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Research Article

Development of Agglomerated Crystlas of Irbesartan by Spherical Crystalization Technique for Enhancing the Micromeritic and Solubility Property

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ABSTRACT

Irbesartan was practically insoluble in water. The aim of the present work is to increase the solubility of drug and bioavailability without modifying the properties of drug. In this present work solubility was increased by spherical crystallization method and converted into a tablet. Various solvents like N, N dimethyl formamide as a good solvent, bridging solvent chloroform & bad solvent water were selected. Spherical crystals are prepared by using β-cyclodextrin and HP-β-cyclodextrin in various ratios by quasi emulsion solvent diffusion method. Spherical agglomerates are prepared and converted into orodispersible tablets by direct compression technique. Various super disintegrating agents (SSG and Croscarmalose and crospovidone) batch F36 of 1:3 rations shown high dissolution efficiency of 98.09% and when compared with the marketed product shown better dissolution value. NOVA significance value of $P<0.05$ which will indicates the co-processing parameters variability within the specified limits. F36 shown higher plasma concentration which will indicates the increased bioavailability. When F36 batch execute in pilot plant scale will increases the production rate and available the tablet in affordable cost to the poor people.

INTRODUCTION

The first step in the formulation is often milling or granulation, in order to provide for better properties for the final tabletting or to increase bioavailability. Often very small particles are required in order to increase the dissolution rate, and reach sufficient bioavailability. However, micronisation by milling is extremely inefficient, can cause physical and chemical instability, and produces powders with a wide size distribution and poor flowability. The alternative is to produce quite small crystals directly in the crystallization. In some cases thin needles are produced having a high surface area to volume ratio, but likewise may be quite difficult to handle. An interesting alternative is to manufacture larger particles in situ by agglomeration of the small crystals during the crystallization. In addition, it has been revealed that agglomerates have properties that make suitable for direct compression tableting[1].

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Crystals could be generated employing any of the available techniques like sublimation, solvent evaporation, vapor diffusion, thermal treatment and crystallization from melt precipitation by change in pH, growth in presence of additives or the grinding[2]. Thus the novel agglomeration technique that transforms crystals themselves directly into a compacted spherical form during crystallization process has been desired[3]. The use of spherical crystallization as a technique appears to be efficient alternative for obtaining suitable particles for direct compression[4,5].

This technique of particle design of drugs has emerged as one the areas of active research currently of interest in pharmaceutical manufacturing and recently came into the forefront of interest or gained interest due to the fact that crystal habit can be modified during crystallization process which would result in better micrometric properties like particle size those can enhance the flowability of the powder drug and prepared spherical crystals can be compress directly without performing granulation, drying and so many steps those are require in wet granulation and in dry granulation process of tablet manufacturing.

Spherical crystallization:

Spherical crystallization is a particle design technique, by which crystallization and agglomeration can be carried out simultaneously in one step and which has been successfully utilized for improvement of flowability and compactability of crystalline drugs[6].

The various parameters optimized were type, amount and mode of addition of bridging liquid, temperature, and agitation speed to get maximum amount of spherical crystals. These were characterized for micromeritic properties (particle size and shape, flowability), packability (bulk density), wettability (contact angle) and compressibility. It was revealed from the studies that spherical agglomerates exhibited improved solubility, flowability, wettability and compaction behavior[7, 8].

The present study, an attempt was made to improve physicochemical properties by preparing spherically agglomeration of olmesartanmedoxomil in the presence of hydrophilic carrier for the enhancement of overall physicochemical performance. Therefore, in the present study, an attempt has been made to increase solubility of Olmesartanmedoxomil by spherically agglomeration technique.

IMMEDIATE RELEASE[9]

These preparations are primarily intended to achieve faster onset of action for drugs such as analgesics, antipyretics, and coronary vasodilators. Other advantages include enhanced oral bioavailability through transmucosal drug delivery and pregastric absorption, convenience in administration to dysphasic patients, especially the elderly and bedridden and new business opportunities.

Conventional IR formulations include fast disintegrating tablets and granules that use effervescent mixtures, sodium carbonate (sodium bicarbonate) and citric acid (Tartaric acid) and super disintegrants such as sodium starch glycolate, Croscarmellose sodium and Crospovidone. Current technologies in fast dispersing dosage forms include modified tabletting systems, floss or shear form technology, which employs application of centrifugal force, controlled temperature.

EXPERIMENTAL WORK

Phase solubility studies of Irbesartan[10]

Phase solubility studies were performed according to method reported by Higuchi and Connors. Excess (usually more than1mg/mL concentration) of drug was added to each 25mL of different pH Buffer solutions (pH 1.2 to 7.4), distilled water alone and combination with 0.5%, 1%, 2% SLS taken in stopperred 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.

Table 1: 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

Preparation of Irbesartan Spherical agglomerates:

All spherical agglomerates were prepared by the quasi emulsion solvent diffusion method. Irbesartan (1g) with β-Cyclodextrin /HP- β-Cyclodextrin, PVP K-90/ PVA were dissolved in good solvent N, N-dimethylformamide (12.0 mL). The bridging liquid chloroform (2.0 mL) was added to it. The resulting solution was then poured drop wise in to the poor solvent distilled water (100 mL) containing Aerosil 200 Pharma (0.1 g). The mixture was stirred continuously for a period of 0.5 h using a controlled speed mechanical stirrer (Remi motors, India) at 1000 rpm. As the good solvent diffused into the poor solvent, droplets gradually solidified. Finally the co precipitated microspheres of the drug-polymer were filtered through Whatman filter paper (No.1) and dried in desicator at room temperature. The amount of stabilizer was altered to get desired agglomerates.

Table 2: Preparation of Irbesartan Spherical Agglomerates

Formulation Number	Olmesartan medoxomil (mg)	B-cyclodextrin (mg)	HP β-cyclodextrin (mg)	PVP K-90 (mg)	PVA (mg)	N,N-dimethyl Formamide (ml)	Water (ml)	Chloroform (ml)
F19	1000	500	--	--	--	25	62.5	12.5
F20	1000	750	--	--	--	25	62.5	12.5
F21	1000	1000	--	--	--	25	62.5	12.5
F22	1000	--	500	--	--	25	62.5	12.5
F23	1000	--	750	--	--	25	62.5	12.5
F24	1000	--	1000	--	--	25	62.5	12.5
F25	1000	--	--	500	--	25	62.5	12.5
F26	1000	--	--	750	--	25	62.5	12.5
F27	1000	--	--	1000	--	25	62.5	12.5
F28	1000	--	--	--	500	25	62.5	12.5
F29	1000	--	--	--	750	25	62.5	12.5
F30	1000	--	--	--	1000	25	62.5	12.5

Evaluation of spherical agglomerates:

a) Particle size determination: Particle size determination was carried out using optical microscopy with a calibrated eye piece micrometer and stage micrometer by taking a small quantity of formulation on slide. About 100 spherical agglomerates size was measured individually, average was taken and their size range and mean diameter frequency was calculated. Average Particle size is calculated by the following formula:

Average Particle size= £nd/ n

b) Solubility studies[11]**:**

The solubility of spherical agglomerates in water was determined by taking excess quantity of spherical agglomerates and adding to screw-capped 50 ml glass vials filled with water. The vials were shaken for two hours on mechanical shaker. The solution was filtered through Whatmann filter paper No.1 and the drug concentration was determined spectrophotometrically at 244 nm.

Table 3: Solubility studies of Irbesartan spherical agglomerates prepared by agglomeration technique

Formulation	Particle size (µm)	Solubility mg/ml)
Pure drug	-	0.005
F16	256	0.0636
F17	278	0.0747
F18	294	0.0866
F19	312	0.0563
F20	334	0.0649
F21	356	0.0758
F22	346	0.0441
F23	367	0.0526
F24	386	0.0652
F25	378	0.0332
F26	394	0.0428
F27	413	0.0542

c) Drug Content Estimation:

The percentage drug content in spherical agglomerates was estimated by dissolving 50 mg of spherical agglomerates in methanol, mixed thoroughly by shaking and the volume was made up to the mark with in 0.1N Hcl (1.2 pH). 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 [12].

Table 4: Drug content of Irbesartan spherical agglomerates prepared by agglomeration technique

Formulation	% of Drug content
F19	99.26
F20	99.54
F21	99.36
F22	99.41
F23	99.39
F24	99.24
F25	99.45
F26	99.73
F27	99.21
F28	99.22
F29	99.33
F30	99.11

d) Dissolution studies of agglomerates[13]**:**

In-vitro dissolution studies of pure drug and spherical agglomerates were carried out for 60 minutes using USP Dissolution test apparatus type II (Lab India DISSO 2000, eight stages) at 50 rpm.Spherical agglomerates equivalent to 75 mg of pure drug (Irbesartan) used for dissolution

study at 37±0.5^0 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} and k^{-1} values were calculated from dissolution data.

Preparation of Irbesartan immediate release Tablets containg superdisintegrants:

Irbesartan containing immediate release tablets were prepared by direct compression process. All the ingredients (shown in Table No:-17) were properly mixed and passed through mesh no. 80. The resulting blend was lubricated with magnesium stearate and talc and compressed into tablets using the Cadmach sixteen stationary punching (round shaped, 7mm thick) machine.

Preparation of Irbesartan immediate release Tablets containing co-processed superdisintegrants[15]:

Irbesartan containing immediate release tablets were prepared by direct compression process. All the ingredients were properly mixed and passed through mesh no. 80. The resulting blend was lubricated with magnesium stearate and talc and compressed into tablets using the Cadmach sixteen stationary punching (round shaped, 7mm thick) machine [111].

Evaluation of micromeritic properties of the blend[16-24]:

The powder blend of immediate release tablets of Irbesartan were evaluated for bulk density, tapped density, carr's index, Hausner's ratio and angle of repose as per the procedures specified earlier for olmesartan medoxomil orodispersible tablets powder blend.

Evaluation of Irbesartan immediate release Tablets: The prepared tablets were evaluated for Weight variation test, disintegration time; friability, hardness, and wetting time were as per the procedures specified earlier for olmesartan medoxomil orodispersible tablets.

a) Weight variation test

Weight variation test was done by weighing 20 tablets individually, calculating the average weight and comparing the individual tablet weight to the average weight.

b) Disintegration Time:

The disintegration time was determined in distilled water at 37±0.5^0 C using disintegration test apparatus[11] USP ED-2L (Electro lab, Mumbai).

c) Friability:

Roche Friabilator was used to determine the friability. Pre weighed tablets were placed in Friabilator and rotated at a speed of 25 rpm for 4 minutes or up to 100 revolutions. The tablets are dropped from a distance of 6 inches in each revolution. The tablets were then reweighed after removal of fines and the percentage of weight loss was calculated.

d) Hardness:

Hardness of the tablet was determined using the Monsanto hardness tester. The lower plunger was placed in contact with the tablet and a zero reading was taken. The plunger was then forced against a spring by tuning threaded bolts until the tablet fractured. Then the final reading was recorded.The hardness was computed by deducting the initial pressure from the final pressure.

e) Drug content:

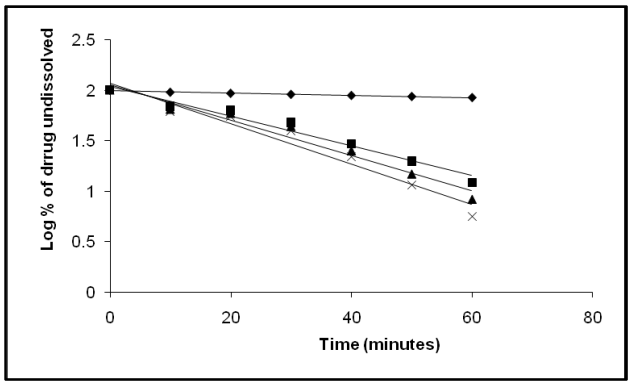
Twenty tablets were powdered, and 75 mg equivalent weight of Irbesartan in tablet powder was accurately weighed and transferred into a 100 ml volumetric flask. Initially, 5 ml methanol was added and shaken for 10 min. Then, the volume was made up to 100 ml with 0.1N Hcl(1.2 pH). The solution in the volumetric flask was filtered, diluted suitably and analyzed spectrophotometrically at 244 nm [112] using UV-visible spectrophotometer.

f) Dissolution studies:

Dissolution studies for immediate release tablets of Irbesartan were performed in 0.1N Hcl (1.2 pH) using USP dissolution test apparatus (Electrolab, Mumbai, India) with a paddle stirrer. The paddles were allowed to rotate at speed of 100 rpm. The dissolution medium was maintained at a temperature of 37+0.5 ^{0}C and samples were withdrawn at an interval of every 5 min the volume of the withdrawn samples were replaced by fresh dissolution medium in order to kept the volume of the dissolution medium as constant. The withdrawn samples were filtered and absorbance was measured at absorption maxima of 244 nm using UV-visible spectrophotometer .The in vitro dissolution kinetic parameters, dissolution rate constants (K^{-1}), correlation coefficient (r), the times (t_{50}) for 50 % drug released (t_{50}), the times for 90 % drug released (t_{90}) and dissolution efficiency [D.E.] were calculated.

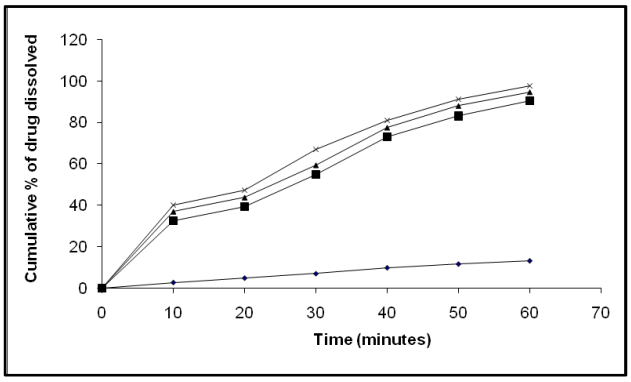
Table 5:*In-vitro* dissolution data of Irbesartan spherical agglomerates prepared with B-cyclodextrin in different ratios

S.No.	Sampling time (min)	Cumulative % of drug dissolved ($\overline{X}$ ± S.D.)			
		Pure Drug	F_{19}	F_{20}	F_{21}
1	0	0	0	0	0
2	10	4.22	33.34	37.79	40.42
3	20	6.08	42.44	48.23	50.34
4	30	8.16	61.03	65.02	67.40
5	40	10.35	70.02	75.87	79.31
6	50	12.75	81.94	86.25	88.40
7	60	15.15	89.47	93.28	95.44



(-♦-) Irbesartan pure drug
(-■-) Spherical agglomerates prepared with Irbesartan and B-cyclodextrinin 1: 0.5 ratio
(-▲-)Spherical agglomerates prepared with Irbesartan and B-cyclodextrinin 1: 0.75 ratio
(-×-) Spherical agglomerates prepared with Irbesartan and B-cyclodextrinin 1: 1 ratio

Figure 2: First order plots of Irbesartan pure drug and spherical agglomerates prepared with B-cyclodextrin in different ratios



(-♦-) Irbesartan pure drug
(-■-) Spherical agglomerates prepared with Irbesartan and B-cyclodextrinin 1: 0.5 ratio
(-▲-)Spherical agglomerates prepared with Irbesartan and B-cyclodextrinin 1: 0.75 ratio
(-×-) Spherical agglomerates prepared with Irbesartan and B-cyclodextrinin 1: 1 ratio

Figure 1: Dissolution profiles of Irbesartan pure drug and spherical agglomerates prepared with B-cyclodextrin in different ratios

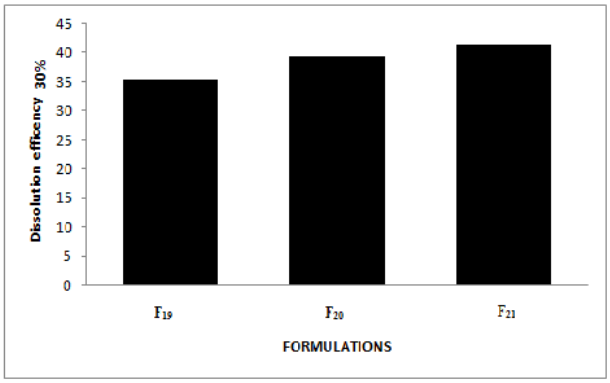


Figure 3: Comparison for dissolution efficiencies of Irbesartan spherical agglomerates prepared with β-cyclodextrin in different ratios

Table 6:*In-vitro* dissolution kinetics of Irbesartan spherical agglomerates prepared with B-cyclodextrin in different ratios

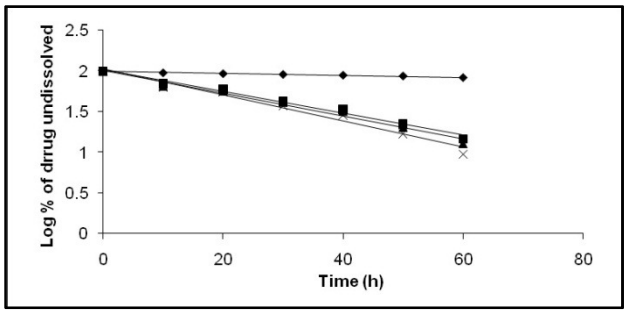
S.No.	Formulation	T_{50}(min)	T_{90} (min)	DE_{30} (%)	K (min^{-1})	Correlation coefficient values	
						Zero Order	First order
1	F_{19}	20.2	67.1	35.43	0.034	0.9466	0.9870
2	F_{20}	17.2	57.0	39.51	0.040	0.9250	0.9836
3	F_{21}	15.4	51.2	41.49	0.044	0.9135	0.9768

Table 7: Statistical treatment for dissolution efficiencies of Irbesartan spherical agglomerates prepared with B-cyclodextrin in different ratios

Trial	Dissolution efficiencies (%) (DE_{30})			ANOVA Parameters		
	F_{19}	F_{20}	F_{21}	Calculated value (F)	Degree of freedom	Significance
1	35.54	39.67	41.84	434.02	2,6	P<0.05
2	35.11	39.45	41.23			
3	35.64	39.41	41.40			

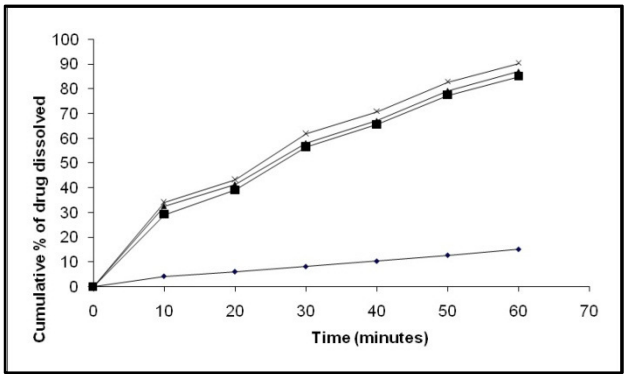
Table 8:*In-vitro* dissolution data of Irbesartan spherical agglomerates prepared with HP β-cyclodextrin in different ratios

S.No.	Sampling time (min)	Cumulative % OF DRUG Dissolved ($\overline{X}$ ± S.D.)		
		F_{22}	F_{23}	F_{24}
1	0	0	0	0
2	10	29.14	32.55	34.12
3	20	39.00	41.38	43.23
4	30	56.53	58.13	61.82
5	40	65.49	67.11	70.82
6	50	77.39	79.28	82.74
7	60	84.90	87.05	90.28



(-♦-) Irbesartan pure drug
(-■-) Spherical agglomerates prepared with Irbesartan and HP β-cyclodextrinin 1: 0.5 ratio
(-▲-)Spherical agglomerates prepared with Irbesartan and HP β-cyclodextrinin 1: 0.75 ratio
(-×-) Spherical agglomerates prepared with Irbesartan and HP β-cyclodextrin in 1: 1 ratio

Figure 5: First order plots of Irbesartan spherical agglomerates prepared with HP β-cyclodextrin in different ratios



(-♦-) Irbesartan pure drug
(-■-) Spherical agglomerates prepared with Irbesartan and HP β-cyclodextrin in 1: 0.5 ratios
(-▲-)Spherical agglomerates prepared with Irbesartan and HP β-cyclodextrin in 1: 0.75 ratios
(-×-) Spherical agglomerates prepared with Irbesartan and HP β-cyclodextrinin 1: 1 ratio

Figure 4: Dissolution profiles of Irbesartan spherical agglomerates prepared with HP β-cyclodextrin in different ratios

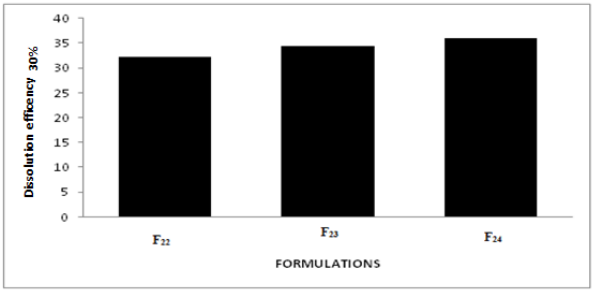


Figure 6: Comparison for dissolution efficiencies of Olmesartan medoxomil spherical agglomerates prepared with HP β-cyclodextrin in different ratios

Table 9: *In-vitro* dissolution kinetics of Irbesartan spherical agglomerates prepared with HP β-cyclodextrin in different ratios

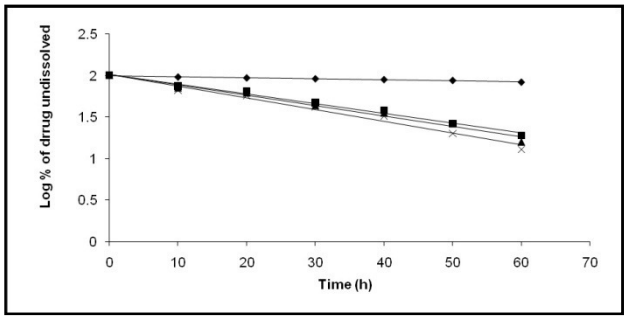
S.No.	Formulation	T_{50} (min)	T_{90} (min)	DE_{30} (%)	K (min^{-1})	Correlation coefficient values	
						Zero Order	First order
1	F_{22}	23.5	78.0	32.14	0.029	0.9544	0.9919
2	F_{23}	22.0	73.1	34.34	0.032	0.9480	0.9888
3	F_{24}	19.6	65.2	36.09	0.035	0.9438	0.9857

Table 10: Statistical treatment for dissolution efficiency of Irbesartan spherical agglomerates prepared with HP β-cyclodextrin in different ratios

Trial	Dissolution efficiencies (%) (DE_{30})			ANOVA Parameters		
	F_{22}	F_{23}	F_{24}	Calculated value (F)	Degree of freedom	Significance
1	32.24	34.62	36.34	3665	2,6	P<0.05
2	32.33	34.23	36.13			
3	31.85	34.17	35.80			

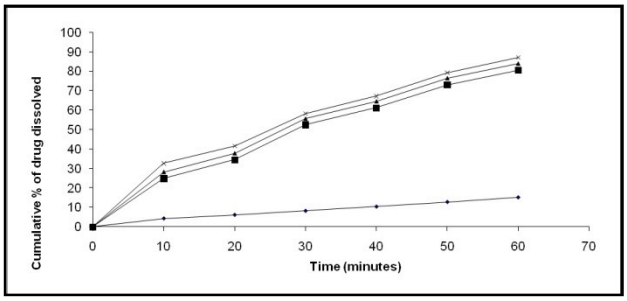
Table 11: *In-vitro* dissolution data of Irbesartan spherical agglomerates prepared with PVP –K90 in different ratios

S.No.	Sampling time (min)	Cumulative % of drug dissolved ($\overline{X}$ ± S.D.)		
		F_{25}	F_{26}	F_{27}
1	0	0	0	0
2	10	24.94	28.09	32.55
3	20	34.52	37.69	41.38
4	30	52.55	55.47	58.13
5	40	61.23	64.42	67.11
6	50	73.10	76.32	79.28
7	60	80.58	83.82	87.05



(-♦-) Irbesartan pure drug
(-■-) Spherical agglomerates prepared with Irbesartan and PVP –K90 in 1: 0.5 ratio
(-▲-)Spherical agglomerates prepared with Irbesartan and PVP –K90 in 1: 0.75 ratio
(-×-) Spherical agglomerates prepared with Irbesartan and PVP –K90 in 1: 1 ratio

Figure 8: First order plots of Irbesartan spherical agglomerates prepared with PVP –K90 in different ratios



(-♦-) Irbesartan pure drug
(-■-) Spherical agglomerates prepared with Irbesartan and PVP –K90 in 1: 0.5 ratio
(-▲-)Spherical agglomerates prepared with Irbesartan and PVP –K90 in 1: 0.75 ratio
(-×-)Spherical agglomerates prepared with Irbesartan and PVP –K90 in 1: 1 ratio

Figure 7: Dissolution profiles of Irbesartan spherical agglomerates prepared with PVP –K90 in different ratios

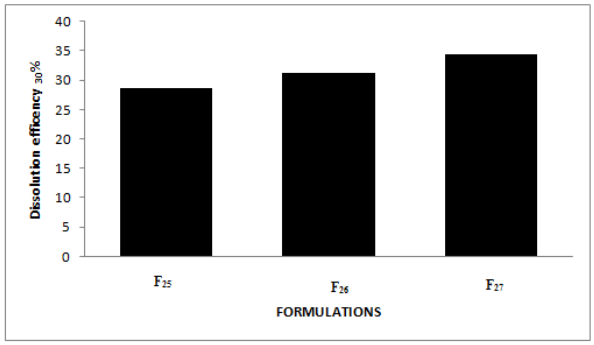


Figure 9: Comparison for dissolution efficiencies of Irbesartan spherical agglomerates prepared with PVP –K90 in different ratios

Table 12: *In-vitro* dissolution kinetics of Irbesartan spherical agglomerates prepared with PVP –K90 in different ratios

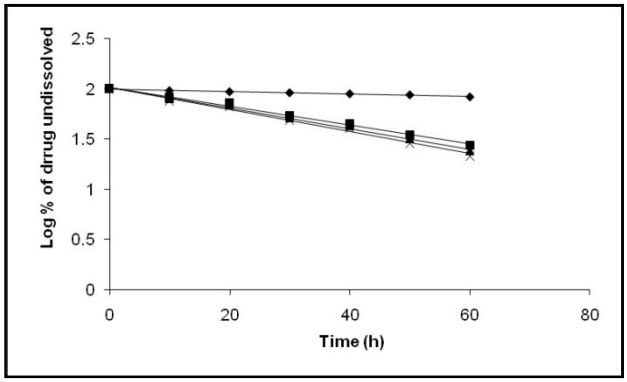
S.No.	Formulation	T_{50} (min)	T_{90} (min)	DE_{30} (%)	K (min^{-1})	Correlation coefficient values	
						Zero Order	First order
1	F_{25}	26.8	88.9	28.58	0.025	0.9742	0.9935
2	F_{26}	24.3	80.7	31.17	0.028	0.9633	0.9924
3	F_{27}	22.0	73.1	34.34	0.031	0.9980	0.9888

Table 13: Statistical treatment for dissolution efficiencies of Irbesartan spherical agglomerates prepared with PVP –K90 in different ratios

Trial	Dissolution efficiencies (%) (DE_{30})			ANOVA Parameters		
	F_{25}	F_{26}	F_{27}	Calculated value (F)	Degree of freedom	Significance
1	28.53	31.62	34.83	190.99	2,6	P<0.05
2	28.12	31.13	34.20			
3	29.09	30.76	33.99			

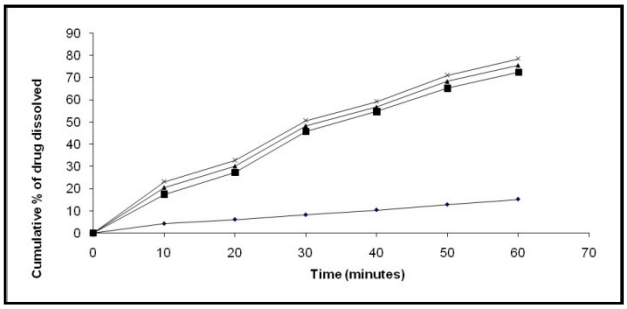
Table 14: *In-vitro* dissolution data of Irbesartan spherical agglomerates prepared with PVA

S.No.	Sampling time (min)	Cumulative % of drug dissolved ($\bar{X}$ ± S.D.)		
		F 28	F29	F 30
1	0	0	0	0
2	10	17.34	20.49	23.11
3	20	27.14	30.04	32.68
4	30	45.64	48.30	50.69
5	40	54.55	56.70	59.10
6	50	65.08	68.28	70.96
7	60	72.25	75.48	78.43



(-♦-) Irbesartan pure drug
(-■-) Spherical agglomerates prepared with Irbesartan and PVA in 1: 0.5 ratio
(-▲-)Spherical agglomerates prepared with Irbesartan and PVA in 1: 0.75 ratio
(-×-) Spherical agglomerates prepared with Irbesartan and PVA in 1: 1 ratio

Figure 11: First order plots of Irbesartan spherical agglomerates prepared with PVA



(-♦-) Irbesartan pure drug
(-■-) Spherical agglomerates prepared with Irbesartan and PVA in 1: 0.5 ratio
(-▲-)Spherical agglomerates prepared with Irbesartan and PVA in 1: 0.75 ratio
(-×-) Spherical agglomerates prepared with Irbesartan and PVA in 1: 1 ratio

Figure 10: Dissolution profiles of Irbesartan spherical agglomerates prepared with PVA

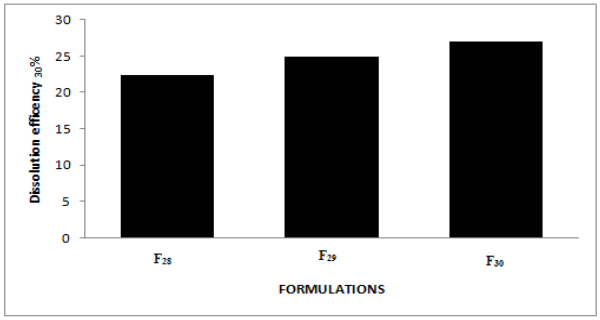


Figure 12: Comparison for dissolution efficiencies of Irbesartan spherical agglomerates prepared with PVA in different ratios

Table 15: *In-vitro* dissolution kinetics of Irbesartan spherical agglomerates prepared with PVA

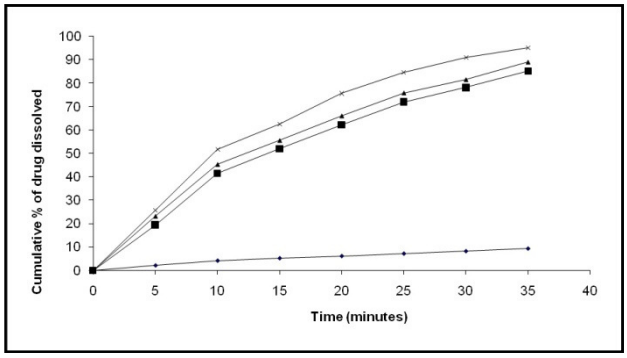
S.No.	Formulation	T_{50} (min)	T_{90} (min)	DE_{30} (%)	K (min^{-1})	Correlation coefficient values	
						Zero Order	First Order
1	F_{28}	33.6	111.7	22.44	0.020	0.9875	0.9949
2	F_{29}	30.8	102.5	24.90	0.022	0.9825	0.9946
3	F_{30}	28.5	94.6	27.05	0.024	0.9770	0.9940

Table 16: Statistical treatment for dissolution efficiencies of Irbesartan spherical agglomerates prepared with PVA in different ratios

Trial	Dissolution efficiencies (%) (DE_{30})			ANOVA Parameters		
	F_{28}	F_{29}	F_{30}	Calculated value (F)	Degree of freedom	Significance
1	22.18	24.14	27.11	58.05	2,6	P<0.05
2	22.35	24.76	27.16			
3	22.79	25.80	26.88			

Table 17: Composition of Irbesartan Immediate Release Tablets prepared with various superdisintegrants

Ingredients	F_{31}	F_{32}	F_{33}
Irbesartan agglomerates	150	150	150
Sodium Starch Glycolate(SSG)	12.5	--	-
Croscarmalose sodium	--	12.5	--
Crospovidone	--	--	12.5
Manitol	7.5	7.5	7.5
Avicel pH 102	76	76	76
Talc	2	2	2
Mg streate	2	2	2
Total weight	250	250	250



(-♦-) Irbesartan pure drug
(-■-) Irbesartan tablets prepared with sodium starch glycolate
(-▲-) Irbesartan tablets prepared with croscarmalosesodium
(-×-) Irbesartan tablets prepared with crosspovidone

Figure 13: Dissolution profiles of Irbesartan Immediate Release tablets prepared with superdisintegrants

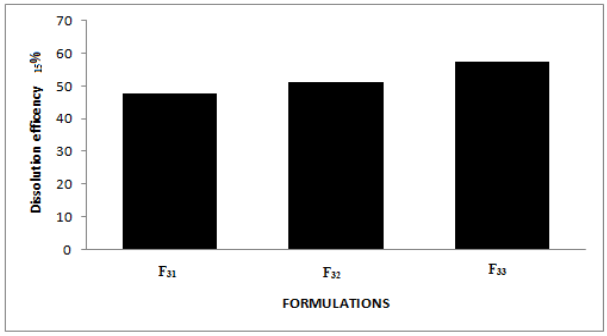
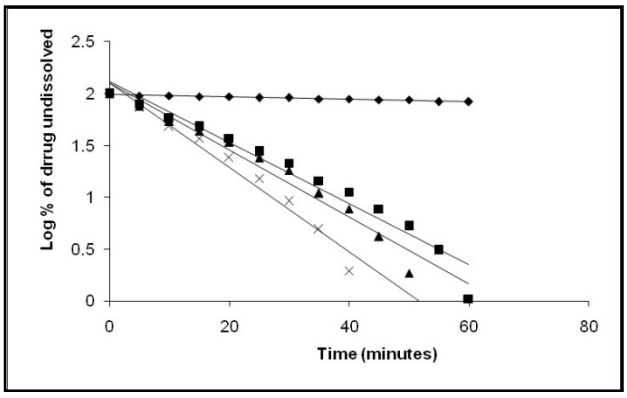


Figure 15: Comparison for dissolution efficiencies of Irbesartan Immediate Release tablets prepared with various superdisintegrants

Table 18: *In-vitro* dissolution data of Irbesartan Immediate Release tablets prepared with various superdisintegrants

S.No.	Sampling time (min)	Cumulative % of drug dissolved ($\bar{X}$ ± S.D.)		
		F_{31}	F_{32}	F_{33}
1	0	0	0	0
2	5	19.44	23.11	25.73
3	10	41.57	45.26	51.57
4	15	52.03	55.48	62.35
5	20	62.28	66.01	75.54
6	25	72.06	75.82	84.61
7	30	78.23	81.48	90.84
8	35	85.21	89.00	95.01
9	40	88.56	92.11	98.41
10	45	92.19	95.75	--
11	50	94.78	98.10	--
12	55	96.86	--	--
13	60	98.95	--	--



(-♦-) Irbesartan pure drug
(-■-) Irbesartan tablets prepared with sodium starch glycolate
(-▲-) Irbesartan tablets prepared with croscarmalosesodium
(-×-) Irbesartan tablets prepared with crosspovidone

Figure 14: First order plots of Irbesartan Immediate Release tablets prepared with superdisintegrants

Table 19: *In-vitro* dissolution kinetics of Irbesartan Immediate Release tablets prepared with various superdisintegrants

S.No.	Formulation	T_{50} (min)	T_{90} (min)	DE_{15} (%)	K (min^{-1})	Correlation coefficient values	
						Zero Order	First Order
1	F_{31}	11.3	37.6	47.75	0.061	0.8520	0.9708
2	F_{32}	10.3	34.3	51.07	0.067	0.8806	0.9764
3	F_{33}	8.0	26.6	57.54	0.086	0.8973	0.9707

Table 20: Statistical treatment for dissolution efficiencies of Irbesartan Immediate Release tablets prepared with various superdisintegrants

Trial	Dissolution efficiencies (%) (DE_{15})			ANOVA Parameters		
	F_{31}	F_{32}	F_{33}	Calculated value (F)	Degree of freedom	Significance
1	47.71	51.14	57.37	278.97	2,6	P<0.05
2	47.12	51.36	57.13			
3	48.42	50.71	58.12			

Table 21: Composition of Irbesartan Immediate Release Tablets prepared with co processed superdisintegrants

Co processed superdisintegrants composition ratio	1:1	1:2	1:3
Ingredients	**F_{34}**	**F_{35}**	**F_{36}**
Irbesartan Agglomerates	150	150	150
Croscarmalose sodium+ Crospovidone	12.5	12.5	12.5
Manitol	7.5	7.5	7.5
Avicel pH 102	76	76	76
Talc	2	2	2
Mg streate	2	2	2
Total weight	250	250	250

Table 22: Evaluation parameters of Irbesartan Immediate Release tablets prepared with co processed superdisintegrants

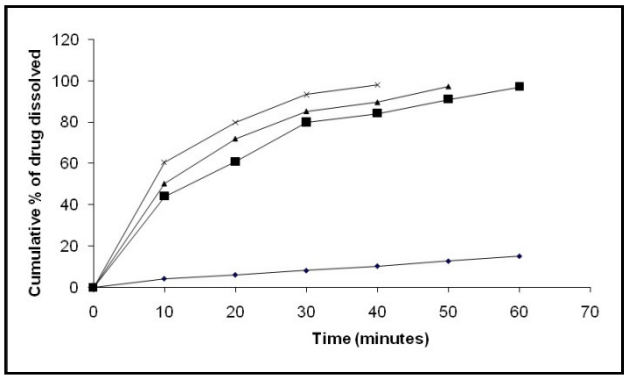
S.No.	Parameters	F_{34}	F_{35}	F_{36}
1	Average weight (mg)	250+0.3	250+0.1	250+0.2
2	Drug content (%)	98.54	99.8 1	99.19
3	Disintegration time (sec)	163	147	125
4	Friability (%)	0.44	0.28	0.13
5	Hardness (kg/sqcm)	4.2	4.2	3.8

Table 23: Micrometric properties for formulation blends of Irbesartan Immediate Release tablets prepared with co processed superdisintegrants

Formulation code	Bulk density (gm/cm^3)	Tapped Density gm/cm^3)	Carr's index (%)	Hausner's ratio	Angle of repose (°)
F_{34}	0.435	0.523	16.82	1.20	27.42
F_{35}	0.463	0.551	15.97	1.19	26.56
F_{36}	0.484	0.572	15.38	1.18	25.27

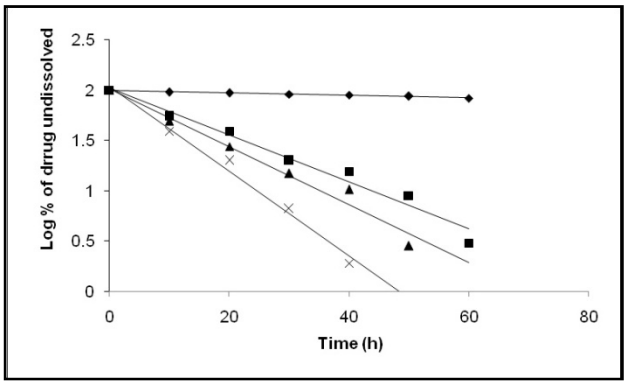
Table 24: *In-vitro* dissolution data of Irbesartan Immediate Release tablets prepared with co processed superdisintegrants

S.No.	Sampling time (min)	Cumulative % of drug dissolved ($\overline{X}$ ± S.D.)		
		F_{34}	F_{35}	F_{36}
1	0	0	0	0
2	5	44.09	50.12	60.61
3	10	60.85	71.90	79.82
4	15	79.81	85.15	93.38
5	20	84.18	89.55	98.09
6	25	90.94	97.12	--
7	30	96.94	--	--



(-♦-) Irbesartan pure drug
(-■-) Irbesartan tablets prepared with sodium starch glycolate
(-▲-) Irbesartan tablets prepared with croscarmalosesodium
(-×-) Irbesartan tablets prepared with crosspovidone

Figure 16: Dissolution profiles of Irbesartan Immediate Release tablets prepared with co processed superdisintegrants



(-♦-) Irbesartan pure drug
(-■-) Irbesartan tablets prepared with sodium starch glycolate
(-▲-) Irbesartan tablets prepared with croscarmalosesodium
(-×-) Irbesartan tablets prepared with crosspovidone

Figure 17: First order plots of Irbesartan Immediate Release tablets prepared with co processed superdisintegrants

Table 25: *In-vitro* dissolution kinetics of Irbesartan Immediate Release tablets prepared with co processed superdisintegrants

S.No.	Formulation	T_{50} (min)	T_{90} (min)	DE_{15} (%)	K (min^{-1})	Correlation coefficient values	
						Zero Order	First Order
1	F_{34}	6.6	22.0	48.28	0.104	0.8425	0.9851
2	F_{35}	5.3	17.7	54.87	0.131	0.8349	0.9864
3	F_{36}	3.7	12.3	62.38	0.180	0.8484	0.9932

Table 26: Comparison for dissolution efficiencies of Irbesartan Immediate Release tablets prepared with co processed superdisintegrants in different ratios

Trial	Dissolution efficiencies (%) (DE_{15})			ANOVA Parameters		
	F_{34}	F_{35}	F_{36}	Calculated value (F)	Degree of freedom	Significance
1	48.22	55.17	62.34	2635.04	2,6	P<0.05
2	48.19	54.73	62.11			
3	48.43	54.71	62.69			

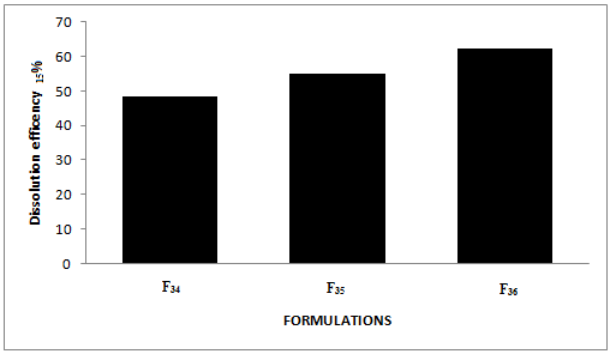


Figure 18: Comparison for dissolution efficiencies of Irbesartan Immediate Release tablets prepared with co processed superdisintegrants in different ratios

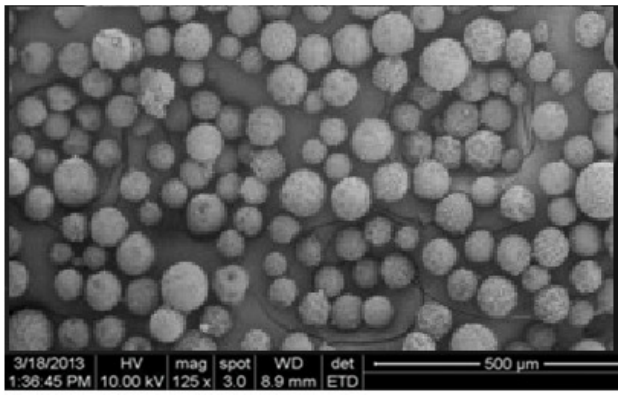


Figure 19: Scanning Electron Microscope Photograph of Olmesartan Medoxomil agglomerates

Table 27: *In vitro* dissolution data of Irbesartan Immediate Release tablets stored at 25±20 C/60±5% RH and 40±20 C/75±5% RH

S.No	Time (h)	Initial	Percentage of Glebenclamide Released ($\bar{x}$ ± sd)					
			25±2⁰ C/60±5% RH			40±2⁰ C/75±5% RH		
			1st month	2nd month	3rd month	1st month	2ndmonth	3rd month
1.	0	0	0	0	0	0	0	0
2.	5	60.61	60.49	60.32	60.23	60.28	60.17	60.09
3.	10	79.82	79.73	79.64	79.55	79.60	79.54	79.46
4.	15	93.38	93.32	93.27	93.22	93.25	93.18	93.12
5	20	98.09	98.07	98.96	98.88	98.92	98.86	98.81

Table 28: Dissolution Kinetics of Irbesartan Immediate Release tablets stored at 25±20 C/60±5% RH and 40±20 C/75±5% RH

Storage conditions	Time interval	K (min^{-1})	T_{50} (min)	T_{90} (min)	DE_{15} (%)
25±2⁰ C/ 60±5% RH	1st month	0.18	3.7	12.3	62.38
	2nd month	0.18	3.7	12.3	62.38
	3rd month	0.18	3.7	12.3	62.38
40±2⁰ C/ 75±5% RH	1st month	0.18	3.7	12.3	62.38
	2nd month	0.18	3.7	12.3	62.38
	3rd month	0.18	3.7	12.3	62.38

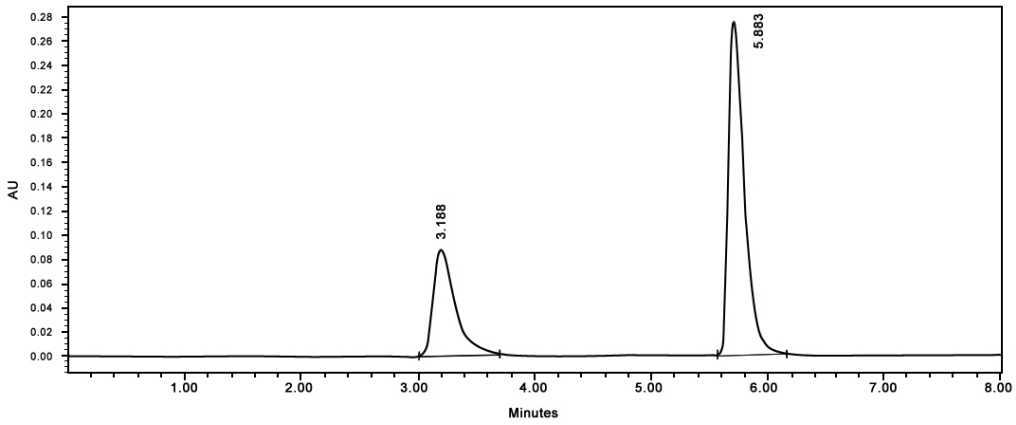


Figure 20: HPLC chromatogram showing Irbesartan and internal standard peaks

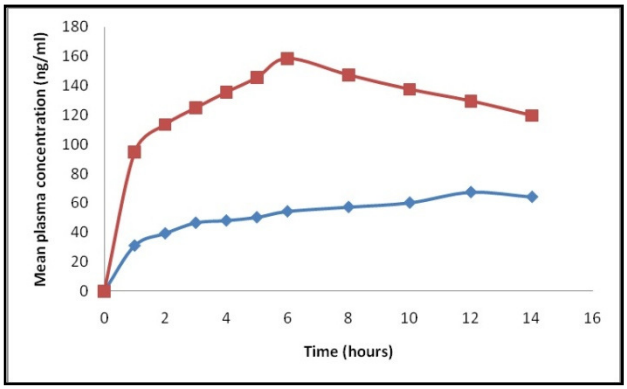
	Name	Retention Time (min)	Area (µV*sec)	Height (µV)
1	**Losartan**	2.363	420503	36289
2	**Irbesartan**	7.461	257535	15073

Table 29: Calibration Curve values of Irbesartan in plasma

Concentration of Irbesartan (µg/ml)	Peak Area Ratio			
	Trail – 1	Trail – 2	Trail – 3	Mean + S.E.M
0.1	0.0134	0.0156	0.0185	0.0158+ 0.0026
0.5	0.0427	0.0468	0.0396	0.0430+0.0036
1	0.1029	0.1069	0.1015	0.1037+0.0047
1.5	01585	0.1463	0.1624	0.1557+0.0081
2	0.2154	0.2298	0.2168	0.2207+0.087
2.5	0.2687	0.2764	0.2674	0.2705+0.008

Table 30: Plasma Concentration of Irbesartan following pure drug administration and Irbesartan Immediate Release tablets administration

Time (h)	Plasma concentration (ng/ml) (Mean ± s.d) Pure drug	Irbesartan Immediate Release tablets
0	0	0
0.5	27.52 ±1.32	82.34 ±0.25
1	31.24±1.45	94.83±0.15
1.5	34.67±1.53	102.36±0.51
2	39.54±1.12	113.45±0.13
3	46.75±1.43	124.83±0.72
4	48.28±1.23	135.47±0.49
5	50.46±1.24	145.43±0.55
6	54.49±1.37	158.46±0.47
8	57.45±1.68	147.17±1.52
10	60.39±1.54	137.42±1.59
12	67.56±1.24	129.52 ±1.68
14	64.35±1.26	119.64±1.26
16	59.46±1.47	105.52±1.38
18	48.72±1.39	97.45±1.15
20	35.67±1.214	83.62±1.67
24	22.43±1.28	77.34±1.38



(-♦-) Plasma Concentration -Time Curve of Irbesartan following pure drug administration

(-■-) Plasma Concentration -Time Curve of Irbesartan following optimized Irbesartan Immediate Release tablets administration

Figure 21: Comparative plasma Concentration - Time Curve of Irbesartan following pure drug and optimized Irbesartan Immediate Release tablets administration

Table 31: Statistical Treatment of Pharmacokinetic Parameters (Mean ⍰ S.D.) of Irbesartan obtained with pure drug and Irbesartan Immediate Release tablets

Pharmacokinetic parameter	Pure Drug	Irbesartan Immediate Release tablets	Calculated value of 't'
C_{max} (ng/ml)	67.56 ± 0.43	158.46 ± 0.15	12.53***
$t_{1/2}$ (h)	11.42 ± 0.32	6.15 ± 0.14	8.96***
K_{el} (h^{-1})	0.96 ± 0.004	0.82 ± 0.003	5.70***
K_a (h^{-1})	2.92 ± 0.01	7.76 ± 0.01	85.68***
$AUC_{0-⍰}$ (ng h/ml)	126 ± 1.23	464.9.± 1.36	146.40***

Null hypothesis (H_o): There is no significant difference between the pharmacokinetic parameters of Irbesartan obtained with pure drug and Irbesartan Immediate Release tablets value of 't' with 10 DF at the 0.001 level is 4.587.

Result: H_o is not accepted as the calculated 't' value more than the table Value of't' with 10 DF at 0.001 levels of significance. It was therefore concluded that there was significant difference between the pharmacokinetic parameters of obtained with pure drug and optimized Irbesartan Immediate Release tablets.

4.18. SEM Analysis: The samples for the SEM analysis were prepared by sprinkling the spherical agglomerates on one side of the double adhesive stub[114]. The stub was then coated with fine gold dust. The spherical agglomerates were then observed with the scanning electron microscope (Leica Electron Optics, Cambridge, USA) at 10 kV.

4.19. Stability study: The optimized formulation was subjected to accelerated stability studies as per ICH (The International Conference of Harmonization) guidelines. The optimized formulations were filed into packed in the screw capped bottles and stored at 25 ± 2ºC, 60 ± 5% RH and at 40 ± 2 ºC, 75 ± 5% RH for 3 months. Tablets were periodically removed and evaluated for physical characteristics and in-vitro drug release.

Pharmacokinetic evaluation of Irbesartan immediate release tablets [25-26]:

The pharmacokinetic performance of Irbesartan immediate release tablets was studied in a randomized crossover study design in rabbits. Twelve healthy rabbits with a mean age of 10±2 weeks and with a mean body weight of 3±0.2 kg were used. Two groups of rabbits with 6 in each were fasted for 12 hrs prior to study. The animal dose of pure Irbesartan and its immediate release tablets was calculated relevant to human dose. A dose of 1mg/kg of pure Irbesartanand 1mg/kg Irbesartanequalent immediate release tablets were administered orally in the form of suspension for two groups of rabbits. The rabbits were restrained in a wooden rabbit holder. The ears of the rabbits were cleaned and the hair was removed with the help of depilatory. Before withdrawal, the ear veins were dilated by swabbing with cotton or by application of warm water. The marginal ear vein of the left ear was punctured with a help of a 24 gauge needle. About 1 ml of blood samples were drawn at 0 (before drug administration), 0.5, 1.0, 2.0, 3.0, 4.0 and 6.0 hrs after pure drug administration and at 0,1, 2, 4, 6, 8, 12, 16, 20, and 24 hrs after administration of Irbesartan immediate release tablets [27]. Blood sample volume was replaced by administration of isotonic saline. . The blood samples were collected in a micro centrifuge tube and centrifuged at 3500 rpm for 10 min. Later the plasma was collected and utilized for estimation of Irbesartanconcentration.

Estimation of Irbesartan in rabbit plasma by HPLC [26]:

HPLC method is a sensitive and accurate method that provides a good choice to study the pharmacokinetics of Irbesartan*in vivo*. A summary of the chromatographic conditions used in HPLC is as follows**.**

Preparation of standard solutions:

The stock standard solution of Irbesartan was prepared by dissolving the accurately weighed Irbesartan in methanol to give a final concentration of 1.0 mg/ ml. The solution was then successively diluted with methanol to achieve 100 µg/ ml and 5 µg / ml. An internal standard and working solution, of losartan potassium 10µg/ ml was prepared as the former.

Chromatographic conditions:

Chromatograph	:	Waters 2695 liquid chromatogram
Mobile phase	:	Acetronitrile: Phosphate buffer (80:20 % v/v) pH adjusted to 3.5 with orthophosphoric acid.
Internal standard	:	Losartan potassium
Column	:	XterraC_{18} Size - 100×4.60 mm. 5 µm
Flow rate	:	0.6 ml/min
Detector	:	UV-Visible detector - 2487 Dual absorbance λdetector
Wave length	:	253 nm
Injection volume	:	20 µl
Temperature	:	Ambient
Retention time of the	:	7.461 min analyte
Retention time of the	:	2.363 min internalstd
Total run time	:	10 min
Soft ware	:	Empower 2

Preparation of plasma calibration curve samples:

To 250 µl of plasma 20,100,200,300,400,500 µl of 5 µg/ ml Irbesartan stock solution and 100 µl of internal standard metformin (10 µg/ ml) was added. To this acetronitrile was added as precipitating agent to get a final volume of 1000 µl containing 0.1,0.5,1.0,1.5,2.0,2.5 µg/ ml of Irbesartan respectively. The sample was vortexed for 10 min and then centrifuged at 5000 rpm for 10 min at room temperature. The supernatant layer was separated and filtered through 0.22 µm membrane filter, and 20 µl of the filterate was injected and the calibration curve was constructed[28]. The peak area ratio was calculated and plotted against concentration of Irbesartan. From the plot peak area ratio versus concentration, the regression equation was computed and furnished below.

The regression equation is **y= 0.108x- 0.0035, R^2 = 0.0996.**

Evaluation of pharmacokinetic parameters in rabbit serum [26]:

The pharmacokinetic parameters of Irbesartan such as K_e (1/hr), $t_{1/2}$ (hr), K_a (1/hr), AUC $_{(0-\alpha)}$ (µg-hr/ml), MRT (hr), C_{max} (µg/ml), T_{max} (hr) were estimated by non-compartmental methods by using the formulas as describe earlier.

RESULTS

All the results are listed in Table 1-31 and in Figures 1-21.

CONCLUSION

Present study concluded that spherical agglomerates prepared by the quasi emulsion solvent diffusion method showed an improvement in the solubility, dissolution rate, compatibility, wettability, flowability and bioavilability.These spherical agglomerates also showed excellent physico-chemical characters as compared with plain drug which indicates that the spherical agglomerates can suitable for directly compressible tablet process.

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