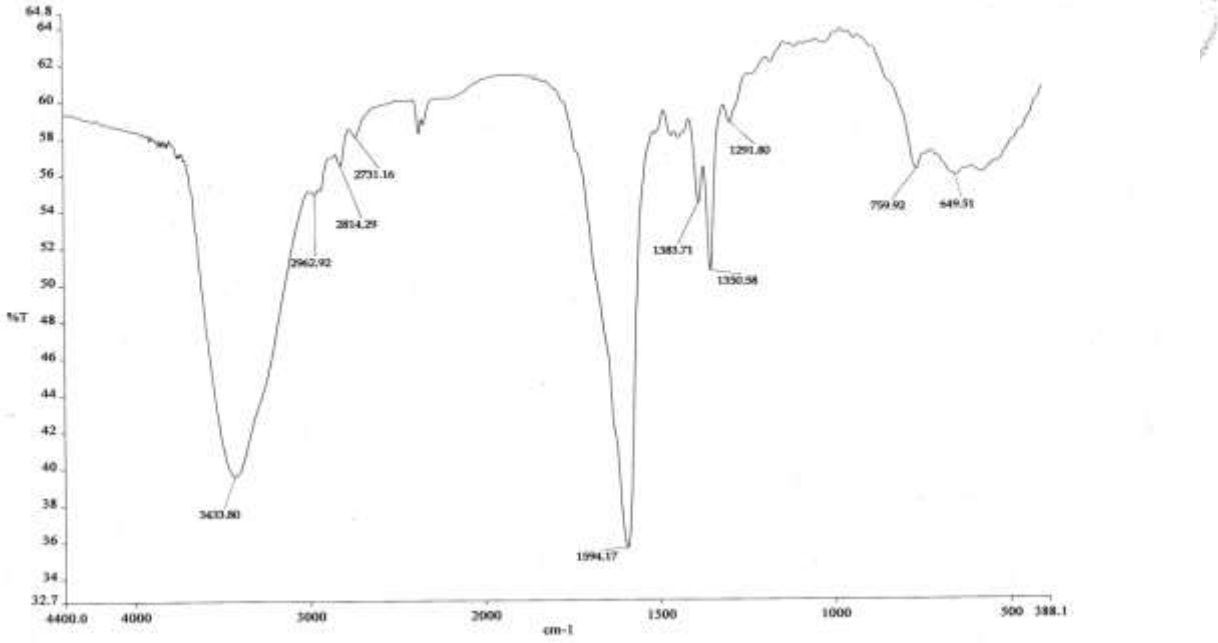
Fig 7: IR spectrum of Irbesartan, pure carriers, solid dispersion (solvent evaporation) systems.



IRBESARTAN



CP



Irbe:CP

Table 14: Pre-Formulation Studies of Irbesartan alone and its Solid Dispersions

System	Angles of repose (°)	Bulk density	Taped density	Carr's index	Hausner's ratio
Irbesartan	31	0.52	0.64	18.75	1.23
Irbe: MCC (1:4) SE	28.4	0.61	0.72	18.03	1.18
Irbe: CCS (1:4) SE	25.34	0.63	0.74	17.46	1.17
Irbe: SSG (1:4) SE	26.21	0.63	0.62	16.98	1.16
Irbe: CP (1:4) SE	25.8	0.57	0.61	7.01	1.07

From the preformulation studies of the Irbesartan solid dispersions, it is clear that all the Irbesartan solid dispersions fulfilled the official requirements for compression tablets through direct compression method.

Table 15: Formulae of Irbesaratn tablets employing solid dispersions

Ingredients (mg/ tablet)	F1	F2	F3	F4	F5
Pure Irbesartan	150	-	-	-	-
Irbe:MCC (1:4)SE	-	750	-	-	-
Irbe:CCS (1:4)SE	-	-	750	-	-
Irbe:SSG (1:4)SE	-	-	-	750	-
Irbe:CP (1:4)SE	-	-	-	-	750
Lactose anhydrous	707	107	107	107	107
MCC	30	30	30	30	30
Manitol	10	10	10	10	10
Magnesium sterate	2	2	2	2	2
Talc	1	1	1	1	1
Total weight of tablet (mg)	**900**	**900**	**900**	**900**	**900**

Table 16: Evaluation of tablets

Tablet formulation	Hardness (kg/sq.cm)	Disintegration time (sec)	Friability (%)	Drug content (%)

F1	4.5	130	0.38	99.78
F2	2.5	120	0.34	99.87
F3	4	115	0.29	98.40
F4	2.5	105	0.30	99.09
F5	3	95	0.22	98.81

From the physico-mechanical parameters of the formulated tablets, it is clear that all the tablets fulfilled the official requirements of the compressed tablets. The results of the disintegration test revealed that F5 has faster disintegration and it disintegrates within two minutes (95sec).

Table 17: Dissolution parameters of Irbesartan tablets

Formulations	**Dissolution parameters**				
	% Drug dissolved in 10 minutes	**T_{50} (min)**	**DE_{30}%**	**K_1 (min)**	**R^2 value**
F1	6.67	55	12.3	0.0161	0.9930
F2	38.65	15	40.29	0.0484	0.9900
F3	40.48	14	41.93	0.0553	0.9723
F4	45.99	15	40.43	0.0345	0.9896
F5	53.52	8	52.23	0.0991	0.9936
Irbesartan MP	46.49	15	40.66	0.0345	0.9524

From the dissolution profiles and dissolution parameters, it is clear that among all in-house formulations F5 showed maximum dissolution and it is on par with marketed formulation.

DISSCUSSION OF RESULTS

Solid dispersions of Irbesartan were prepared by physical mixing and solvent evaporation method. The carriers like microcrystalline cellulose, croscarmellose sodium, sodiumstarchglycolate and crospovidone were used in the preparation of solid dispersions. Various ratios of drug and carrier such as 1:1, 1:2 and 1:4 were used in the preparation.

All the solid dispersions prepared by physical mixing and solvent evaporation method were found to be fine free flowing powders. The percent drug content data of solid dispersions are given in table-8, 9. Low s.d in the percent drug content values indicated uniformity of drug content in each batch of solid dispersions. Dissolution rate studies of Irbesartan as such and its solid dispersions were studied in 0.1N HCI. The results are given in tables- 10 to 17 and dissolution, first order plots are shown in fig-5,6.

Solid dispersions prepared by physical mixing and solvent evaporation method gave improved and higher dissolution of Irbesartan when compared to pure drug. Dissolution data of Irbesartan followed first order kinetics. First order dissolution rate constant (K_1) were calculated from the slopes of the linear regressions are given in tables -18, 19.

T_{50}, T_{90} and DE_{30}% values for solid dispersions were calculated from the dissolution data and profiles are given in tables-12, 13.

CONCLUSION

The enhancement of dissolution rate and oral bioavailability of poorly soluble drugs remains one of the most challenging aspects of drug development. Among the various methods of enhancement of the dissolution

rate and oral bioavailability, solid dispersion technologies were found to be more successful with a number of drugs. In the present investigation studies were carried out on enhancement of dissolution rate of Irbesartan by solid dispersion technology employing various water dispersible carriers. A new class of tablet excipients called 'super disintegrants' was evaluated as carriers for solid dispersions and for enhancing the dissolution rate of poorly soluble drugs.

From the results obtained the following conclusions were drawn:

- All the solid dispersions prepared were found to be fine free flowing powders.
- The drug content was uniform in a batch of solid dispersions in all the cases.
- The dissolution of Irbesartan from all the solid dispersions was rapid and several times higher than the dissolution of the corresponding pure drug.
- Drug dissolution from all solid dispersions followed first order kinetics.
- All the dissolution parameters estimated i.e. T_{50}, T_{90}, DE_{30}% and K_1 values indicated rapid and higher dissolution of the drug (Irbesartan) from solid dispersions than that of corresponding pure drug.
- Among the superdisintegrants tested CP gave highest enhancement of dissolution rate and efficiency of Irbesartan.
- In each case the dissolution rate (K_1) and DE_{30}% were increased as the concentration of carriers (superdisintegrants) in the solid dispersions was increased.
- The order of increase in dissolution rate with various superdisintegrants CP > SSG > CCS > MCC with Irbesartan.
- Over all the superdisintegrants gave marked enhancement of Irbesartan.
- Among all CP was found to be good carrier for solid dispersions for enhancing the dissolution rate of Irbesartan.
- All formulated tablets employing solid dispersions in superdisintegrants exhibited rapid and higher drug dissolution when compared to plain tablets, formulation with pure drug and also commercial tablets of Irbesartan.
- The increasing order of dissolution rate F5 > F4 > F3 > F2 > F1.

BIBLIOGRAPHY

1. Lachman L. and Lieberman H.A., *Pharmaceutical Dosage Forms,* In; Tablets, Vol. 2, Marcel Dekker, Inc., New York.
2. Remington: *The science and practice of pharmacy,* 20th edition volume1, Page. No: 858-863
3. Fincher, J. H., *J. Pharm. Sci.***, 1968,** Page. No: 57.
4. Sekiguchi, K. and obi. N**,** *Chem. Pharm. Bull*, **1961,** Page. No: 9.
5. Batra, Shirolkar V.S. and Deshpande A.D., *Indian J. Pharma. Educ. Res, 42(4),* Oct – Dec. **2008,** Page. No: 373- 378.
6. Indian Pharmacopiea, 4th Edn., Controller of Publications, New Delhi, **1996**, A-80,82
7. Indian Pharmacopiea, 4th Edn., Controller of Publications, New Delhi, **1996**, Page No: 734- 740.

WEB SEARCH:

8. www.rxlist.com