ENHANCING THE FLOW PROPERTIES AND DISSOLUTION RATE OF IRBESARTAN BY USING SPHERICAL CRYSTALLIZATION TECHNIQUE

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ABSTRACT: Spherical crystallization is a 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. It is a simple process and inexpensive enough for scaling up to a commercial level, which reduces time and cost by involving faster operation, less machinery, and fewer personnel, with great advances in tabletting technology, especially the introduction of a number of directly compressible excipients. Irbesartan is slightly soluble in alcohol and methylenechloride and practically insoluble in water. Irbesartan is clinically used alone or combined with other antihypertensive agents to treat hypertension. Irbesartan is a fluffy material, with relatively low bulk and tapped densities. These properties make it difficult to formulate a large amount of the drug into a small tablet. Irbesartan is a nonpeptide tetrazole derivative and an angiotensin II antagonist that selectively blocks the binding of angiotensin II to the AT 1 receptor. Spherical agglomerates prepared by the quasi emulsion solvent diffusion method showed an improvement in the solubility, dissolution rate, compactability, wettability, flow ability and bioavailability. 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.

KEYWORDS: IRBESARTAN, PVP-K90, CMC, MC, HPMC

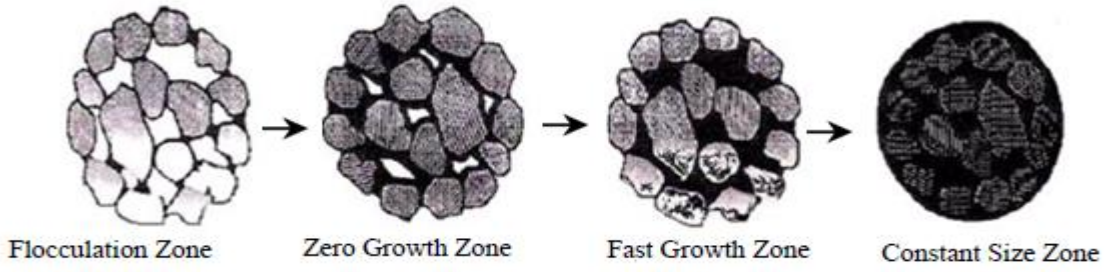
INTRODUCTION

Tablet is the most stable readily portable and consumed dosage form. The formulation of tablet is optimized to achieve goals. The focus today in the business is better drug delivery concepts, but also makes the simple standard formulations as economical as possible to produce. One of the most economical solutions is to find directly compressible formulations and this is especially at interest for large volume products. These have been renewed interest in examining the potential of direct compression tabletting over recent years since in comparison to the used at the more traditional granulation process. Such manufacturing of the tablets involves simple mixing and compression of powders which gives benefits like time and cost saving. [1] thus direct tabletting technique has been widely used successfully for various drugs. But it strongly depends upon the quality of the crystals used. Micronisation by milling is extremely inefficient and 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 tabletting. 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]

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. 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, flow ability, wettability and compaction behavior.

The Principle Steps Involved In The Process Of Spherical Crystallization

Bermer and Zuider Wag proposed four steps in the growth of agglomeration as shown as



1. Flocculation Zone:

In this zone the bridging liquid displaces the liquid from the surface of the crystals and these crystals are brought in close proximity by agitation, the adsorbed bridging liquid links the particles by forming bridge or lens between them. In this zone, loose open flocs of particles are formed by pendular bridges and this stage of agglomeration process where the ratio of liquid to the void volume is low and air is the continuous phase, is known as the pendular state. Mutual attraction of particles is brought about by surface tension of the liquid and the liquid bridges. The capillary stage is reached when all the void space within the agglomerate is completely filled with the liquid. An intermediate state known as funicular state exists between the pendular and capillary stage. The cohesive strength of agglomerate is attributed to the bonding forces exerted by the pendular bridges and capillary suction pressure.

2. Zero Growth Zone:

Loose flocs get transferred into tightly packets pellets, during which the entrapped fluid is squeezed out followed by the squeezing of the bridging liquid on to the surface of the small flocs causing pore space in the pellet to be completely filled with the bridging liquid. The driving force for the transformation is provided by the agitation of the slurry causing liquid turbulence, pellet-pellet and pellet-stirrer collision.

3. Fast Growth Zone:

The fast growth zone of the agglomerate takes place when sufficient bridging liquid has squeezed out of the surface of the small agglomerates. This formation of large size article following random collision of well formed nucleus is known as coalescence. Successful collision occurs only if the nucleus has slight excess surface moisture. This imparts plasticity on the nucleus and enhances article deformation and subsequent coalescence.

4. Constant Size Zone:

In this zone agglomerates cease to grow or even show slight decrease in size. Here the frequency of coalescence is balanced by breaking frequency of agglomeration. The size reduction is may be due to attrition, breakage and shatter. The rate determining step in agglomeration occurs in zero growth zones when bridging liquid is squeezed out of the pores as the initial flocs are transformed into small agglomerates. Another view process that the rate determining step is the collision of particle with the bridging liquid droplets prior to formation of liquid bridges. The rate is governed by rate of agitation. The strength of agglomerates is determined by interfacial tension between the bridging liquid and the continuous liquid phase, the contact angle and the ratio of volume of bridging liquid and solid particles.

Parameters of pharmaceutical ingredients improved by spherical crystallization technique

Spherical crystallization technique causes improvement of following properties.

1. Particle Size and Size Distribution:

Particle size and shape of pharmaceutical ingredients can be modified by this technique. Usually a large size and spherical shape particle are formed. Size of particles are improved due to the aggregation if particles influenced by the bridging solvent. Similarly, agitation of solvent system during process results in the spherical shape of particles. Particle size and shape of spherical crystals can be determined by using optical microscopy (or)scanning electron microscopy (or) X-ray Powder Diffraction technique. [6]

2.**Mechanical Strength:**

Spherical crystals should posses good mechanical strength as that directly reflects the mechanical strength of compact or tablet. This may be due to increased intra partical force within spherical agglomerated crystals. Mechanical Strength can be determined by measuring the tensile strength or crushing strength. The tensile strength of tablets prepared from agglomerated crystals was always higher than the tablets prepared from single crystal at the same compression pressure. This was due to plastic deformation of the agglomerated crystals resulting in greater permanent particle contact and stronger bond force than in case of the original crystals. It has been established that the production of fresh surface by fracturing during the compression process is necessary to expose to air to bind the particles strongly for tabletting. If fractured surface is exposed to air for a long time after

breaking, no improvement in inter particle bond occurs because of the reduction in free energy of the surface when absorbed with air [7].

3.**Flow Property:**

Flow property of the material depends on the force developed between the particle size, particle shape, surface texture and surface area. The improvement in the flowability of spherical crystals could be attributed to the significant reduction in inter particle friction, due to their spherical shape and a lower static electric charge. The improvement in the flowability of spherical crystals can be determined by measuring the Angle of Repose or Carr's Index or Hausner Ratio[8].

4.**Packability:**

Improve packability has been reported for agglomerates prepared by spherical crystallization. The angle of friction, shear cohesive stress and shear indexes are lower then that of single crystals, which can improve the packability of the agglomerates[9].

5. **Compression Behaviour Analysis:**

Good compactibility and compressibility are essential properties of directly compressible crystals. The compaction behavior of agglomerated crystals and single crystals is obtained by plotting the relative volume against the compression pressure. Spherical agglomerates possess superior strength characteristics incomparison to conventional crystals. It is suggest that the surface are freshly prepared by fracture during compression of agglomerates, which enhances the plastic inter particle bonding, resulting in a lower compression force required for compressing the agglomerates under plastic deformation compared to that of single crystals.

6.**Wettability:**

Wettability of agglomerated crystals by water is investigated by measuring the contact angle of water to the compressed crystals. The wettability depends on the crystallinity and elementary crystal size of the agglomerated crystals. As the contact angle decreases the wettability increases. Crystals with low crystallinity are more wettable than crystals with higher crystallinity.

7. Dissolution Rate and Bioavailability:

The dissolution rate and bioavailability of agglomerated crystal depends on particle size, particle density and specific surface area of the agglomerated crystals. It has been elucidated that the dissolution of agglomerates increases as apparent specific surface area increases.

EXPERIMENTAL WORK:

Phase solubility studies of Irbesartan:

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

Calibration curve for the estimation of Irbesartan in 0.1N HCl (1.2 pH):

Standard solution: Irbesartan (10mg) was dissolved in 5 ml of methanol in 10 ml volumetric flask and the solution was made up to volume with 0.1N HCl (1.2 pH).

Procedure:

Calibration curve for the estimation of Irbesartan was constructed employing 0.1N HCl (1.2 pH). The standard solution of Irbesartan was subsequently diluted with 0.1N HCl to obtain series of dilutions containing 5, 10, 15, 20 and 25µg of Irbesartan in 1.0ml of solution. The absorbance of the above solutions was measured in Elico UV Spectrophotometer at 244nm.

Table 2: Calibration curve for the estimation of Irbesartan in 0.1N HCl (1.2 pH)

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

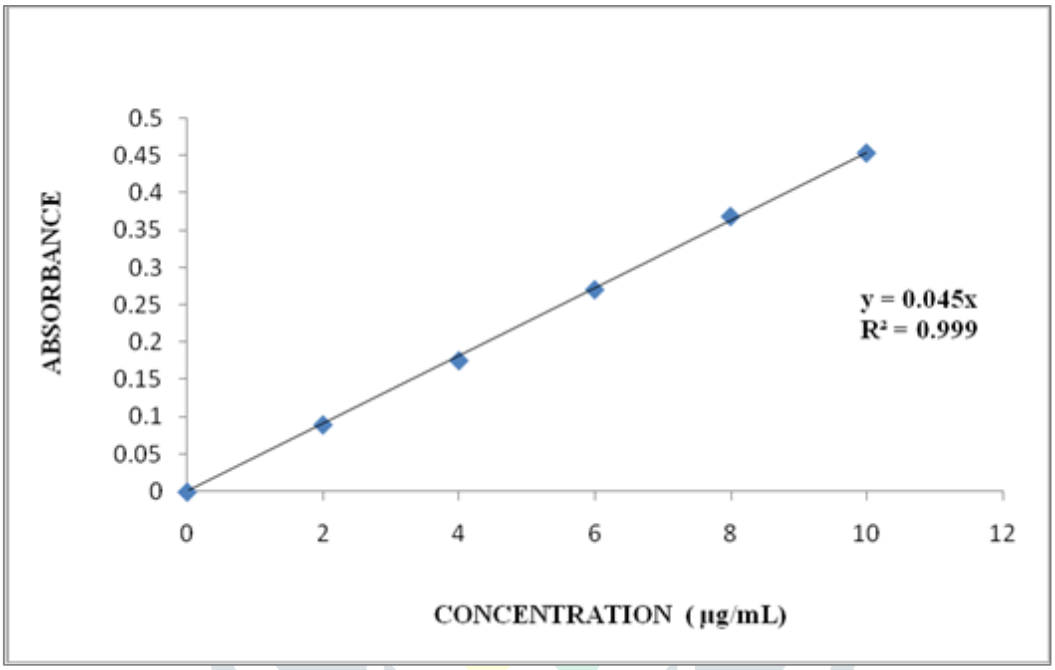


FIGURE 1: Calibration curve for the estimation of Irbesartan in 0.1N HCl (1.2 pH)

Preparation of Irbesartan Spherical agglomerates:

All spherical agglomerates were prepared by the quasi emulsion solvent diffusion method [3]. Irbesartan (1g) with PVPK90 /HPMC/NaCMC/MC was dissolved in good solvent N,N-dimethyl formamide (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 spherical agglomerates were filtered through Whatman filter paper (No.1) and dried in desiccators at room temperature. The amount of stabilizer was altered to get desired agglomerates. The composition is given in Table 3.

Table 3: List of Irbesartan Spherical agglomerates formulated with different carriers

Formulation Number	Irbesartan (mg)	PVP K-90 (mg)	HPMC (mg)	NaCMC (mg)	MC (mg)	N,N-dimethyl Formamide (ml)	Water (ml)	Chloroform (ml)
F1	1000	500				25	62.5	12.5
F2	1000	750				25	62.5	12.5
F3	1000	1000				25	62.5	12.5

F4	1000		500			25	62.5	12.5
F5	1000		750			25	62.5	12.5
F6	1000		1000			25	62.5	12.5
F7	1000			500		25	62.5	12.5
F8	1000			750		25	62.5	12.5
F9	1000			1000		25	62.5	12.5
F10	1000				500	25	62.5	12.5
F11	1000				750	25	62.5	12.5
F12	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,

$$Average\ Particle\ Size = \frac{\sum nd}{n}$$

b) Solubility studies:-

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 spectro photometrically at 244 nm.

Table 4: Solubility studies of Irbesartan spherical agglomerates prepared by agglomeration technique

Formulation	Particle size (µm)	Solubility (mg/ml)
Pure drug	-	0.005
F1	256	0.0636
F2	278	0.0747
F3	294	0.0866
F4	312	0.0563
F5	334	0.0649
F6	356	0.0758
F7	346	0.0441
F8	367	0.0526
F9	386	0.0652
F10	378	0.0332
F11	394	0.0428
F12	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.

Table 5: Drug content of Irbesartan spherical agglomerates prepared by agglomeration technique

Formulation	% of Drug content
F1	99.26
F2	99.54
F3	99.36
F4	99.41
F5	99.39
F6	99.24
F7	99.45

F8	99.73
F9	99.21
F10	99.22
F11	99.33
F12	99.11

D) Dissolution studies of agglomerates:

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 HCI (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 [6]

Table 6: In-vitro dissolution data of Irbesartan spherical agglomerates prepared with PVP K-90 in different ratios

S. No	Sampling time (min)	Cumulative % of drug dissolved ($\bar{X}$ ± S.D.)			
		Pure Drug	F 1	F 2	F 3
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

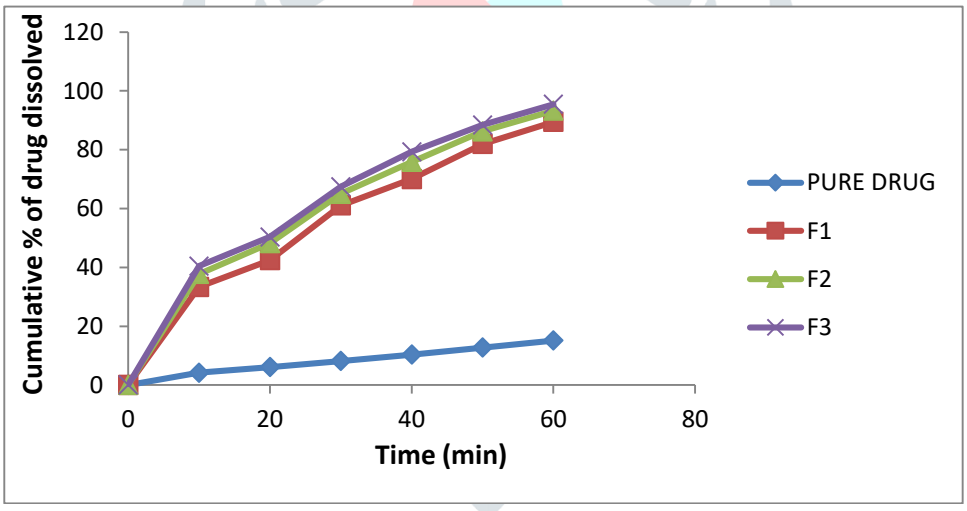


Figure2:Dissolution profiles of Irbesartan pure drug and spherical agglomerates prepared with PVP K90 in different ratios

(-♦-) 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

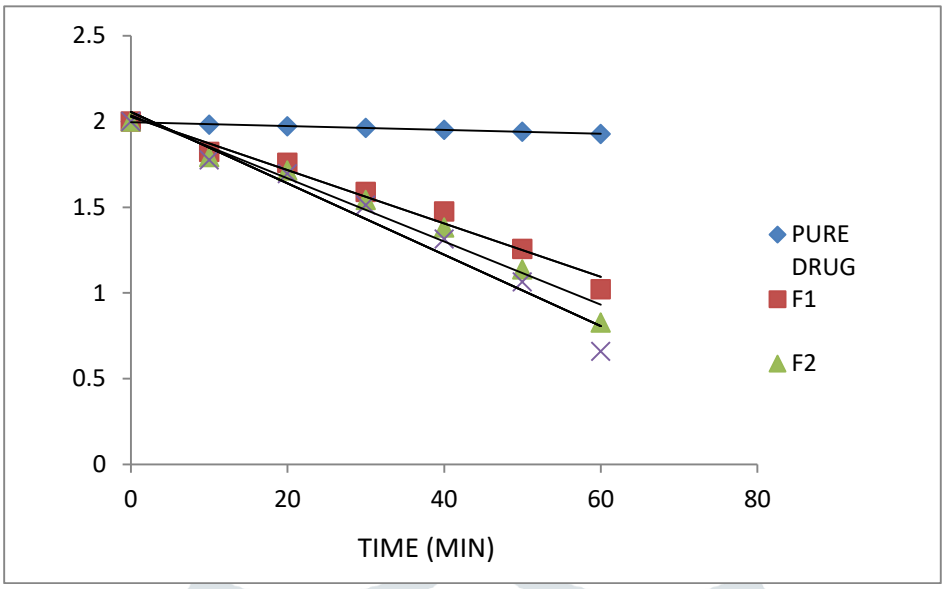


Figure 3: First order plots of Irbesartan pure drug and spherical agglomerates prepared with PVP K90 in different ratios

(-♦-) 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

Table 7: *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_1	20.2	67.1	35.43	0.034	0.9466	0.9870
2	F_2	17.2	57.0	39.51	0.040	0.9250	0.9836
3	F_3	15.4	51.2	41.49	0.044	0.9135	0.9768

Table8: Statistical treatment for dissolution efficiencies of Irbesartan spherical agglomerates prepared with PVPK90 in different ratios

Trial	Dissolution efficiencies (%) (DE_{30})			ANOVA Parameters		
	F_1	F_2	F_3	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			

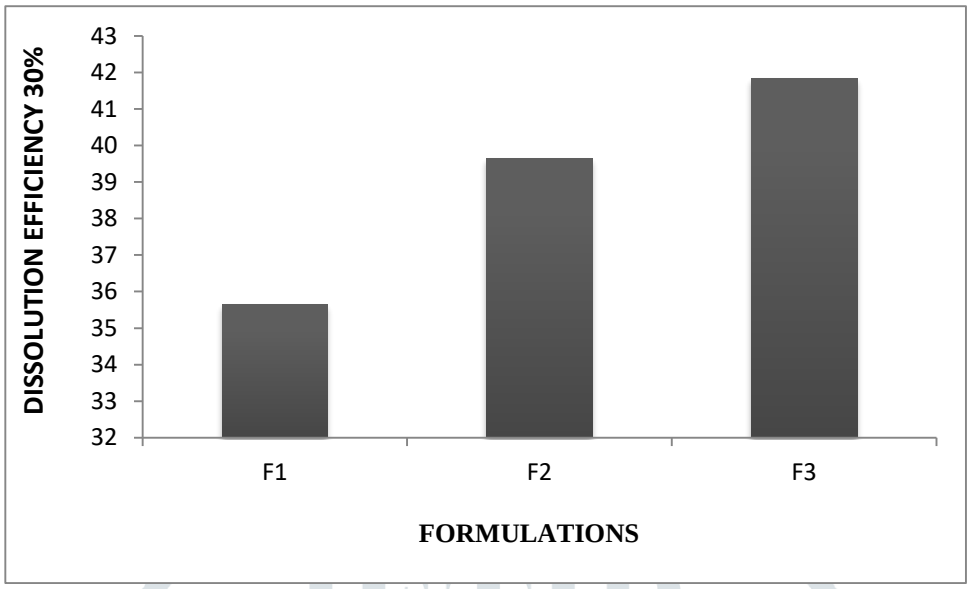


Figure 4: Comparison for dissolution efficiencies of Irbesartan spherical agglomerates prepared with PVP K90 in different ratios

Table 9: In-vitro dissolution data of Irbesartan spherical agglomerates prepared with HPMC in different ratios

S. No	Sampling Time (min)	CUMULATIVE % OF DRUG DISSOLVED ($\overline{X}$ ± S.D.)			
		PURE DRUG	F_4	F_5	F_6
1	0	0	0	0	0
2	10	4.22	29.14	32.55	34.12
3	20	6.08	39.00	41.38	43.23
4	30	8.16	56.53	58.13	61.82
5	40	10.35	65.49	67.11	70.82
6	50	12.75	77.39	79.28	82.74
7	60	15.15	84.90	87.05	90.28

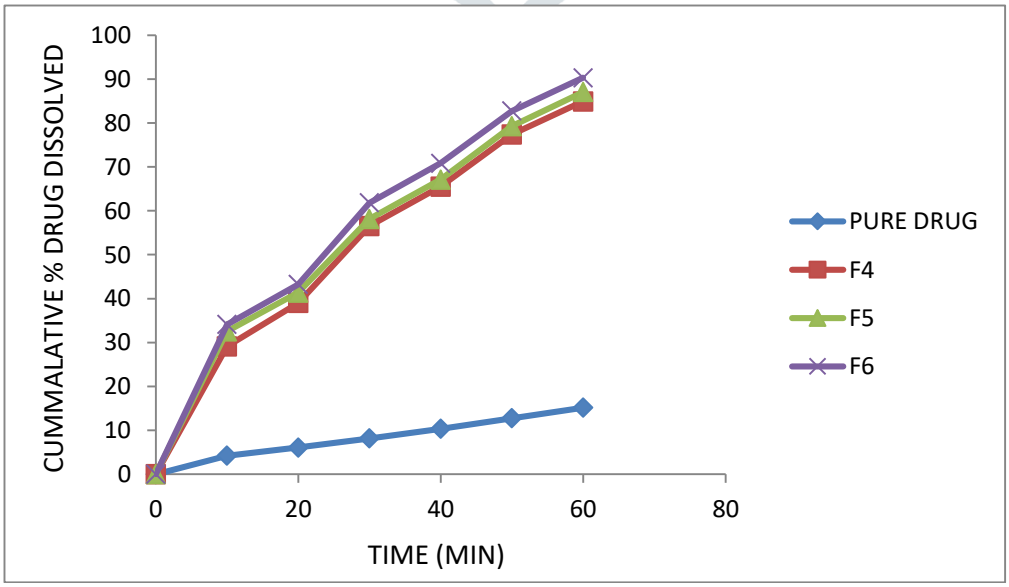


Figure 5: Dissolution profiles of Irbesartan spherical agglomerates prepared with HPMC in different ratios

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

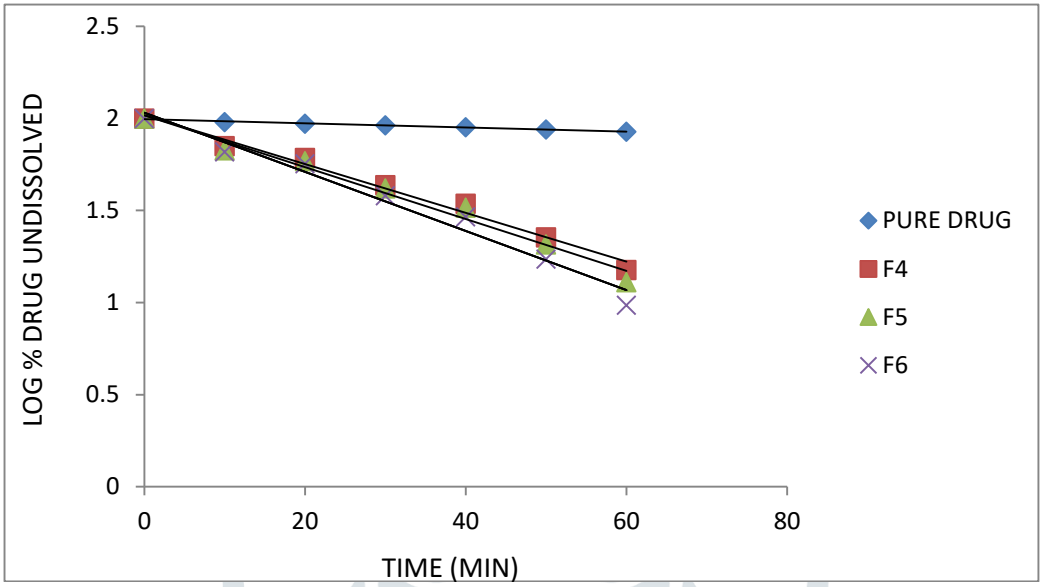


Figure 6: First order plots of Irbesartan spherical agglomerates prepared with HPMC in different ratios

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

Table 10: *In-vitro* dissolution kinetics of Irbesartan spherical agglomerates prepared with HPMC 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_4	23.5	78.0	32.14	0.029	0.9544	0.9919
2	F_5	22.0	73.1	34.34	0.032	0.9480	0.9888
3	F_6	19.6	65.2	36.09	0.035	0.9438	0.9857

Table 11: Statistical treatment for dissolution efficiency of Irbesartan spherical agglomerates prepared with HPMC in different ratios

Trial	Dissolution efficiencies (%) (DE_{30})			ANOVA Parameters		
	F_4	F_5	F_6	Calculated value (F)	Degree of freedom	Significance
1	32.24	34.62	36.34			
2	32.33	34.23	36.13	3665	2,6	P<0.05
3	31.85	34.17	35.80			

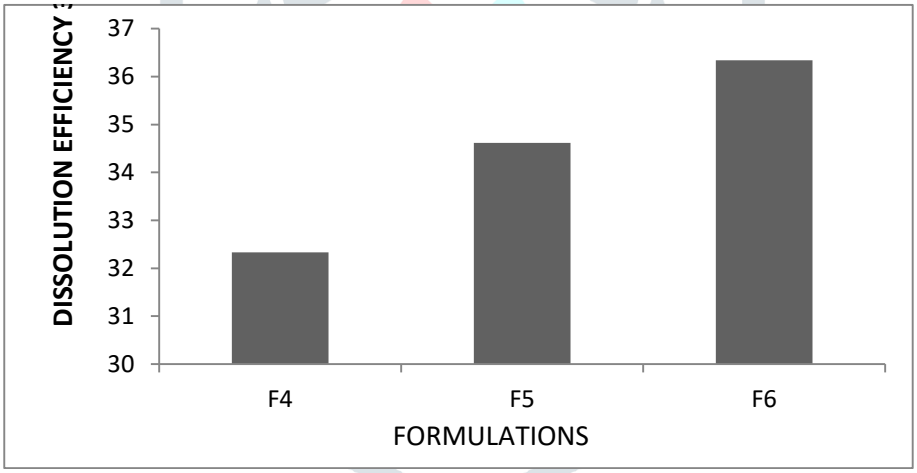


Figure 7: Comparison for dissolution efficiencies of Irbesartan spherical agglomerates prepared with HPMC in different ratios

Table 12: In-vitro dissolution data of Irbesartan spherical agglomerates prepared with NaCMC in different ratios

S. No	Sampling Time (min)	Cumulative % of drug dissolved ($\overline{X}$ ± S.D.)			
		PURE DRUG	F_7	F_8	F_9
1	0	0	0	0	0
2	10	4.22	24.94	28.09	32.55
3	20	6.08	34.52	37.69	41.38
4	30	8.16	52.55	55.47	58.13
5	40	10.35	61.23	64.42	67.11
6	50	12.75	73.10	76.32	79.28
7	60	15.15	80.58	83.82	87.05

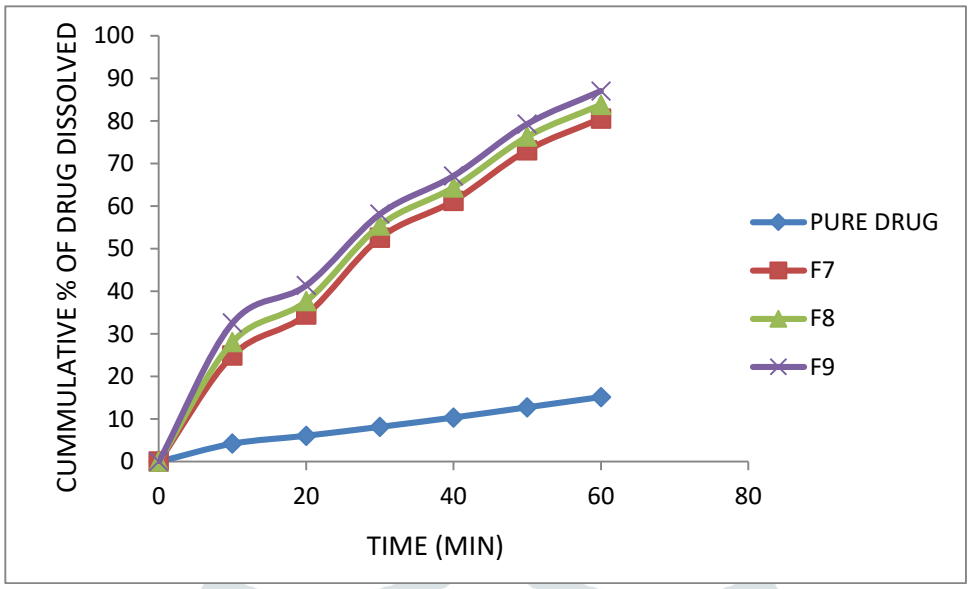


Figure 6.8: Dissolution profiles of Irbesartan spherical agglomerates prepared with NaCMC in different ratios
(-♦-) Irbesartan pure drug
(-■-) Spherical agglomerates prepared with Irbesartan and NaCMC in 1: 0.5 ratio
(-▲-) Spherical agglomerates prepared with Irbesartan and NaCMC in 1: 0.75 ratio
(-×-) Spherical agglomerates prepared with Irbesartan and NaCMC in 1: 1 ratio

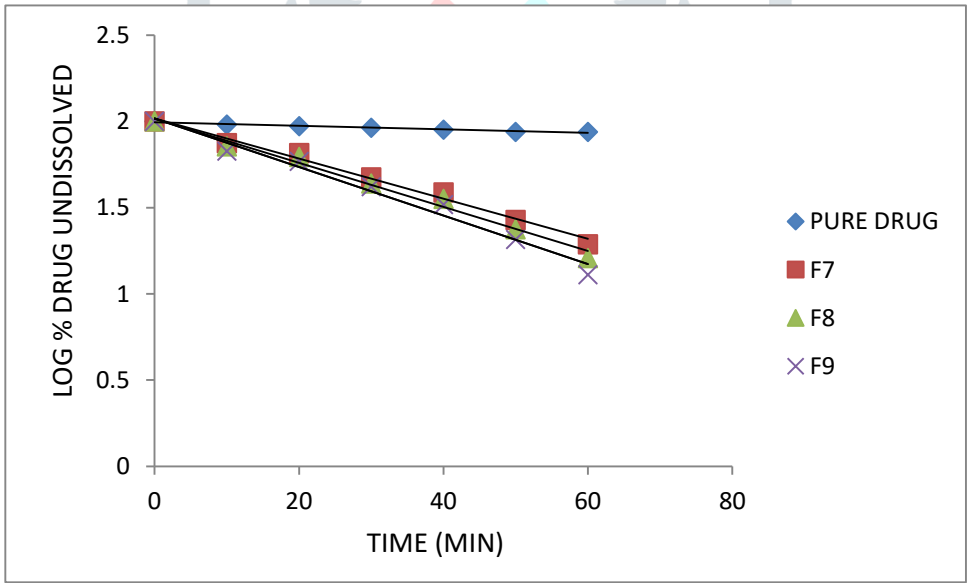


Figure 6.9: First order plots of Irbesartan spherical agglomerates prepared with NaCMC in different ratios
(-♦-) Irbesartan pure drug
(-■-) Spherical agglomerates prepared with Irbesartan and NaCMC in 1: 0.5 ratio
(-▲-) Spherical agglomerates prepared with Irbesartan and NaCMC in 1: 0.75 ratio
(-×-) Spherical agglomerates prepared with Irbesartan and NaCMC in 1: 1 ratio

Table 13: *In-vitro* dissolution kinetics of Irbesartan spherical agglomerates prepared with NaCMC 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_7	26.8	88.9	28.58	0.025	0.9742	0.9935
2	F_8	24.3	80.7	31.17	0.028	0.9633	0.9924
3	F_9	22.0	73.1	34.34	0.031	0.9980	0.9888

Table 14: Statistical treatment for dissolution efficiencies of Irbesartan spherical agglomerates prepared with NaCMC in different ratios

Trial	Dissolution efficiencies (%) (DE_{30})			ANOVA Parameters		
	F_7	F_8	F_9	Calculated value (F)	Degree of freedom	Significance
1	28.53	31.62	34.83			
2	28.12	31.13	34.20	190.99	2,6	P<0.05
3	29.09	30.76	33.99			

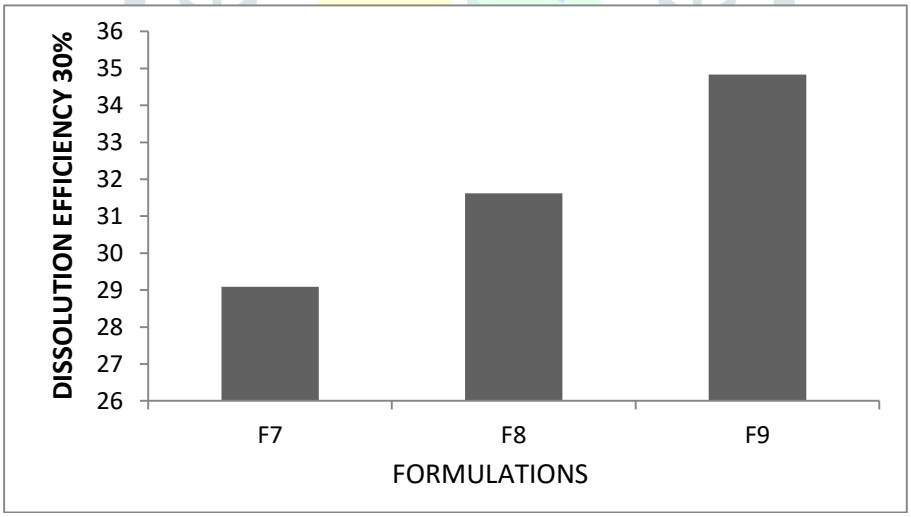


Figure 10: Comparison for dissolution efficiencies of Irbesartan spherical agglomerates prepared with NaCMC in different ratios

Table 15: In-vitro dissolution data of Irbesartan spherical agglomerates prepared with Methyl cellulose

S. No	Sampling time (min)	Cumulative % of drug dissolved ($\bar{X}$ ± S.D.)			
		PURE DRUG	F 10	F11	F 12
1	0	0	0	0	0
2	10	4.22	17.34	20.49	23.11
3	20	6.08	27.14	30.04	32.68
4	30	8.16	45.64	48.30	50.69
5	40	10.35	54.55	56.70	59.10
6	50	12.75	65.08	68.28	70.96
7	60	15.15	72.25	75.48	78.43

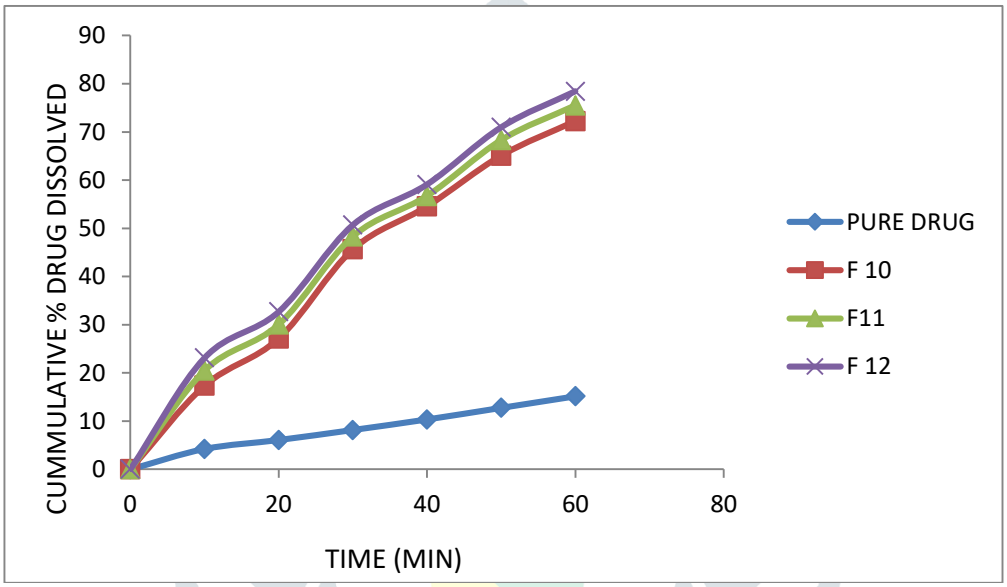


Figure 11: Dissolution profiles of Irbesartan spherical agglomerates prepared with Methyl cellulose

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

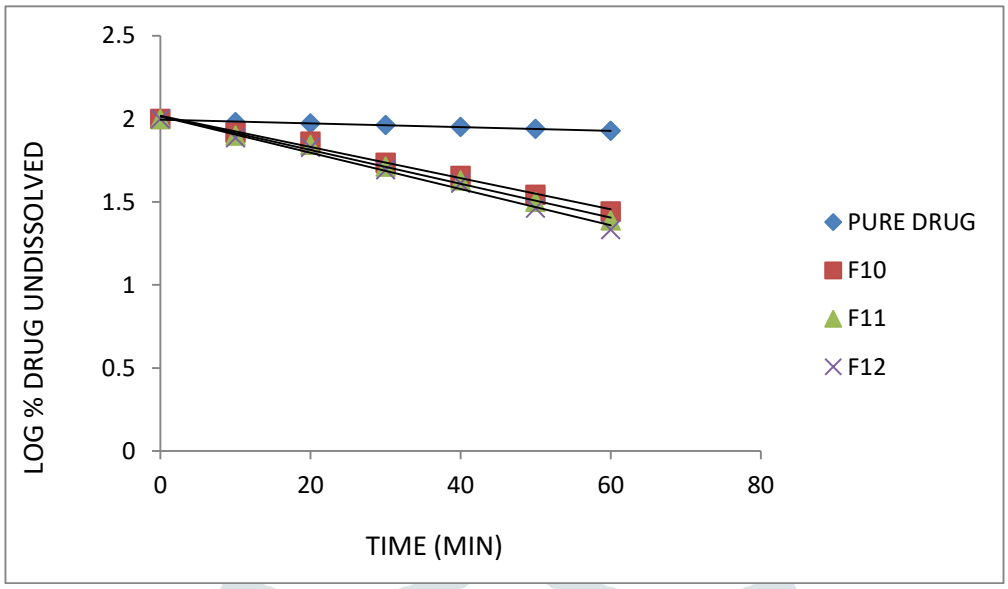


Figure 12: First order plots of Irbesartan spherical agglomerates prepared with Methyl cellulose

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

Table 16: *In-vitro* dissolution kinetics of Irbesartan spherical agglomerates prepared with Methyl cellulose

S. No	Formulation	T_{50} (min)	T_{90} (min)	DE_{30} (%)	K (min^{-1})	Correlation coefficient values	
						Zero Order	First order
1	F_{10}	33.6	111.7	22.44	0.020	0.9875	0.9949
2	F_{11}	30.8	102.5	24.90	0.022	0.9825	0.9946
3	F_{12}	28.5	94.6	27.05	0.024	0.9770	0.9940

Table 17: Statistical treatment for dissolution efficiencies of Irbesartan spherical agglomerates prepared with Methyl cellulose in different ratios

Trial	Dissolution efficiencies (%) (DE_{30})			ANOVA Parameters		
	F_{10}	F_{11}	F_{12}	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			

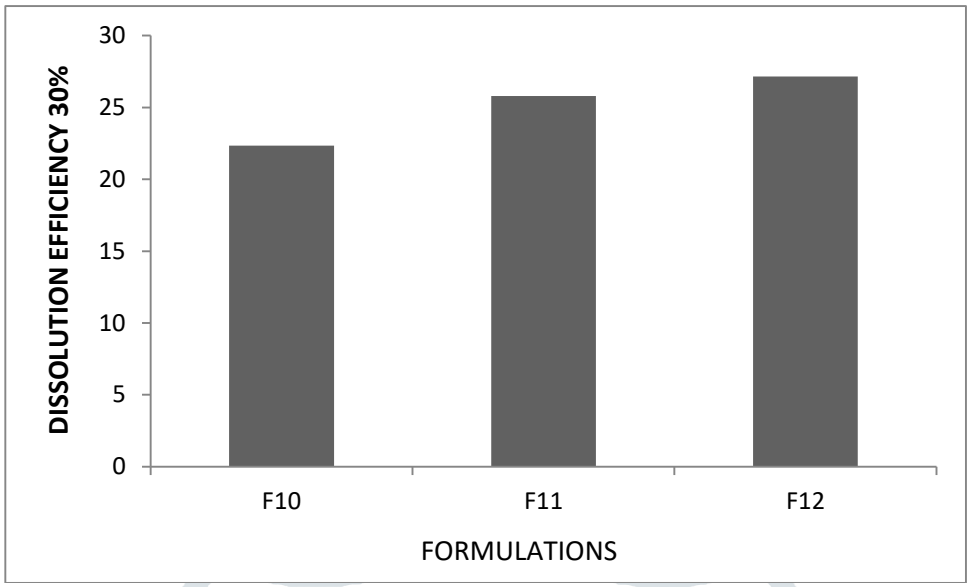


Figure 13: Comparison for dissolution efficiencies of Irbesartan spherical agglomerates prepared with Methyl cellulose in different ratios

Preparation of Irbesartan immediate release Tablets containing super disintegrants:-

Irbesartan containing immediate release tablets were prepared by direct compression process. All the ingredients (shown in Table 5.35) 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.

INGREDIENTS	F_{13}	F_{14}	F_{15}
Irbesartan agglomerates	150	150	150
Sodium Starch Glycolate (SSG)	12.5		-
Croscarmellose sodium		12.5	
Crospovidone			12.5
Mannitol	7.5	7.5	7.5
Avicel pH 102	76	76	76
Talc	2	2	2
Magnesium stearate	2	2	2
Total weight	**250**	**250**	**250**

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Evaluation of Micromeritic properties of the blend:-

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 .

Evaluation of Irbesartan immediate release Tablets:-

The prepared tablets were evaluated for Weight variation test, disintegration time, friability, hardness and wetting time.

a) 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 spectro photometrically at 244 nm using UV-visible spectrophotometer.

b) Dissolution studies:-

Dissolution studies for immediate release tablets of Irbesartan were performed in 0.1N HCl (1.2 pH) using USP dissolution test apparatus (Electro lab, 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 ^{O}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 19: In-vitro dissolution data of Irbesartan Immediate Release tablets prepared with various super disintegrants

S. No	Sampling time (min)	Cumulative % of drug dissolved ($\overline{X}$ ± S.D.)		
		F_{13}	F_{14}	F_{15}
1	0	0	0	0
2	10	41.57	45.26	51.57
3	20	62.28	66.01	75.54
4	30	78.23	81.48	90.84
5	40	88.56	92.11	98.41
6	50	94.78	98.10	
7	60	98.95		

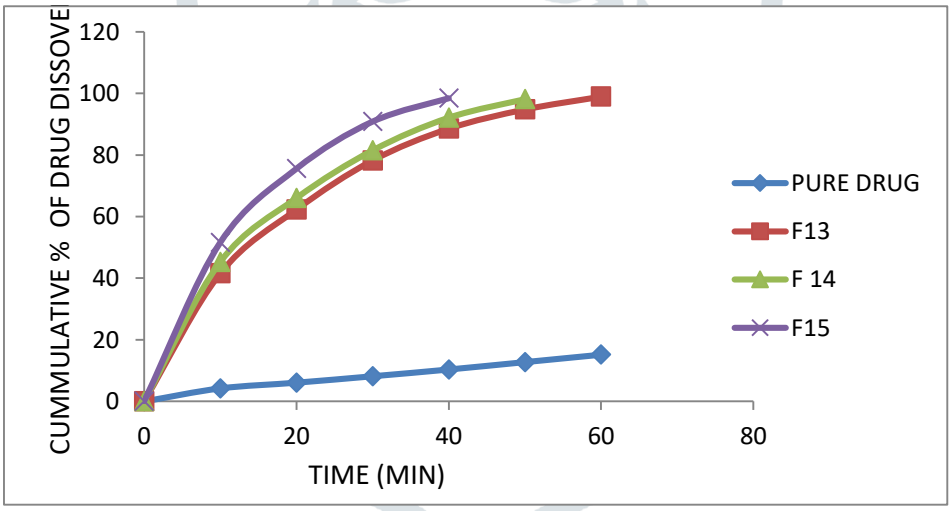

Figure 6.14: Dissolution profiles of Irbesartan Immediate Release tablets prepared with super disintegrants

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

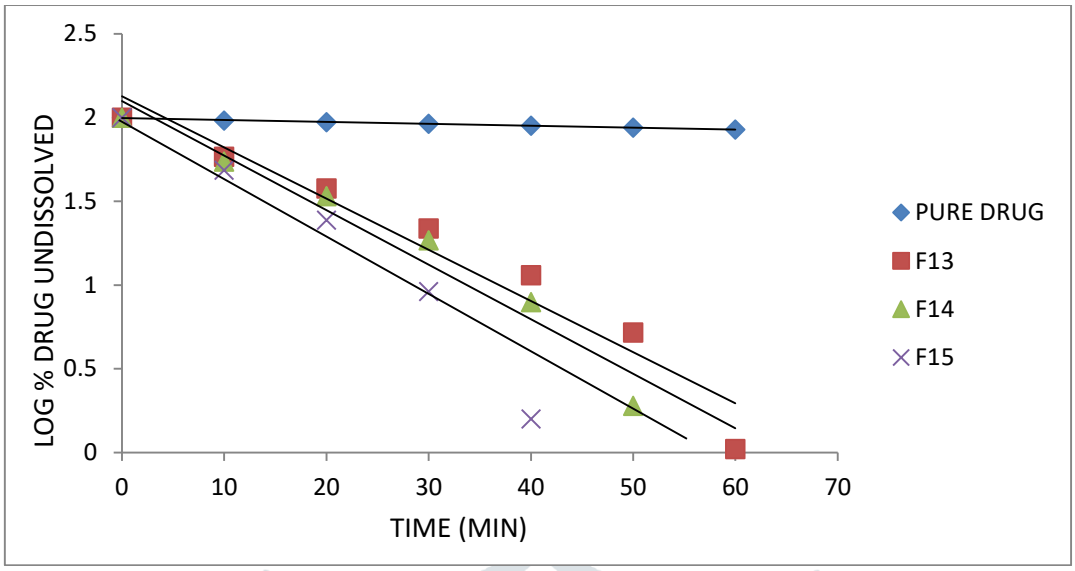

Figure 15: First order plots of Irbesartan Immediate Release tablets prepared with super disintegrants

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

TABLE 20: *In-vitro* dissolution kinetics of Irbesartan Immediate Release tablets prepared with various super disintegrants

S. No	Formulation	T_{50} (min)	T_{90} (min)	DE_{15} (%)	K (min^{-1})	Correlation coefficient values	
						Zero Order	First order
1	F_{13}	11.3	37.6	47.75	0.061	0.8520	0.9708
2	F_{14}	10.3	34.3	51.07	0.067	0.8806	0.9764
3	F_{15}	8.0	26.6	57.54	0.086	0.8973	0.9707

Table 21: Statistical treatment for dissolution efficiencies of Irbesartan Immediate Release tablets prepared with various super disintegrants

Trial	Dissolution efficiencies (%) (DE_{15})			ANOVA Parameters		
	F_{13}	F_{14}	F_{15}	Calculated value (F)	Degree of freedom	Significance
1	47.71	51.14	57.37			
2	47.12	51.36	57.13	278.97	2,6	P<0.05
3	48.42	50.71	58.12			

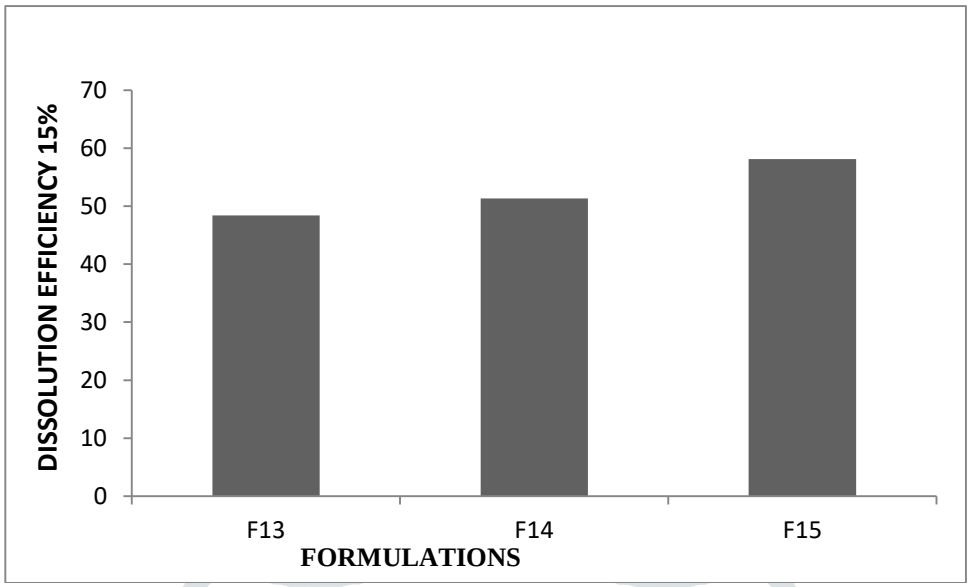

Figure 16: Comparison for dissolution efficiencies of Irbesartan Immediate Release tablets prepared with various super disintegrants

Preparation of Irbesartan immediate release Tablets containing co processed super disintegrants:-

Irbesartan containing immediate release tablets were prepared by direct compression process. All the ingredients (shown in Table 5.37) 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.

Table 22: Composition of Irbesartan Immediate Release Tablets prepared with coprocessed super disintegrants

Co processed super disintegrants composition ratio	**1:1**	**1:2**	**1:3**
Ingredients	**F_{16}**	**F_{17}**	**F_{18}**
Irbesartan Agglomerates	150	150	150
Croscarmellose sodium + Crospovidone	12.5	12.5	12.5
Mannitol	7.5	7.5	7.5
Avicel pH 102	76	76	76
Talc	2	2	2
Magnesium stearate	2	2	2
Total weight	**250**	**250**	**250**

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

Formulation code	Bulk density (gm/cm^3)	Tapped Density gm/cm^3)	Carr's index (%)	Hausner's ratio	Angle of repose (°)
F_{16}	0.435	0.523	16.82	1.20	27.42
F_{17}	0.463	0.551	15.97	1.19	26.56
F18	0.484	0.572	15.38	1.18	25.27

Table 24: Evaluation parameters of Irbesartan Immediate Release tablets prepared with co processed super disintegrants

S. No	Parameters	F_{16}	F_{17}	F_{18}
1	Average weight (mg)	250±0.3	250±0.1	250±0.2
2	Drug content (%)	98.54	99.81	99.19
3	Disintegration time (sec)	163	147	125
4	Friability (%)	0.44	0.28	0.13
5	Hardness (kg/sq cm)	4.2	4.2	3.8

Table 25: In-vitro dissolution data of Irbesartan Immediate Release tablets prepared with co processed super disintegrants

S. No	Sampling time (min)	Cumulative % of drug dissolved ($\overline{X}$ ± S.D.)		
		F_{16}	F_{17}	F_{18}
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		

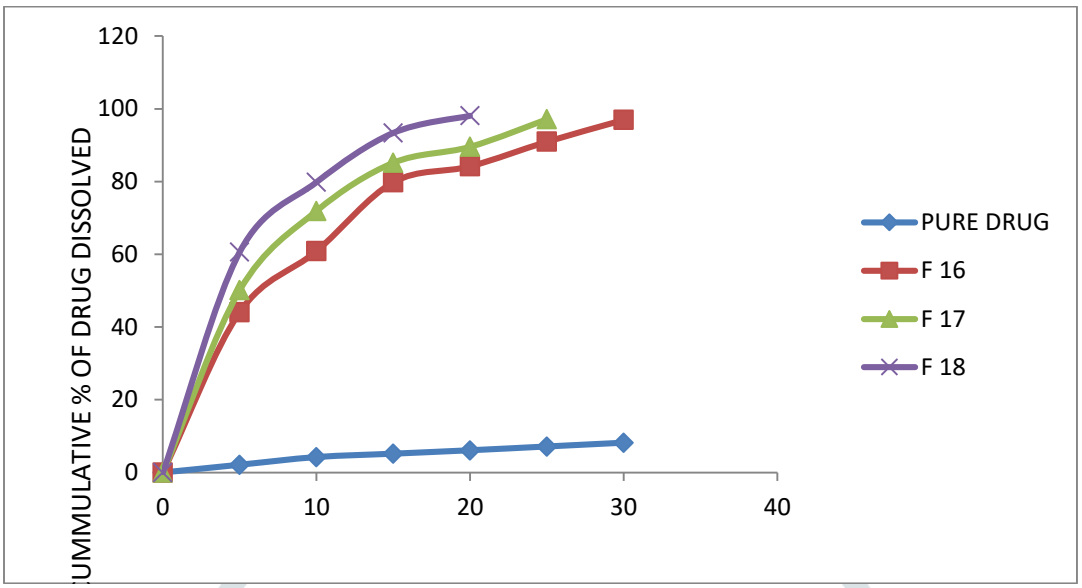

Figure 17: Dissolution profiles of Irbesartan Immediate Release tablets prepared with co processed super disintegrants
(-♦-) Irbesartan pure drug
(-■-) Irbesartan tablets prepared with sodium starch glycolate
(-▲-) Irbesartan tablets prepared with croscarmellose sodium
(-×-) Irbesartan tablets prepared with crospovidone

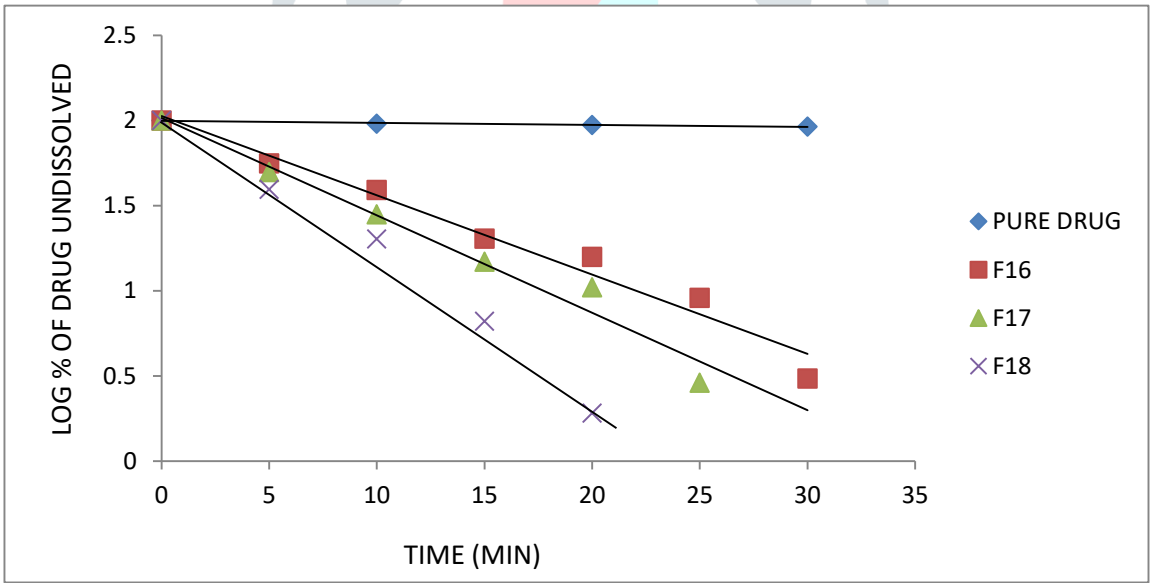

Figure 18: First order plots of Irbesartan Immediate Release tablets prepared with co processed super disintegrants
(-♦-) Irbesartan pure drug
(-■-) Irbesartan tablets prepared with sodium starch glycolate
(-▲-) Irbesartan tablets prepared with croscarmellose sodium
(-×-) Irbesartan tablets prepared with crospovidone

Table 26: *In-vitro* dissolution kinetics of Irbesartan Immediate Release tablets prepared with co processed super disintegrants

S. No	Formulation	T_{50} (min)	T_{90} (min)	DE_{15} (%)	K (min^{-1})	Correlation coefficient values	
						Zero Order	First order
1	F_{16}	6.6	22.0	48.28	0.104	0.8425	0.9851
2	F_{17}	5.3	17.7	54.87	0.131	0.8349	0.9864
3	F_{18}	3.7	12.3	62.38	0.180	0.8484	0.9932

Table 27: Comparison for dissolution efficiencies of Irbesartan Immediate Release tablets prepared with co processed super disintegrants in different ratios

Trial	Dissolution efficiencies (%) (DE_{15})			ANOVA Parameters		
	F_{16}	F_{17}	F_{18}	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			

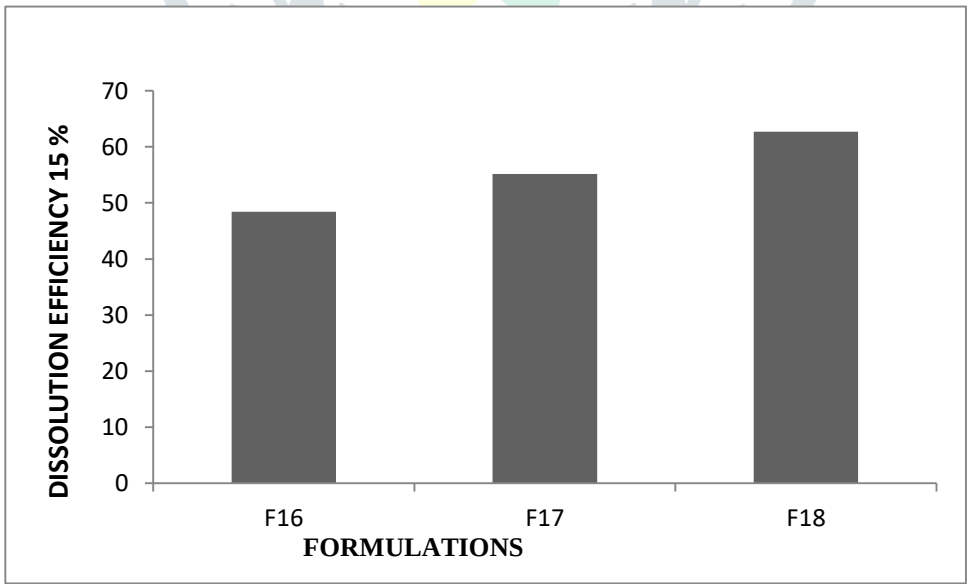

Figure 19: Comparison for dissolution efficiencies of Irbesartan Immediate Release tablets prepared with co processed super disintegrants in different ratios

SEM Analysis:-

The samples for the SEM analysis were prepared by sprinkling the spherical agglomerates on one side of the double adhesive stub. 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.

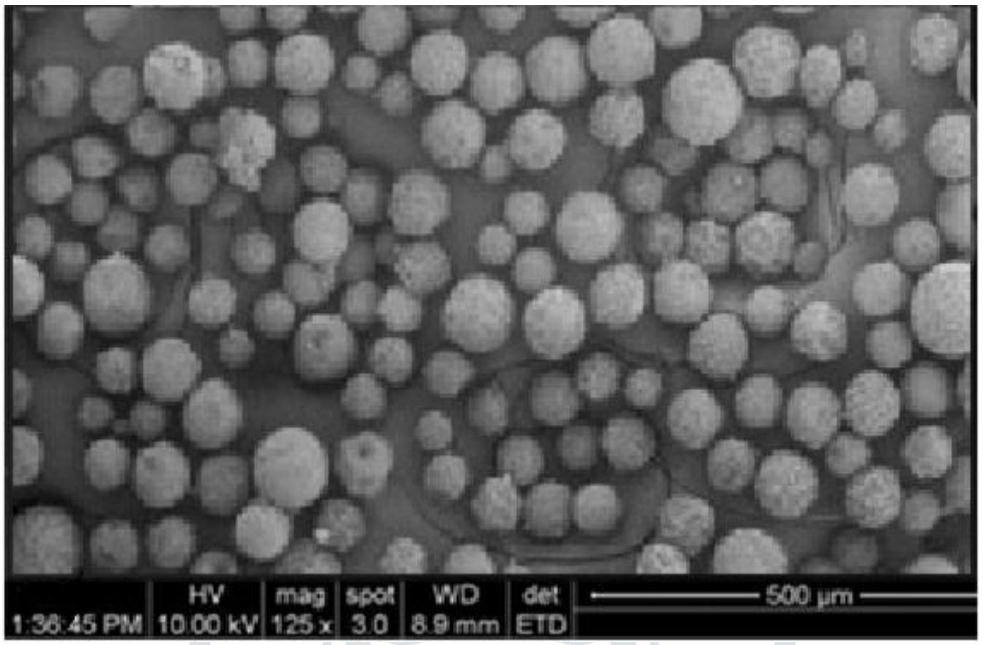

Figure 20 Scanning Electron Microscope Photograph of Irbesartan agglomerates

IR spectral studies:-

The IR Spectra for the formulation, pure drugs and excipients were recorded on JASCO FT-Infra Red Spectrophotometer using KBr pellet technique (1:100) at the resolution rate of 4 cm^{-1}. Spectrum was integrated in transmittance mode at the wave number range 380 to 4368 cm^{-1}.

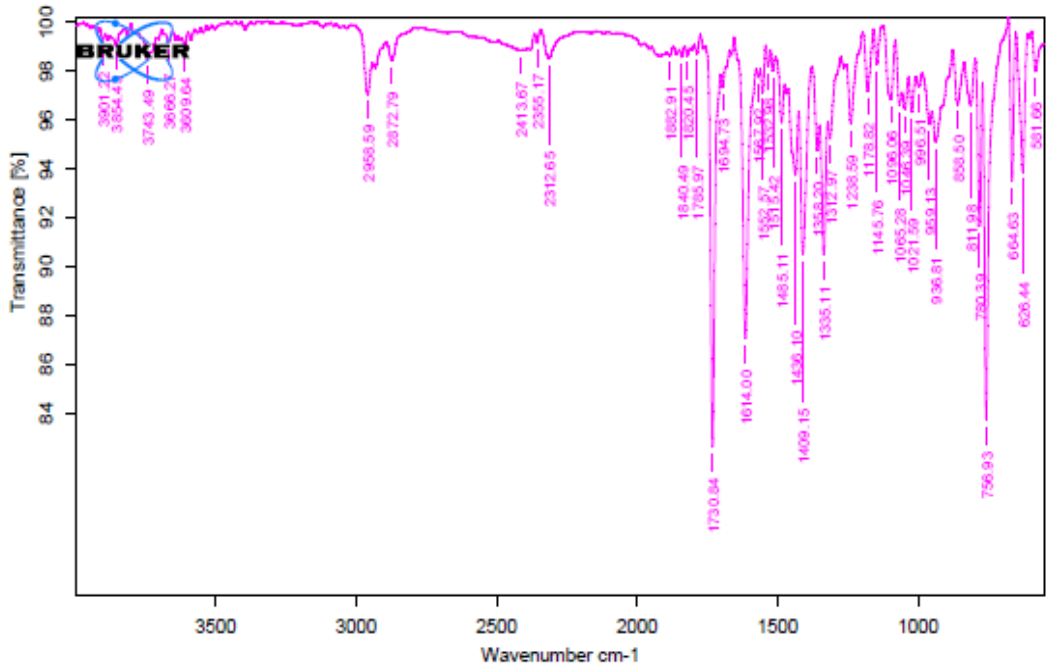

Figure 21: FTIR spectrum of Irbesartan Pure Drug

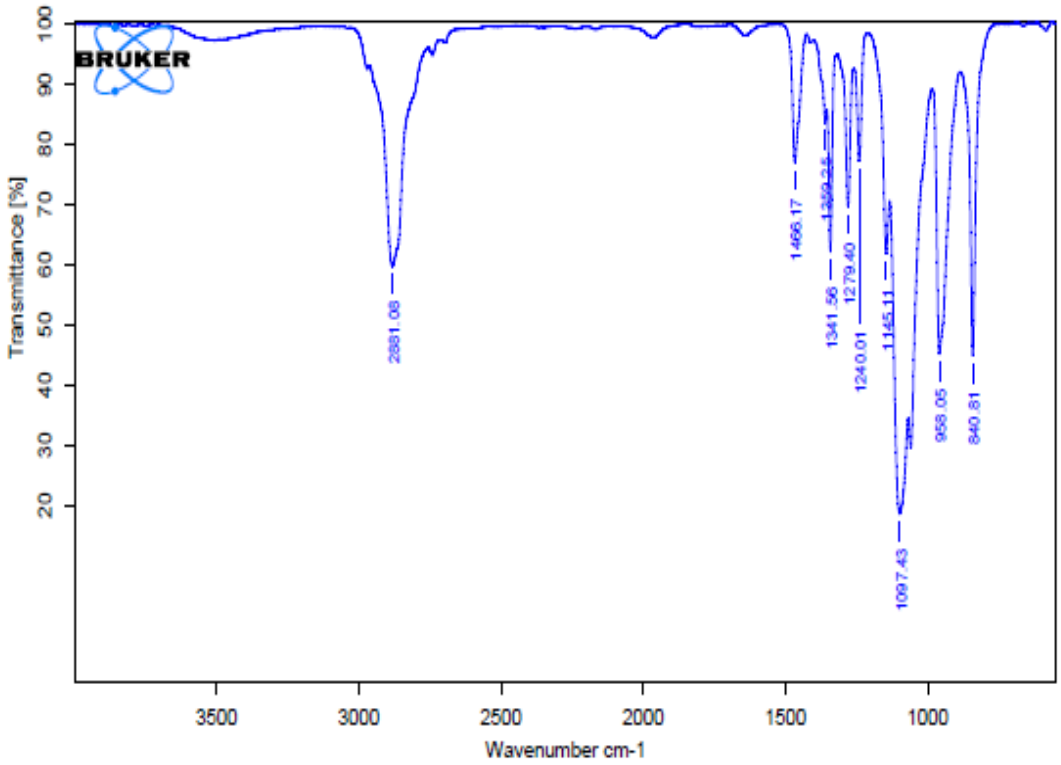

Figure 22: FTIR spectrum of PVP K-90

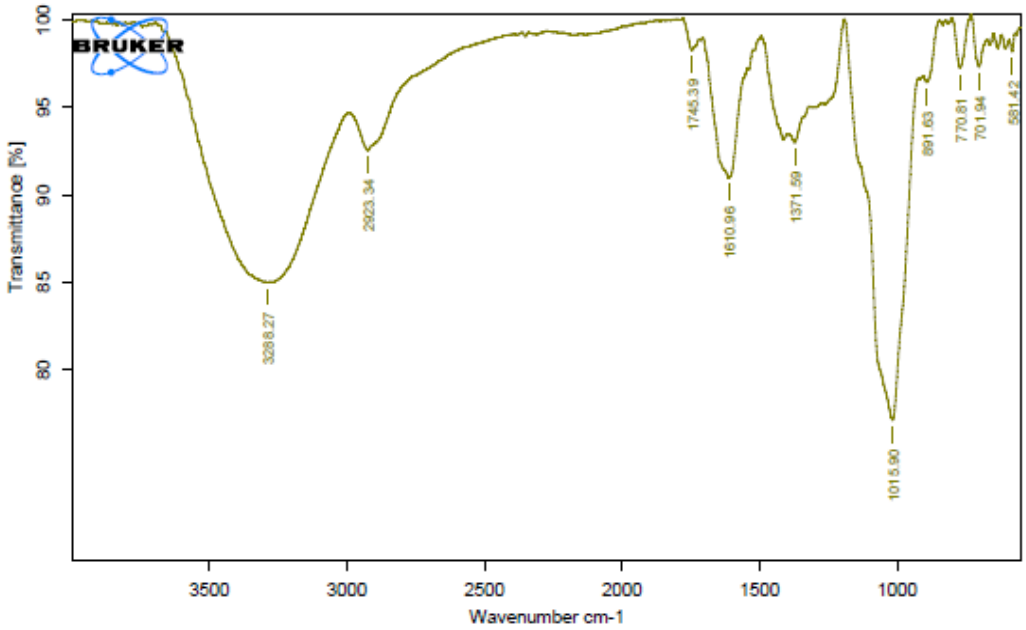

Figure 23: FTIR spectrum of crosscarmellose sodium

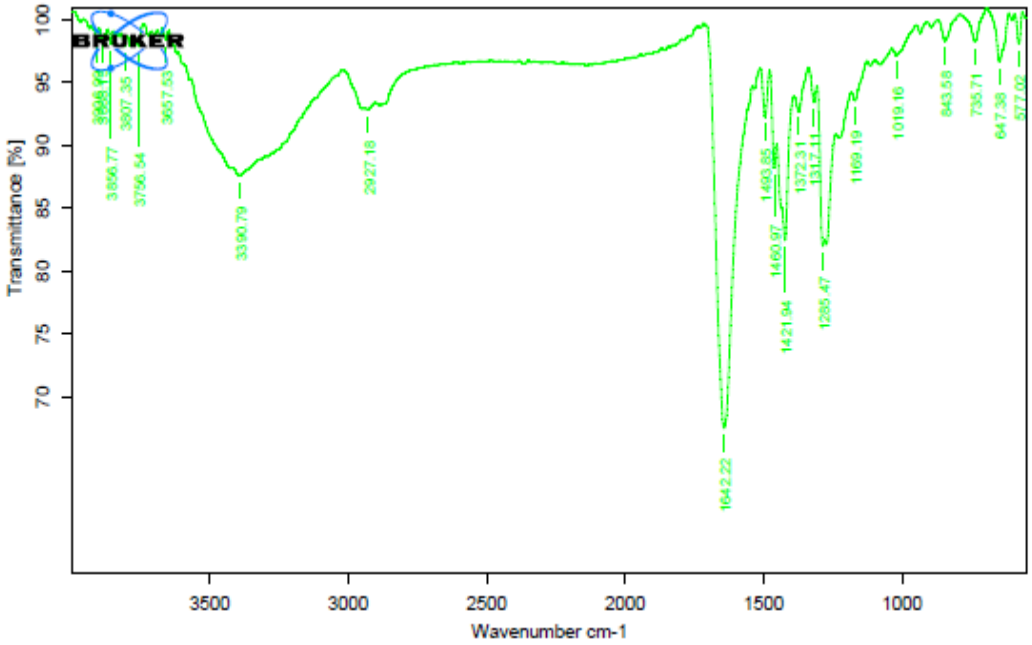

Figure 24: FTIR spectrum of Crosspovidone

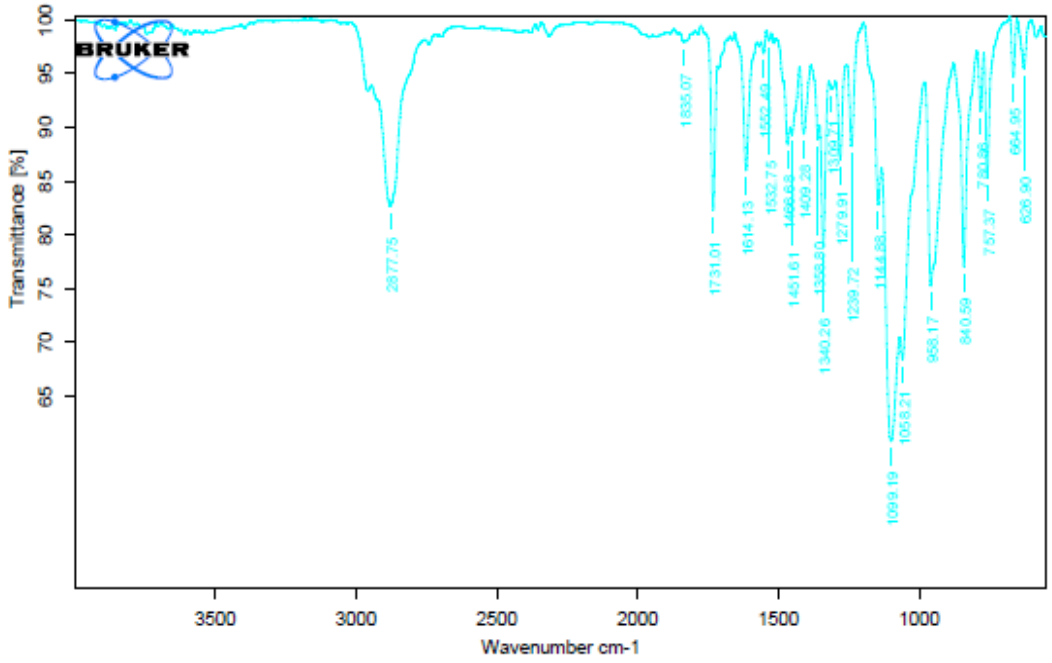

Figure 25: FTIR spectrum of Optimized formulation of Irbesartan

5.13. Stability study:-

The optimized formulations were 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 [13]. Tablets were periodically removed and evaluated for physical characteristics and in-vitro drug release.

Table 28: **Dissolution Kinetics of Irbesartan Immediate Release tablets stored at 25±2^0 C/60±5% RH and 40±2^0 C/75±5% RH.**

Storage conditions	Time interval	K (min^{-1})	T_{50} (min)	T_{90} (min)	DE_{15} (%)
25±2^0 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±2^0 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

SUMMARY:-

The following conclusions were drawn from the results

1. Based on phase solubility studies 0.1N Hydrochloric acid (1.2 pH**)** was selected for the dissolution medium for the evaluation of Irbesartan.
2. 25% /12.5% /62.5% proportions of di methyl formide /chloroform/water, with stirring rate at 1000 ± 50 rpm for a period of 20 minutes were found to be suitable for the preparation of spherical agglomerates by the emulsion solvent diffusion method.
3. Incorporation of polymer during agglomeration significantly enhanced the dissolution. Mixing of drug with a hydrophilic carrier (polymer) results in greater wetting and increase surface available for dissolution by reducing interfacial tension between the hydrophobic drug and dissolution media.
4. The cumulative percentage of drug (Irbesartan) released from different agglomerates was increased in the following order for agglomerates prepared with polymers

Agglomerates Irbesartan spherical agglomerates prepared with PVP –K90 > Irbesartan spherical agglomerates prepared with HPMC > Irbesartan spherical agglomerates prepared with NaCMC > Irbesartan spherical agglomerates prepared with MC

6. The dissolution rate of drug (Irbesartan) was found to be effected by the concentration of the polymer used in the preparation of agglomerates. The dissolution rate followed first-order kinetics as the graphs drawn between log % drug un dissolved vs. time were found to be linear
7. Among all the formulations prepared, spherical agglomerates prepared with PVP –K90 showed highest drug release in 60 minutes.
8. The dissolution rate of Irbesartan was found to be effected by nature of the super disintegrant used in the preparation of tablets. Based on the dissolution rate, super disintegrants can be rated as SSG < Croscarmalose sodium < Crospovidone.
9. The dissolution rate of Irbesartan was found to be effected by ratio's of co-processed superdisintegrants (Croscarmalose sodium: Crospovidone) used in the preparation of tablets.
10. The formulation prepared with co-processed super disintegrants (Croscarmalose sodium: Crospovidone) in 1:3 ratio was offered relatively rapid release of Irbesartan when compared with other ratios employed in this investigation.
11. The IR spectra of all the tested samples showed the prominent characterizing peaks of pure drugs which confirm that no chemical modification of the drug has been taken place.
12. The Stability studies results indicated that the drug release from the optimized formulations was not changed significantly when stored at25 ± 2ºC, 60 ± 5% RH and at 40 ± 2 ºC, 75 ± 5% RH for 3 months.

Conclusion:-

Present study concluded that spherical agglomerates prepared by the quasi emulsion solvent diffusion method showed an improvement in the solubility, dissolution rate, compactibility, wettability, flow ability 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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