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Research Article

ENHANCEMENT OF SOLUBILITY AND DISSOLUTION RATE OF IRBESARTAN BY SOLID DISPERSION TECHNIQUE

G. ASHWINI KUMAR*[1], RAM KUMAR CHOUDHARY[1] AND CH. CHAITANYA[2]

[1]Department of Pharmaceutics, Bharat Institute of Technology (Pharmacy), Ibrahimpatnam, Hyderabad, Andhra Pradesh, India.
[2]Therdose Pharma Pvt. Ltd, Kukatpally, Hyderabad, Andhra Pradesh, India
E mail: ashwinn4u@gmail.com

ABSTRACT

The purpose of present work was to enhance the solubility and dissolution rate of Irbesartan by solid dispersion technology employing various super disintegrants such as sodium starch glycolate (SSG), crosspovidone (CP), croscarmellose sodium (CCS) and microcrystalline cellulose (MCC). Solid dispersions were prepared by physical mixing and solvent evaporation method. Various ratios of drug and carriers were used in the preparation in the ratio of 1:1, 1:2 and 1:4. Phase solubility studies of pure drug and solid dispersion was performed. It was found that solubility of Irbesartan was increased. All the solid dispersions prepared were found to be fine free flowing powders and the drug content was uniform in all batches. The results of the disintegration test revealed that F5 has faster disintegration and it disintegrates within two minutes (95secs). The dissolution of Irbesartan from all the solid dispersions was rapid and several times higher than the dissolution of the corresponding pure drug and followed first order kinetics. All the dissolution parameters estimated i.e. T_{50}, T_{90}, DE_{30}% values indicated rapid and higher dissolution of the drug (Irbesartan) from solid dispersions than that of corresponding pure drug. CP showed 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 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 i.e. 4.25 and 6.15 fold increase in DE_{30}% and dissolution rate (K_1) were observed with formulation F5. FT-IR studies revealed that there was no chemical interaction between drug and carrier when formed as solid dispersion.

Keywords: Superdisintegrants, solid dispersions, crosspovidone, Microcrystalline cellulose.

INTRODUCTION

Solid dispersion technology is the science of dispersing one or more active ingredients in an inert matrix in the solid state in order to achieve increased dissolution rate, sustained release of drugs, altered solid state properties and enhanced release of drugs from ointment and suppository bases and improved solubility and stability[1].

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[2].

In case 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[3].

A solid dispersion may be obtained in different ways e. g. by employing organic solvents or by dispersing or dissolving the active substance in another suitable medium (e.g. an oily material that is in liquid form at room temperature or at elevated temperatures). Solid dispersions (solvent method) are prepared by dissolving a physical mixture of the active substance (e.g. a drug substance) and the carrier in a common organic solvent, followed by evaporation of the solvent[4]. The carrier is often a hydrophilic polymer. Suitable organic solvents include pharmaceutical acceptable solvent in which the active substance is soluble such as methanol, ethanol, methylene chloride, chloroform, ethyl acetate and acetone.

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[5]. 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[6]. Many hydrophilic excipients like PEG 4000, PEG 6000, Mannitol, PVP, and poloxamers can be used to enhance the dissolution of drug[7]. 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 Irbesartan was selected for enhancement of solubility and dissolution rate as it 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[8,9].

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 Irbesartan by solid dispersion using physical mixing (PM) and solvent evaporation (SE) technique of Irbesartan with SSG, CP, CCS and MCC and to improve the dissolution of drug. The aim of the present work is to enhance the solubility, dissolution rate and oral bioavailability of poorly soluble drug Irbesartan by solid dispersion technology using various carriers.

MATERIALS AND METHODS

Irbesartan was received as a gift sample from Matrix Laboratories Ltd, Hyderabad. Microcrystalline cellulose was procured from Kemphasol, Mumbai. Sodium starch glycolate was purchased from Central Drug House, New Delhi. Crosspovidone procured from Ozone International, Mumbai. Croscarmellose sodium (procured from Ozone International, Mumbai). Methanol (Qualigens chemicals Ltd., Mumbai). Lactose anhydrous (Sd fine chemicals Ltd., Mumbai). Mannitol (Sd fine chemicals Ltd., Mumbai). Talc (Sd fine chemicals Ltd., Mumbai). Magnesium stearate (Sd fine chemicals Ltd., Mumbai). The commercial products of Irbesartan

were procured from the local market. All other chemicals/solvents used were of AR grade.

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 shown in Table 1.

Physical mixing method:

Irbesartan and each of surface active carriers (MCC, CCS, SSG and CP) were weighed accurately and mixed thoroughly in mortar 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.

Solvent evaporation method[10]:

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^{0}C. The resulting solid dispersions were stored for 24 hrs in dessicator 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.

Table 1: List of Irbesartan solid dispersions prepared and their compositions

Formulation code	Carrier	Drug : Carrier
PM1	MCC	1:1
PM2	MCC	1:2
PM3	MCC	1:4
PM4	CCS	1:1
PM5	CCS	1:2
PM6	CCS	1:4
PM7	SSG	1:1
PM8	SSG	1:2
PM9	SSG	1:4
PM10	CP	1:1
PM11	CP	1:2
PM12	CP	1:4
SE1	MCC	1:1
SE2	MCC	1:2
SE3	MCC	1:4
SE4	CCS	1:1
SE5	CCS	1:2
SE6	CCS	1:4
SE7	SSG	1:1
SE8	SSG	1:2
SE9	SSG	1:4
SE10	CP	1:1
SE11	CP	1:2
SE12	CP	1:4

PM = Physical Mixing and SE = Solvent Evaporation

Pre-formulation studies of Irbesartan and optimized Solid Dispersions

Pre-formulation studies such as angle of repose, bulk density, tapped density; Carr's index and Hausner's ratio were performed.

Formulation of Irbesartan tablets[1, 5]

Based on maximum solubility, optimized solid dispersions were formulated as tablets and the composition of tables is shown in Table 2. 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. 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.

Table 2: Formulae of Irbesartan tablets employing solid dispersions

Ingredients (mg/ tablet)	F1	F2	F3	F4	F5
Pure Irbesartan	150	-	-	-	-
SE3	-	750	-	-	-
SE6	-	-	750	-	-
SE9	-	-	-	750	-
SE12	-	-	-	-	750
Lactose anhydrous	707	107	107	107	107
MCC	30	30	30	30	30
Manitol	10	10	10	10	10
Magnesium stearate	2	2	2	2	2
Talc	1	1	1	1	1
Total weight of tablet (mg)	**900**	**900**	**900**	**900**	**900**

Evaluation of Irbesartan Solid Dispersions

Solubility studies[11]

Solubility study was performed according to method reported by Higuchi and Connors[12,13]. 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 Whatmann 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.

Drug content Estimation[14]

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.

Pre-formulation studies of Irbesartan and optimized Solid Dispersions

Pre-formulation studies such as angle of repose, bulk density, tapped density; Carr's index and Hausner's ratio were performed.

Evaluation of Irbesartan tablets:

Various physical parameters such as hardness, friability, disintegration time were evaluated

Content of active ingredient[15]

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.

Disintegration test[16]

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.

***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.

Drug-excipient compatibility studies

FT-IR studies were performed for pure drug alone and in combination with excipients.

Table 3: Solubility and Irbesartan content of all solid dispersions

Formulation code	Solubility (mg/ml)	% Drug content*
PM1	0.0017	98.70 ± 0.32
PM2	0.003	96.64 ± 0.87
PM3	0.0041	95.12 ± 0.36
PM4	0.002	95.87 ± 0.54
PM5	0.0038	96.35 ± 0.65
PM6	0.0072	98.23 ± 0.23
PM7	0.0058	94.74 ± 0.86
PM8	0.0115	97.76 ± 0.45
PM9	0.0147	96.67 ± 0.65
PM10	0.0094	95.83 ± 0.34
PM11	0.024	96.29 ± 0.24
PM12	0.0287	99.10 ± 0.18
SE1	0.0018	96.44 ± 0.78
SE2	0.0027	98.80 ± 0.35
SE3	0.0035	97.56 ± 0.79
SE4	0.004	95.37 ± 0.34
SE5	0.007	97.65 ± 0.23
SE6	0.0098	98.74 ± 0.73
SE7	0.0112	98.34 ± 0.63
SE8	0.0124	94.76 ± 0.37
SE9	0.026	99.36 ± 0.26
SE10	0.0178	96.32 ± 0.65
SE11	0.0264	97.98 ± 0.77
SE12	0.0356	98.61 ± 0.90

Table 4: Pre-Formulation Studies of Irbesartan alone and its Solid Dispersions

System	Angles of repose (º)	Bulk density	Tapped density	Carr's index	Hausner's ratio
Irbesartan	31	0.52	0.64	18.75	1.23
SE3	28.4	0.61	0.72	18.03	1.18
SE6	25.34	0.63	0.74	17.46	1.17
SE9	26.21	0.63	0.62	16.98	1.16
SE12	25.8	0.57	0.61	17.01	1.07

* Indicates mean of three readings.

Table 5: Evaluation of tablets

Tablet formulation	Hardness (kg/sq.cm)	Disintegration time (sec)	Friability (%)	Drug content (%)
F1	4.5±0.43	130±0.88	0.38±0.22	99.78
F2	4.3±0.67	120±0.80	0.34±0.12	99.87
F3	4.0±0.68	117±0.86	0.29±0.15	98.40
F4	4.1±0.69	109±0.78	0.30±0.67	99.09
F5	3.9±0.01	94±0.89	0.22±0.81	99.51

Table 6: Dissolution parameters of Irbesartan tablets

Formulations	Dissolution parameters				
	% Drug dissolved in 10 min	T_{50} (min)	DE_{30}%	K_1(min)	R^2value
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

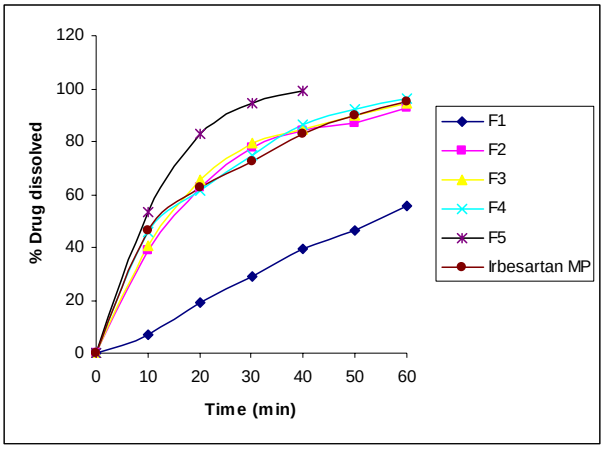

Fig. 1: Dissolution profile comparison of Irbesartan tablets with marketed product

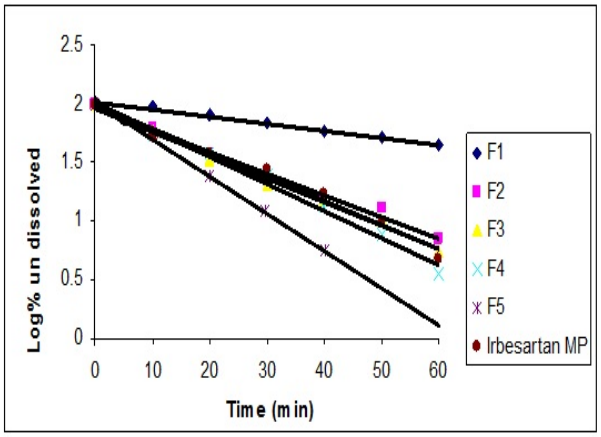

Fig. 2: First order plots comparison of Irbesartan tablets with marketed product

a) IRBESARTAN PURE DRUG

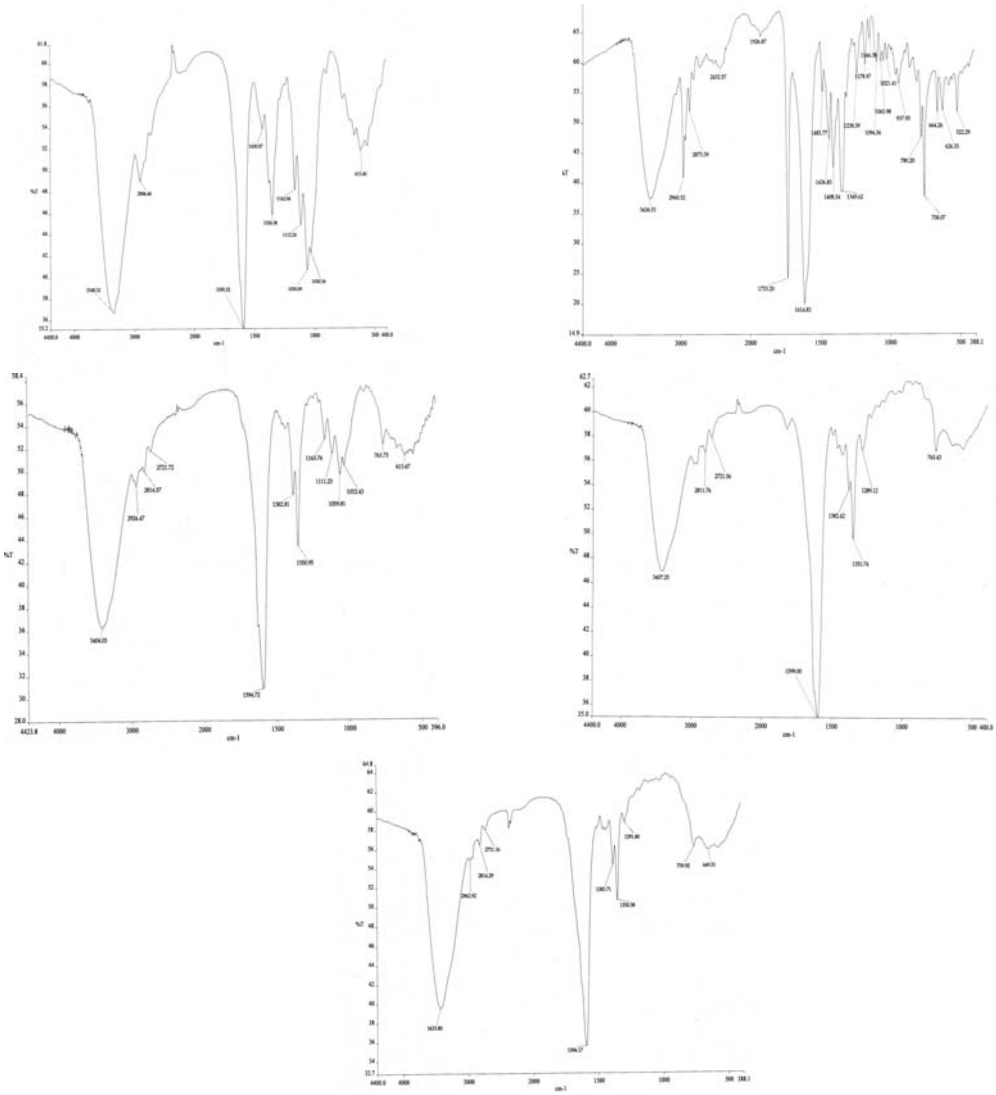

Fig. 3: FT-IR spectrum of Irbesartan pure drug and Formulations F2-F5

RESULTS AND DISCUSSION

Preparation of Irbesartan Solid Dispersions

Solid dispersions of Irbesartan were prepared by physical mixing and solvent evaporation method. The carriers like microcrystalline cellulose, croscarmellose sodium, sodium starch glycolate and crosspovidone 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 were found to be fine free flowing powders.

Drug content and solubility

The percent drug content and solubility data of all solid dispersions are given in table 3. Low standard deviation in the percent drug content values indicated uniformity of drug content in each batch of solid dispersions.

It was observed that as the concentration of carrier is increased the solubility was increased and it was also noticed that at the same concentration of carrier, the solid dispersions prepared with solvent evaporation method displayed greater solubility than that of physical mixing method.

Pre-Formulation Studies

Angle of repose, bulk density, tapped density, carr's index and Hasusner's ratio were calculated and were found to be in the range of 25.8-31, 0.52-0.63, 0.61-0.74, 16.98-18.75 and 1.07-1.23 respectively and is shown in table 4. From the preformulation studies of the Irbesartan solid dispersions, it is clear that all the Irbesartan solid dispersions fulfilled the official requirements for compression of tablets through direct compression method.

Evaluation of tablets

Hardness was found to be in the range of 4-4.5 kg/sq.cm with standard deviation not more than 0.7. Disintegration time was found to be 130, 120, 117, 109 and 94 seconds for formulation F1, F2, F3, F4 and F5 respectively, the results of the disintegration test revealed that F5 has faster disintegration and it disintegrates within two minutes (94sec). Friability was found to in between 0.22-0.38 with standard deviation not more than 0.81.

Drug content was above 99% in all the formulations. All the parameters evaluated are shown in table 5. From the physico-mechanical parameters of the formulated tablets, it is clear that all the tablets fulfilled the official requirements of the compressed tablets.

In vitro dissolution studies of Irbesartan tablets

Dissolution studies showed enhanced dissolution of Irbesartan when compared to pure drug and is shown in fig.1. Dissolution data of Irbesartan followed first order kinetics and is shown is fig.2. First order dissolution rate constant (K_1) were calculated from the slopes of the linear regressions are given in table 6. T_{50}, T_{90} and DE_{30}% values for optimized formulations were calculated from the dissolution data and profiles are given in table 6.

Formulation F2 showed 3.01 and 3.27 fold increase in the dissolution rate (K_1) and DE_{30}% respectively while F3 displayed 3.43 and 3.41 fold increase in the dissolution rate (K_1) and DE_{30}% respectively. 2.14 and 3.28 fold increase in the dissolution rate (K_1) and DE_{30}% respectively was observed with formulation F4. It was observed that F5 showed maximum dissolution, a 4.25 and 6.15 fold increase in DE_{30}% and dissolution rate (K_1) respectively were observed. 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. From the dissolution profiles and dissolution parameters, it is clear that among all in-house formulations F5 showed maximum dissolution

Drug- Excipient compatibility studies

Infrared spectroscopy

Infrared spectra were recorded on a Fourier transform Infrared (FTIR) spectrophotometer using KBr dispersion method[14]. 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 Fig. 3.

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.

All Physical mixtures and solid dispersions prepared by solvent evaporation method showed characteristic peaks of Irbesartan drug and carriers. These results indicated that there is no chemical interaction between drug and carrier when formed as solid dispersion.

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. Among the super disintegrants 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 in the solid dispersions was increased. The order of increase in dissolution rate with various superdisintegrants is CP > SSG > CCS > MCC.

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