Dissolution rate enhancement of irbesartan and development of fast-dissolving tablets

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Objective
The objective of the present investigation was to enhance the solubility and dissolution rate of poorly soluble drug irbesartan by preparing it as solid dispersions and formulating it as fast-dissolving tablets (FDTs) using various excipients.
Background
Irbesartan is poorly soluble in water, and this low aqueous solubility in addition to its poor wettability leads to poor bioavailability of the drug.
Materials and methods
Solid dispersions were prepared using Soluplus, PEG 6000, and Kollidon as carriers. The dispersions were prepared using the solvent evaporation and kneading methods in a 1 : 1 ratio of drug and carrier. These formulations were characterized for solid state properties using X-ray powder diffraction and Fourier transform infrared spectroscopy spectral studies. Formulations were further evaluated for dissolution.
Results
The aqueous solubility of irbesartan in solid dispersions was improved by the presence of polymer Soluplus when compared with other carriers. Solid state characterization indicated that irbesartan was present as amorphous material in the formulation with carrier. This was due to efficient entrapment of the drug in polymer matrix. Thus, the solid dispersion prepared with Soluplus would be useful for delivering poorly soluble irbesartan with enhanced solubility and dissolution rate. Furthermore, the solid dispersions that were formulated as FDTs using superdisintegrants showed faster drug release with increased dissolution rate.
Conclusion
FDTs containing irbesartan solid dispersions prepared using the solvent evaporation method and croscarmellose sodium as superdisintegrant showed faster disintegration and increased dissolution rate.

Keywords:
fast dissolving, irbesartan, solid dispersions, soluplus

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Introduction

Although various novel and advanced drug delivery systems have been introduced for therapeutic use, the popularity of oral dosage forms, particularly tablets, have not been eclipsed, because of its numerous advantages [1]. Two widely faced drawbacks in oral drug delivery are dysphagia and delivery of unpalatable drugs, which may be a problem for mainly geriatric, pediatric, and for nauseous patients [2]. Therefore, emphasis is laid on the development of viable dosage alternatives that has led to exploration of certain novel drug delivery systems such as fast-dissolving drug delivery. It is estimated that 50% of the population is affected by the said problem, which results in a high incidence of noncompliance and ineffective therapy. Traditional tablets and capsules administered with 250 ml of water may be inconvenient or impractical for such population. Hence, fast-dissolving/disintegrating tablets (FDDTs) are a perfect fit for them. FDDTs dissolve or more commonly disintegrate rapidly in the saliva without the aid of water [3–5]. The fast-dissolving/disintegrating dosage forms are well established in the management of pain, inflammation, vomiting, headache, and hypertension. Valuable research reports for formulation of rapidly disintegrating tablets are available. Moreover, various technologies for improving dissolution property of poorly water-soluble drugs have been documented to enhance bioavailability following oral absorption. Solubility of poorly soluble drug can be increased by formulating as solid dispersions using various excipients. Irbesartan is indicated for the treatment of hypertension. It may also delay progression of diabetic nephropathy and is also indicated for the

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reduction of renal disease progression in patients with type 2 diabetes, hypertension, and microalbuminuria or proteinuria. Irbesartan shows low, pH-dependent solubility and is rapidly and completely bioactivated by ester hydrolysis to irbesartan during absorption from the gastrointestinal tract. Irbesartan has a terminal elimination half-life ($t_{1/2}$) of ~11–15 h [6]. Soluplus is a novel polymer specially designed for solid solutions. Soluplus can increase the solubility and bioavailability of poorly soluble drugs. Soluplus is a polyvinyl caprolactum (57%)–polyvinyl acetate (30%)–poly ethylene glycol (PEG 6000–13%) graft copolymer. It is a polymeric solubilizer with an amphiphilic chemical structure, and because of its bifunctional characters it is able to act as a matrix polymer for solid solutions on one hand and on the other it is capable of solubilizing poorly soluble drugs in aqueous media [7,8].

As Kollidon VA64 aides in stabilizing the active ingredient in amorphous form, solubility is improved. Kollidon VA64 is vinylpyrrolidone–vinyl acetate copolymer soluble in water and alcohol. The main applications of Kollidon VA64 are soluble binder for granulation and as a dry binder in direct compression technology, as a film-forming agent in sprays and as a pore former in coating and taste-masking applications, as well as solubilizer [9].

The aim of this work was to enhance the aqueous solubility and dissolution rate of irbesartan with carriers such as Kollidon VA64, Soluplus, and PEG 6000 using the solid dispersion technique and formulating the dispersions as FDDTs using superdisintegrants such as sodium starch glycolate (SSG), croscarmellose sodium (CCS) and evaluate the prepared FDDTs for their physiochemical parameters, in-vitro dissolution, and stability studies.

Materials and methods

Materials

Irbesartan was obtained as a gift sample from Apotex Pharma Ltd (Bangalore, Karnataka, India). KollidonVA6 and Soluplus were obtained as a gift sample from Mylan Loboratories (Hyderabad, Telangana, India). SSG and CCS were commercially obtained from SD Fine-Chem Ltd (Mumbai, Maharashtra, India). As we have not conducted any animal experimentation or human experimentation the research work doesn't require any approval.

Saturated solubility studies

Saturated solubility studies of irbesartan were performed in different dissolution media. Irbesartan of 10 mg was weighed and transferred into different conical flasks containing 10 ml of different dissolution media (i.e. water pH 6.8, pH 7.2 phosphate buffer, and 0.1 N HCl) and were closed appropriately. All conical flasks were placed in a REMI incubator (ELLITE Scientific, Shimadzu, India) shaker at 50 rpm and 37±1°C for 24 h. The conical flasks were removed from the incubator shaker and samples were filtered using Whatman filter paper. The clear solution obtained by means of filtration was suitably diluted with appropriate dissolution media and the absorbance values were noted at 244 nm using corresponding dissolution media as blank [10,11].

Preparation of solid dispersion

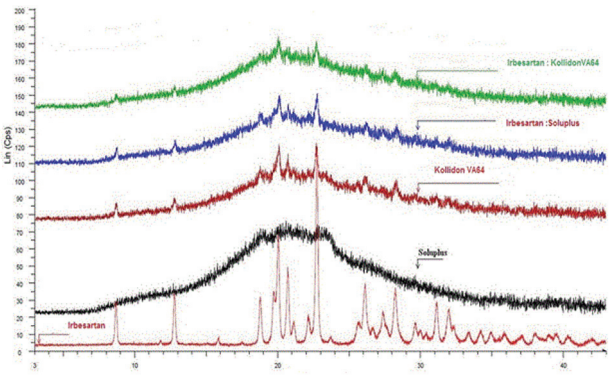
The solid dispersions of irbesartan were prepared using the solvent evaporation and kneading methods using Soluplus, Kollidon, and PEG 6000 as carriers. Irbesartan, Soluplus, Kollidon, and PEG 6000 were weighed accurately in a ratio of 1 : 1 for drug and carrier. The obtained solid dispersions were subjected to X-ray powder diffraction (XRD) studies to confirm the conversion of crystalline drug into amorphous form and Fourier transform infrared spectroscopy for drug–carrier interaction studies. The drug content, solubility studies, dissolution, and stability studies were carried out for solid dispersions prepared [11,12].

Characterization of irbesartan solid dispersions

X-ray powder diffraction

The powder crystallinity of irbesartan and its solid dispersions was determined using Bruker (USA) D8 Advance XRD with copper target instrument. The conditions were maintained at 40 kV voltages, with 40 mA current at room temperature. The scanning rate used was 0.1°/s over a range of 2θ values from 3° to 45°. The diffractograms are shown in Fig. 1.

Figure 1



PXRD data of Irbesartan Pure Drug, Kollidon VA64, solid dispersions prepared with Soluplus and Kollidon using the solvent evaporation method.

Differential scanning calorimetry

A differential scanning calorimeter (DSC 200F3; Shimadzu) was used to obtain the differential scanning calorimetry (DSC) curves of pure drug and formulations F4 and F8 representing the rates of heat flow. About 10 mg of sample was weighed in a standard open aluminum pan and were scanned from 40 to 400°C, at a heating rate of 10°C/min while being purged with dry nitrogen at a rate of 60 ml/min.

Drug content

Solid dispersions equivalent to 30 mg of drug were taken and dissolved in methanol and filtered using 0.45 µ membrane filters. Thereafter, the filtrate was suitably diluted with buffer, and drug content was analyzed against blank using a ultraviolet spectrophotometer at 244 nm. The concentration of drug present in solid dispersion is compared with that of standard solution containing 30 mg of pure drug. The percentage of drug present in the solid dispersions was calculated with respect to standard concentration obtained from calibration curve calculated for irbesartan.

Table 1 Saturated solubility studies of irbesartan different dissolution media

Serial number	Medium	Solubility (mg/10 ml)
1	Distilled water	0.91
2	pH 6.8 phosphate buffer	2.91
3	pH 7.2 phosphate buffer	3.87
4	0.1 N HCl	6.41

In-vitro dissolution studies

Dissolution rate studies of pure irbesartan and irbesartan solid dispersions were performed in dissolution apparatus (LABINDIA DS8000, India) with rotating paddles at 50 rpm using 900 ml of pH 1.2 buffer and the temperature was maintained at 37 ±0.5°C throughout the experiment. A volume of 5 ml of the samples was drawn at various time intervals. The absorbance of the samples was measured at 244 nm for determining the amount of drug release at various intervals. Each time, the equal volume of buffer was replenished for maintaining the constant volume of dissolution medium. The dissolution studies were carried out in triplicate.

Preparation of irbesartan fast-dissolving tablets

Irbesartan fast-dissolving tablets (FDTs) were prepared using direct compression process, using optimized solid dispersion with superdisintegrant such as CCS and SSG along with microcrystalline cellulose as diluent. The compositions of various tablet formulations are given in Table 2. The prepared tablets were evaluated for various physical parameters and the results are given in Table 3. Physical parameters such as weight variation,

Table 2 Composition of irbesartan fast-dissolving tablet formulations

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Drug+Soluplus (equivalent to 30 mg of irbesartan)	60	60	60	60	–	–	–	–	–	–	–	–
Drug+Kollidon (equivalent to 30 mg of irbesartan)	–	–	–	–	60	60	60	60	–	–	–	–
Drug+PEG 6000 (equivalent to 30 mg of irbesartan)	–	–	–	–	–	–	–	–	60	60	60	60
Sodium starch glycolate	20	30	–	–	20	30	–	–	20	30	–	–
Croscarmellose sodium	–	–	20	30	–	–	20	30	–	–	20	30
Talc	2	2	2	2	2	2	2	2	2	2	2	2
Magnesium stearate	2	2	2	2	2	2	2	2	2	2	2	2
MCC (Avicel pH-102)	116	106	116	106	116	106	116	106	116	106	116	106
Total weight of tablet(mg)	200	200	200	200	200	200	200	200	200	200	200	200

Table 3 Physical parameters of irbesartan FDT formulations

Serial number	Tablet formulation	Weight uniformity (mg/tablet)	Friability loss (% w/w)	Hardness (kg/cm^2)	Drug content[a] (mg)
1	F1	198±3	0.24	2.5±0.3	30±0.2
2	F2	200±3	0.24	2.5±0.1	30±0.3
3	F3	199±2	0.20	2.5±0.2	30±0.3
4	F4	199±2	0.26	2.5±0.2	30±0.2
5	F5	198±2	0.24	2.5±0.3	29±0.4
6	F6	200±2	0.28	2.5±0.1	30±0.4
7	F7	199±2	0.20	2.5±0.3	30±0.3
8	F8	199±2	0.26	2.5±0.1	30±0.2
9	F9	198±2	0.24	2.5±0.2	29±0.4
10	F10	200±2	0.20	2.5±0.2	30±0.4
11	F11	199±2	0.26	2.5±0.3	30±0.3
12	F12	199±2	0.24	2.5±0.1	30±0.2

hardness, friability, moisture uptake study, wetting time, water absorption ratio, and disintegration were evaluated for prepared tablets [13].

Evaluation of fast-dissolving/disintegrating tablets

The moisture uptake study is carried out by keeping 10 tablets along with calcium chloride in a desiccator maintained at 37°C for 24 h to ensure complete drying of the tablets. The tablets are then weighed and exposed to 75% relative humidity (RH) at room temperature for 2 weeks. The required humidity can be achieved by keeping saturated sodium chloride solution in the desiccator for 24 h. The tablets are reweighed and the percentage increase in weight is recorded. If the moisture uptake tendency of a product is high, it requires special dehumidified area for manufacturing and packing [14].

Wetting time is determined by taking five circular tissue papers of 10 cm diameter and placing them in the petri dish with 10 cm diameter. A volume of 10 ml of water containing Amaranth water-soluble dye was added to the petri dish. One tablet was carefully placed on the surface of the tissue paper. The time required for water to reach the upper surface of the tablet was noted as the wetting time [15].

Water absorption ratio is determined by taking a piece of tissue paper folded twice and placed in a small petri dish (internal diameter=6.5 cm) containing 5 ml of buffer. A tablet was placed on the tissue paper. The wetted tablet was weighed. The test was carried out in triplicate. The water absorption ratio (R) was determined according to the following equation: water absorption ratio (R)= $Wa–Wb/Wa\times100$, where Wa is the weight of the tablet before the test and Wb is the weight of the tablet after water absorption [16].

Dispersion test of FDTs was carried out by taking a petri dish that was filled with 10 ml of buffer (pH 1.2) and the tablet was carefully placed in the center of the petri dish. and the time taken for the tablet to completely disperse into fine particles was noted [17].

In-vitro dissolution studies

Dissolution studies on each tablet formulation were performed in a calibrated 8 station dissolution test apparatus (LABINDIA DS8000) equipped with paddles (USP apparatus II method) using 900 ml of pH 1.2 buffer as a dissolution medium. The paddles were operated at 50 rpm and temperature was maintained at 37±1°C throughout the experiment. The samples (10 ml) were drawn at 5, 10, 15, 20, 30, and 45 min and replaced with an equal volume of the same dissolution medium to maintain the constant volume throughout the experiment. Samples drawn at various time intervals were suitably diluted with same dissolution medium and the amount of the drug dissolved was estimated using ELICO (India) double beam UV spectrophotometer at 244 nm. The dissolution studies on each formulation were conducted in triplicate. From the dissolution profiles, various parameters such as T_{50}, and $DE_{30\%}$ were calculated. The dissolution parameter T_{50} was directly calculated from the dissolution profiles, whereas $DE_{30\%}$ was estimated using trapezoidal rule to the dissolution profiles. The first order release rate constant was calculated by multiplying the slope value obtained from log percent drug undissolved versus time plot with 2.303.

Accelerated stability studies of irbesartan fast-dissolving tablets

The formulations that showed good in-vitro performance were subjected to accelerated stability studies. These studies were carried out by investigating the effect of temperature on the physical properties of tablets and chemical stability of tablets containing drugs. The tablet formulations such as F4 and F8 were subjected to accelerated stability studies. The above-mentioned formulations were kept in petri dishes after preparation and stored in thermostated oven at a temperature and RH of 25±2°C and 60±5% RH for 6 months and 40±2°C and 75±5% RH for 3 months, respectively. Thereafter, the tablets were evaluated for physical parameters and for drug content uniformity using a known spectrophotometric method as described earlier. These were further subjected to drug release studies.

Results and discussion

Solubility studies

The effect of solubility of irbesartan in various media was assessed using saturation solubility studies. Saturated solubility studies revealed that irbesartan showed maximum solubility in 0.1 N HCl media compared with the other dissolution medium used. The drug concentration was measured at 244 nm using a ultraviolet spectrophotometer for all dissolution media. The results of solubility studies are given in Table 1.

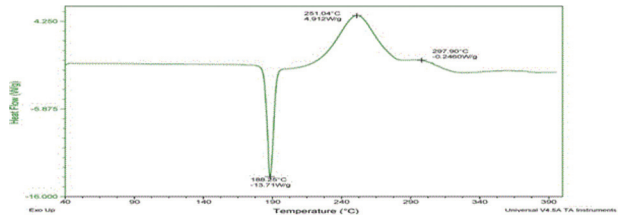
Preparation of solid dispersions

The solid dispersions of irbesartan were prepared with novel carriers such as Kollidon VA64, Soluplus, and PEG 6000 using the solvent evaporation and kneading methods. All dispersions were prepared under similar conditions to avoid batch-to-batch variations. The drug and carrier ratio was maintained as 1 : 1 constant for all formulations.

Characterization of solid dispersions

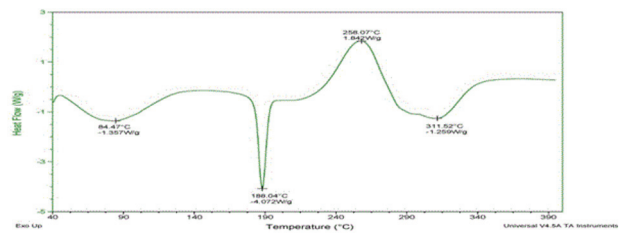
The XRD patterns of irbesartan and solid dispersions prepared with Soluplus and Kollidon as carrier using the solvent evaporation method are shown in Fig. 1. The powder diffraction patterns of pure irbesartan showed characteristic high diffraction peaks. The diffraction patterns of solid dispersions prepared with Soluplus as carrier using the solvent evaporation method showed only few peaks with very weak intensities indicating the amorphous nature. DSC thermographic studies were carried out on irbesartan pure drug and solid dispersions prepared with Soluplus and Kollidon using the solvent evaporation method. These studies exhibited a sharp endothermic peak at 188.25°C for the pure drug irbesartan. For the solid dispersions, endothermic peaks were observed at 186.04 and 184.18°C. These studies revealed that there were no drug and excipient interactions, which were confirmed by obtaining similar thermographic peaks at respective temperature. Solid dispersions of irbesartan prepared with Soluplus and Kollidon VA64 also gave melting peaks but at slightly lower temperatures in the range of 184–186°C with a decrease in peak intensity as compared with pure irbesartan. This is consistent with a weak endothermic reaction between irbesartan and carriers. The decrease in intensity and broadening of peak indicates that the drug is dispersed with carrier. The DSC thermograms are shown in the Figs 2–4.

Figure 2



DSC thermogram of irbesartan pure drug. DSC, differential scanning calorimetry.

Figure 3



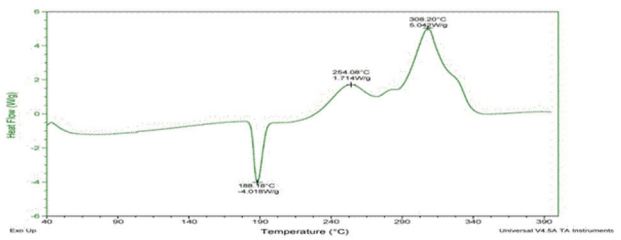
DSC thermogram of irbesartan solid dispersions prepared with Soluplus. DSC, differential scanning calorimetry.

The dissolution studies for the prepared dispersions were carried out in 0.1 N HCl using the paddle method. The dissolution rate of the solid dispersions was more rapid compared with pure drug irbesartan. Among the prepared solid dispersions, the dispersions prepared with Soluplus as carrier using the solvent evaporation method released the drug at a faster rate compared with the other dispersions. The enhanced solubility and dissolution rate was due to intermolecular interactions and complexation originating from H bonding, ionic, and/or van der Waal's interactions of hydrophilic carrier such as Soluplus with drug, which plays an important role in solubilization, stability, and maintaining supersaturation. Soluplus with multiple interaction sites increased the solubility of irbesartan in amorphous dispersions.

Preparation and evaluation of fast-dissolving tablets

The dispersions were prepared using the solvent evaporation method with Soluplus, Kollidon, and PEG 6000. Among the prepared solid dispersions, the dispersions prepared with Soluplus as carrier using the solvent evaporation method released the drug at a faster rate compared with the other dispersions. Hence, these dispersions were further formulated as FDTs using superdisintegrants such as CCS and SSG. The direct compression process was found to be suitable for compressing the tablet formulations as FDTs. The compositions of irbesartan tablet formulations are shown in the Table 2. All batches of tablets were compressed under identical conditions to minimize the processing variables. Thereafter, the compressed FDTs were further evaluated for physical parameters such as weight uniformity, hardness, friability, and drug content. These studies revealed that all tablet formulations were found to be stable and met Indian Pharmacopoeia (I.P)-specified limits for weight uniformity, friability, and drug content. The hardness of all tablet formulations was in the range of 2.5–3.0 kg/cm^2. Weight uniformity of all tablet

Figure 4



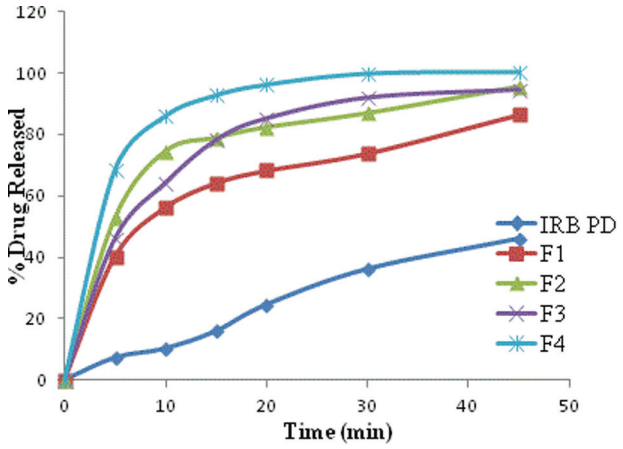
DSC thermogram of solid dispersions prepared with Kollidon. DSC, differential scanning calorimetry.

Table 4 Evaluation parameters of irbesartan FDTs

Serial number	Tablet formulations	Wetting time (s)	Water absorption ratio	In-vitro dispersion time (s)	Moisture uptake (%)
1	F1	26.0±4.0	60.8	31±1.6	5.0±1.8
2	F2	20.8±1.5	62.2	22±3.2	4.4±1.2
3	F3	22.4±4.4	59.3	30±3.6	5.6±1.6
4	F4	18.8±1.5	68.3	16±3.6	5.6±1.0
5	F5	34.5±2.5	60.8	32±3.6	4.6±2.0
6	F6	28.8±1.5	62.2	28±3.6	4.8±1.6
7	F7	30.5±2.5	59.3	30±3.6	4.0±1.8
8	F8	26.8±1.5	68.3	25±3.6	4.4±1.2
9	F9	34.5±2.5	60.8	32±3.6	3.6±1.6
10	F10	28.8±1.5	62.2	25±3.6	3.6±1.0
11	F11	30.5±2.5	59.3	36±3.6	4.6±2.0
12	F12	26.8±1.5	68.3	30±3.6	3.8±1.6

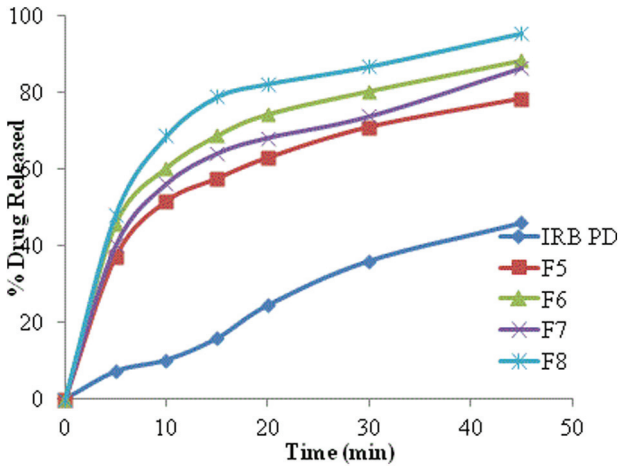
FDT, fast-dissolving tablet.

Figure 5



Represent dissolution profiles of various irbesartan formulations. Figure 5 shows profiles of Formulation F1 to F4, figure 6 shows dissolution profiles of formulations F5 to F8, where as figure 7 shows dissolution profiles of formulations F9 to F12.

Figure 6



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formulations was in the range of 198±3 mg/tablet. Friability losses of all tablet formulations were negligible and were in the range of 0.1–0.2%. Drug content estimated for all tablet formulations was highly uniform, with less than 2.5% variation. The results are given in Table 3.

All tablet formulations were found to be stable within the I.P-specified limits for weight uniformity, friability, and drug content. Moisture uptake studies for FDTs were conducted to assess the stability of formulation. The results indicated that tablets containing a high concentration of superdisintegrant – that is, F4 and F8 (CCS 15%) – get softened and absorb more atmospheric moisture. The results are given in Table 4.

The dissolution studies of FDTs were performed in 0.1 N HCl using the USP-II paddle method. All tablet formulations were found to release the drug at a faster rate compared with pure drug. The dissolution profiles of irbesartan FDDTs are shown in Figs 5–7. It was found that the tablet formulation F4 and F8 prepared with Soluplus and Kollidon with CCS 15% showed more rapid drug release when compared with pure drug and other formulations containing SSG. This can be attributed to improved wettability and dispersibility as well as increased amorphous fraction of drug. It was also found that, as the concentration of superdisintegrants increases, the tablets undergo rapid dissolution and drug release. This may be due to rapid intake of water by superdisintegrants, which leads to faster dissolution of the tablets and showed the improved dissolution profiles of poorly soluble irbesartan. The drug release of tablet formulations in the presence of various superdisintegrants was in the order of CCS>SSG. On the basis of the data obtained from the dissolution studies, various parameters such as T50, DE30%, and first order and zero order release rate

Figure 7

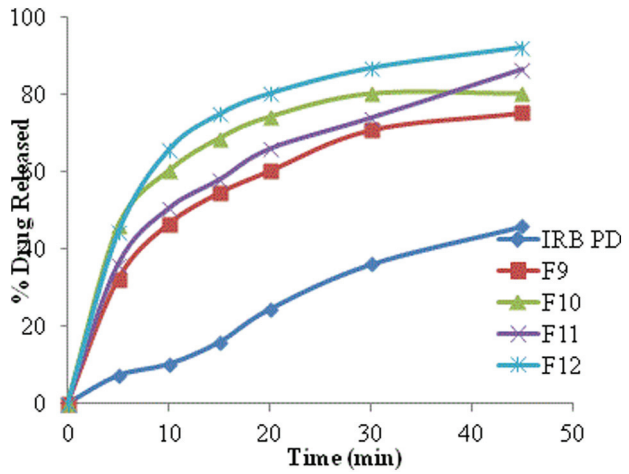

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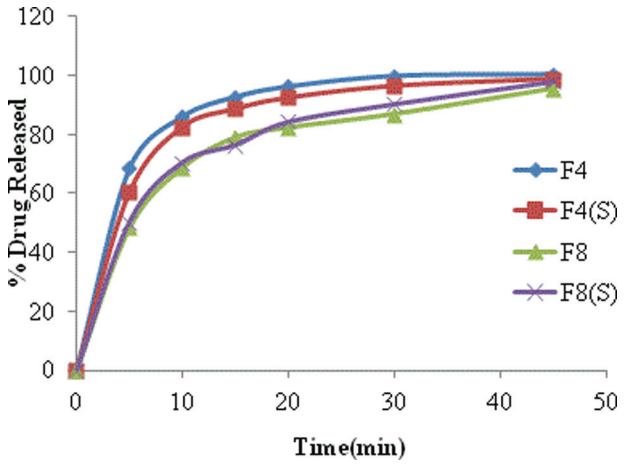
Figure 8



Drug release profiles of optimized irbesartan fast-dissolving tablet formulations before and after stability studies.

Table 5 Dissolution parameters of irbesartan FDTs

Serial number	Tablet formulations	T_{50} (min)	$DE_{30\%}$	Zero order		First order	
				R^2	K (mg/min)	R^2	K (min^{-1})
1	F1	10.0	40.2	0.888	2.29	0.977	0.119
2	F2	5.10	45.9	0.814	2.13	0.991	0.131
3	F3	7.45	40.6	0.922	2.07	0.989	0.092
4	F4	4.80	44.8	0.818	1.95	0.983	0.117
5	F5	9.80	45.6	0.910	1.62	0.937	0.170
6	F6	8.24	39.9	0.910	1.89	0.936	0.103
7	F7	9.60	45.0	0.888	2.29	0.917	0.119
8	F8	8.80	40.9	0.814	2.13	0.931	0.131
9	F9	14.60	40.6	0.922	2.07	0.959	0.092
10	F10	9.80	44.8	0.818	1.95	0.983	0.117
11	F11	10.00	39.6	0.840	1.62	0.937	0.170
12	F12	9.8	45.9	0.810	1.89	0.936	0.103

FDT, fast-dissolving tablet.

constants were estimated. The dissolution rate of all formulations was found to be rapid when compared with pure irbesartan (Figs 5–7). The T_{50} and rate constants (*K*) values of the formulations indicated their rapid drug dissolution than that of pure drug. The kinetics of drug release from all formulations follow first order. The results of kinetic parameters evaluated are given in Table 4 and Table 5.

Stability studies

The accelerated stability studies indicated that there were no visible and physical changes observed in the tablets after storage. It was also observed that there was no significant change in drug release from the tablets. The drug release characteristics of the optimized tablets remained unaltered. Thus, the drug release characteristics of FDTs designed were found to be quite stable and are shown in Fig. 8.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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