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CRYSTAL MODIFICATION OF IRBESARTAN BY SPHERICAL AGGLOMERATION TO IMPROVE MICROMERITICS AND DISSOLUTION RATE

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ABSTRACT

In the present study an attempt was made to prepare spherical agglomerates of Irbesartan, a BCS class II to improve its physicochemical and bulk properties. Irbesartan spherical agglomerates were prepared by solvent change method. It involves good solvent, poor solvent and bridging liquid dimethylformamide (DMF), water, toluene respectively.The prepared spherical agglomerates were evaluated for micromeritic properties (bulk density,tapped density, angle of repose, Hausner's ratio, and Carr's index). The agglomerates were characterized by Fourier transform infrared spectroscopy (FTIR), powder X-ray diffraction (PXRD) and scanning electron microscopy (SEM), solubilityandparticle size. The results of micromeritic studies suggested that the agglomerates showed improved flow properties due to spherical shape and bigger size of agglomerates. The FTIR studies indicated that there is no strong interaction at molecular level. PXRD results suggested that no alteration in the crystal structure of Irbesartan, but the crystallinity being modified. Spherical agglomerates of Irbesartan showed increased solubility and higher dissolution rate compared to Irbesartan.

Keywords: Spherical agglomerates, FTIR, PXRD, Crystallinity, Solubility

INTRODUCTION

Most active pharmaceutical ingredients (APIs) are produced in crystal forms for its chemical stability and convenience in transportation, packaging and storage **[1]**. Crystallization is a way for atoms/molecules to form an ordered structure within a homogeneous phase. Crystallization is also an essential unit operation for purification and separationespecially in pharmaceutical industry **[2]**. A lot of crystallization processes producing solid forms of interest have been reported, for instances temperature cooling, evaporation, ionic liquids, solvent-drop grinding, electric field, seeding procedures, polymer heteronuclei, and gel induced crystallization. For pharmaceutical industry crystallinity, crystal habit, and polymorphism, of an active pharmaceutical ingredient (API) play critical roles in the pharmaceutical development, formulation, and manufacturing. Those are all solvent dependent, solvent screening is fundamental to many chemical process industries, especially the pharmaceutical industry **[3, 4]**. In 1986, Kawashima used the spherical crystallization technique for size enlargement of drugs in the field of pharmacy **[5]**. Spherical crystallization is the novel agglomeration technique that can transform directly the fine crystals produced in the crystallization process into a spherical shape. It is the particle engineering technique by which crystallization and agglomeration can be carried out simultaneously in one step to transform crystals directly into compacted spherical form **[6, 18]** and which has been successfully utilized for improvement of flowability and compactability of crystalline drugs. Spherical agglomeration employs three solvents: good solvent (dissolution medium for drug); bridging liquid (medium which partially dissolves the drug and has wetting property) and bad solvent (solvent which is immiscible with the drug substance) **[7, 8, 10, 18]**. The spherical agglomeration has been applied to several drugs, and it has been found that the product properties are quite sensitive to the amount of the bridging liquid **[9, 18]**.

Irbesartan (IBS) is a potent long-acting angiotensin receptor antagonist used in the treatment of hypertension. The model drug proposed for the present study is a hydrophobic (BCS class II) drug with poor aqueous solubility (< 0.1 mg/ml) and exhibits a solubility-limited bioavailability **[11]**. It is crystalline in nature, exhibits poor flow. Spherical agglomeration improves the flowability and compressibility of crystalline substances. The rationale of this study was to improve the micromeritic properties and

dissolution characteristics of the IBS by spherical agglomeration technique. In the present study an attempt was made to prepare spherical agglomerates of Irbesartan, a BCS class II to improve the physicochemical properties of Irbesartan.

Spherical agglomerates of Irbesartan were prepared by solvent change method using a three solvent system. It involves good solvent, poor solvent and a bridging liquid. The selection of these solvents depends on the mutual miscibility of the solvents and the solubility of drug in individual solvent. Based on the solubility of drug, the solvent system selected includes di methyl formamide (DMF) as good solvent, water as poor solvent, and toluene as bridging liquid. The composition of solvent system was determined with the help of ternary phase diagram **[11]**, the selected ratio for poor solvent and good solvent is 90:09 and the bridging liquid volume was optimized between 0.1mL to 1mL. The stirring speed and stirring time were optimized, the optimized speed is 600 rpm for 30 min **[10]**.

MATERIALS AND METHODS:

Irbesartan was obtained as a gift sample from Hetero drugs limited, Hyderabad., PEG 6000, dimethyl formamide, toluene, methanol, and hydrochloric acid were obtained from SD fine chemicals private limited, Mumbai. Chloroform was obtained from Qualigens chemicals private limited, Mumbai. Carbon tetra chloride was obtained from Hi media laboratories, Mumbai.

Preparation of spherical agglomerates:

Spherical agglomeration was formulated by solvent change method three solvents were used i.e. good solvent, poor solventand a bridging liquid were selected **[12]**. A bridging liquid is used to cause spherical agglomeration **[13]**. Solubility of Irbesartan was determined in various solvents like ethanol, methylene chloride, DMSO (dimethyl sulfoxide), DMF (dimethyl formamide) were taken and shaken for 24hr and filtered by using Whattman filter paper gradeno.41 and were analysed.

On the basis of solubility data procured, DMF was selected as good solvent and water was selected as poor solvent. Various bridging liquids such as cyclohexane, chloroform, ethyl acetate, dichloromethane, butyl acetate, toluene and carbon tetrachloride were tried. Ethyl acetate, and toluene were suitable for preparation of irbesartan spherical agglomerates. But in case of ethyl acetate the agglomerates of irbesartan were irregular in size and shape, hence toluene was selected as bridging liquid.

The effect of various parameter such as stirring speed and stirring time on the

preparation of agglomerates was studied. From the pre-formulation studies it was concluded that 30 min stirring time and 600 rpm was optimum for the preparation of spherical agglomerates **[10, 14]**.

Method of preparation of Irbesartan spherical agglomerates:

Spherical agglomerates were prepared by dissolving Irbesartan in DMF (good solvent) by heating and cooling to 20°C. The resultant drug solution was quickly poured into water (bad solvent) with continuous stirring. Agglomeration is initiated by addition of drop-by-droptoluene (bridging liquid) by continuous stirring for 30 min to obtain spherical agglomerates. The mixture was then filtered and dried at 65°C for 12hrs given in **Table 1**. Among the formulations F1-F9 formulations F3,F4,F5 and F6 has given sphere forms and were selected for further evaluation.

Table 1: Formulation of spherical agglomerates

Formulation code	Poor solvent water (ml)	Good solvent DMF (ml)	Bridging liquid Toluene (ml)	Observation
F 1	90.81	9.08	0.1	Clumps
F 2	90.72	9.07	0.2	Clumps
F 3	90.63	9.06	0.3	Spheres
F 4	90.54	9.05	0.4	Spheres
F 5	90.45	9.04	0.5	Spheres
F 6	90.36	9.03	0.6	Spheres
F 7	90.27	9.02	0.7	Sticking
F 8	90.18	9.01	0.8	Sticking
F 9	90	9	1	Sticking

CHARACTERIZATION OF SPHERICAL AGGLOMERATES:

FTIR analysis of Irbesartan spherical agglomerates:

Spherical agglomerates were analyzed by FTIR spectroscopy (FTIR 1600) for the confirmation of presence of Irbesartan. Sample under analysis was added to powdered potassium bromide in the ratio of 1:100. The mixture was compacted under pressure (10 tons/cm^2) in vacuum to form a transparent pellet (13 mm in diameter) and was subjected to immediate analysis and spectrum obtained was noted.

Differential scanning calorimetry (DSC)

Powder X-ray diffraction studies (PXRD):

X-ray diffraction analysis was employed on Irbesartan and spherical agglomerates to study the diffraction pattern using XRD-6000 diffractometer (Shimadzu, Japan). The powder was placed in a glass sample holder. CuK radiation was generated at 30mAand 40 kV. Samples were scanned from 10 to 80°with a step size of 0.02°.

Optical Microscopy of Agglomerates:

The optical microscope was used to study the external morphology of the TLS spherical

agglomerates prepared for size and shape under 10X,45X,100X magnification **[15, 16]**.

Scanning Electron Microscopy:

Scanning electron microscopy is used to analyze the surface topography and crystal type (polymorphism and crystal habit) of the Irbesartan spherical agglomerates. Spherical agglomerates size was determined by scanning electron microscope (OXFORD instruments, model – INCA wave) **[16]**.

Particle size analysis:

Particle size of Irbesartan and prepared spherical agglomerates was determined by using optical microscopy (Magnus MLX). Two hundred particles were measured in each sample and the surface volume mean diameter was recorded. Average was taken and their size range and mean diameter frequency was calculated **[15, 16]**.

Solubility determination of spherical agglomerates:

Solubility studies were performed by taking excess amount of Irbesartan and prepared spherical agglomerates was added to 10ml of 0.01N HCl. The mixtures were shaken for24 hrs at 100rpm. The solutions were filtered and analyzed **[10, 17]**.

Precompression properties of Irbesartan agglomerates and Irbesartan:

Irbesartan agglomerates, Irbesartan were evaluated for micromeritic properties which includes angle of repose, bulk density, tapped density, Hausner's ratio and Carr's index **[15, 16, 17]**.

Preparation of Irbesartan agglomerates tablets by direct compression method:

Direct compression method was used for the preparation of tablets. In this, microcrystalline cellulose (MCC) was used a s direct compressible excipient. Lactose, mannitol were used as diluents and talc, magnesium stearate as lubricant and glidants respectively. All the ingredients were blended in a mortar and pestle. The blend of powder was compressed into tablets by using single punch tablet machine **[7]**. The composition for the preparation of tablets is presented in **Table 2**.

Table 2: Preparation of tablets of Irbesartan and agglomerates by direct compression

Ingredients	Tablet (pure drug) (mg)	Agglomerates (F3,F4,F5,F6) (mg)
Irbesartan	150	150
Lactose	307	307
Micro crystalline cellulose	30	30
Mannitol	10	10
Magnesium stearate	02	02
Talc	01	01
Total weight	500	500

EVALUATION OF PREPARED IRBESARTAN AGGLOMERATES TABLETS:

a) Post compression parameters:

The prepared tabletswere evaluated for various post compression parameters like weight variation, thickness, hardness, diameter, friability, drug content respectively **[15]**.

b) *In vitro* drug release:

Irbesartan release from tablets was studied using 8 station dissolution rate test apparatus (Lab India, Disso 8000) employing a paddle stirrer at 50 rpm and at 37±0.5°C. using 0.1 NHCl as buffer. The percentage cumulative drug release (% CDR) was calculated **[8]**.

c) Stability Studies:

The selected formulation was evaluated for its stability at 40 ± 2 ^{0}C / 75 ± 5 % RH for about 3 months as per ICH guidelines. The samples were taken out after 3 months and evaluated for the drug content, solubility and *in vitro* release study **[10]**.

RESULTS AND DISCUSSION:

Characterization of spherical agglomerates of Irbesartan:

FTIR spectroscopic analysis:

The FTIR studies were done to determine the possible interaction between the Irbesartan and Irbesartan agglomerates given in **Figure 1 & 2**. The FTIR spectrum of Irbesartan pure drug showed characteristic peaks at 2964.59 cm^{-1}(C-H stretch), 1735.93 cm^{-1}(C=O stretch), 2311.32 cm^{-1} (C=N 3stretch), 3442.76 cm^{-1} (N-H stretch). Similar characteristic peaks with very slight variation in their wavelength were observed with Spherical agglomerates which indicates the compatibility between the Irbesartan and solvents used **[19, 20]** as shown in **Table 3 & Figure 1 & 2**.

X- Ray Diffraction Studies:

Comparison of powder X-Ray diffraction spectra of Irbesartan and Irbesartan spherical agglomerates is given in **Figure 3 & 4** indicates that considerable decrease in crystallinity of spherical agglomerates. After the recrystallization no polymorphic phenomenon was detected, as all powder X-ray diffraction patterns of agglomerates were consistent with the pattern of original crystals. The decrease in crystallinity of the drug indicates increase in amorphous nature the drug, which may increase in the solubility of the Irbesartan.

Optical Microscopy of Agglomerates:

The Optical Microscopic images of the Irbesartan agglomerates revealed the presence of spherical shaped particles which complies with the specified description of the drug given in **Figure 5**.

Scanning electron microscopy:

Morphology and appearance of irbesartan spherical agglomerates were examined by scanning electron microscope (INCA wave, OXFORD instruments). The photographs are depicted in **Figure 6 and 7**. As seen from the photographs the agglomerates were spherical in appearance, and had a smooth surface which leads to enhanced flow when compared to pure drug.

Differential Scanning Calorimetry Studies:

The DSC studies for pure Irbesartan and spherical agglomerates were conducted using Differential Scanning Calorimeter **[10, 17]**. The DSC thermograms of pure irbesartan and its spherical agglomerate forms were shown in Fig 8 and 9. Pure irbesartan showed a sharp endotherm at 185°C corresponding to its melting point. Irbesartan spherical agglomerates showed sharp endotherm at 188.2°C. There was negligible change in the melting endotherms of the spherical agglomerates compared to pure drug indicating the absence of interaction **Figure 8**.

EVALUATION OF IRBESARTAN TABLETS:

Irbesartan tablets (F3, F4, F5 and F6) were prepared and evaluated for Precompression parameters. The studies revealed that Irbesartan spherical agglomerates (F3, F4, F5, F6) exhibited good flow properties compared to Irbesartan as given in **Table 4**.

All prepared spherical agglomerates exhibited indicate good packability as compared to pure drug. All the prepared agglomerates exhibited low Carr's index **[11.963(F3)** to **14.732 (F6)]**, Hausner's ratio **[1.135 (F3)** to **1.172 (F6)]**, and angle of repose **[29.95° (F3)** to **31.226° (F6)]**, values indicated excellent flow properties and compressibility. Pure drug irbesartan exhibited poor flow properties than spherical agglomerates, due to irregular shape and smaller crystal size. The higher flowability of spherical agglomerates was due to perfect sphericity and larger size of agglomerates. The improved flowability and compressibility of spherical agglomerates may be due to the sphericity, regular and larger size of crystals **[10, 11]**.

Post compression parameters of Irbesartan tablets

All the prepared formulations of Irbesartan were evaluated for uniformity of weight, thickness, diameter, hardness, friability, drug content. From the obtained results it was found that all are within the range and the results were given in **Table 5**.

***In vitro* drug release study:**

For the dissolution studies, 0.1 N HCl was selected as a dissolution medium. Dissolution studies were conducted using

dissolution apparatus USP - Type II (Paddle type), at 50 rpm at 37±0.5°C **[10]**. The dissolution – time profiles of irbesartan tablets of pure drug and agglomerates in 0.1 N HCl were recorded in **Figure 10**. All the agglomerates showed better drug release than pure drug in 0.1N HCl, is due to the spherical shape of agglomerates which leads to increase in the surface area hence wetting.

Table 3: FT-IR spectral comparison of irbesartan pure drug and optimized formulation

Characteristic bands	Irbesartan pure drug cm^{-1}	Agglomerates cm^{-1}
NH bending	1616.35	1616.35
NH stretching	3442.76	3442.76
C=O stretch, sharp	1735.93	1728.22
C≡N stretch	2311.32	2318.44
CHstretching	2964.59	2962.66
Aromatic rings (C-C=C Asymmetric Stretch)	1485.19	1482.04

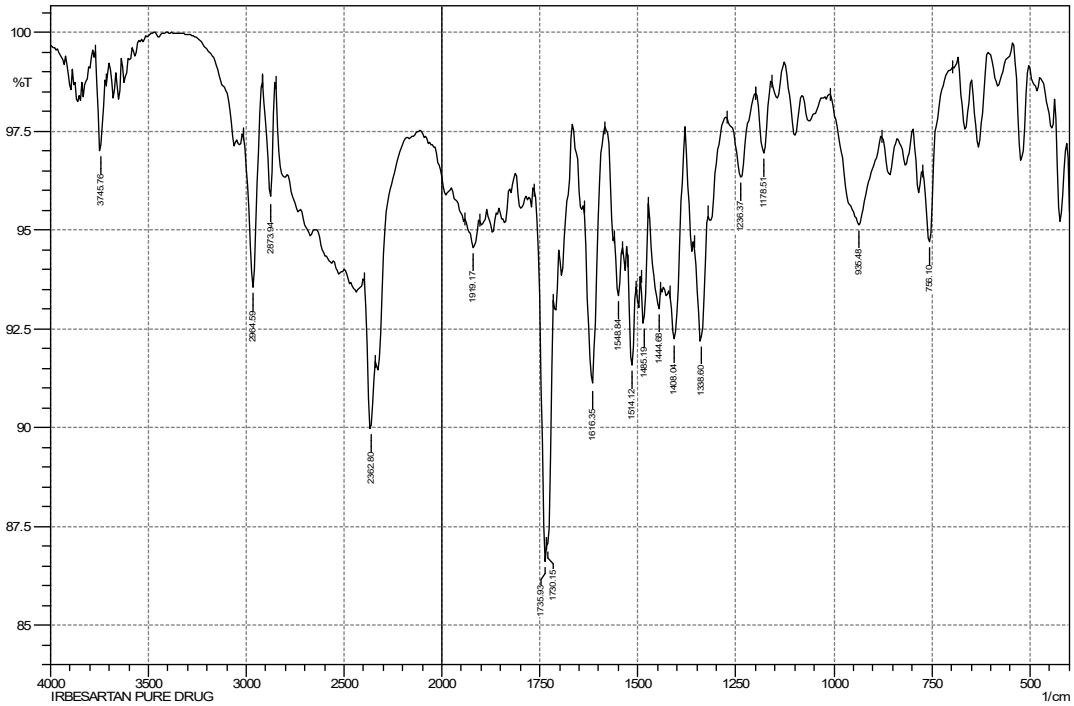

Figure 1: FTIR spectra of Irbesartan pure drug

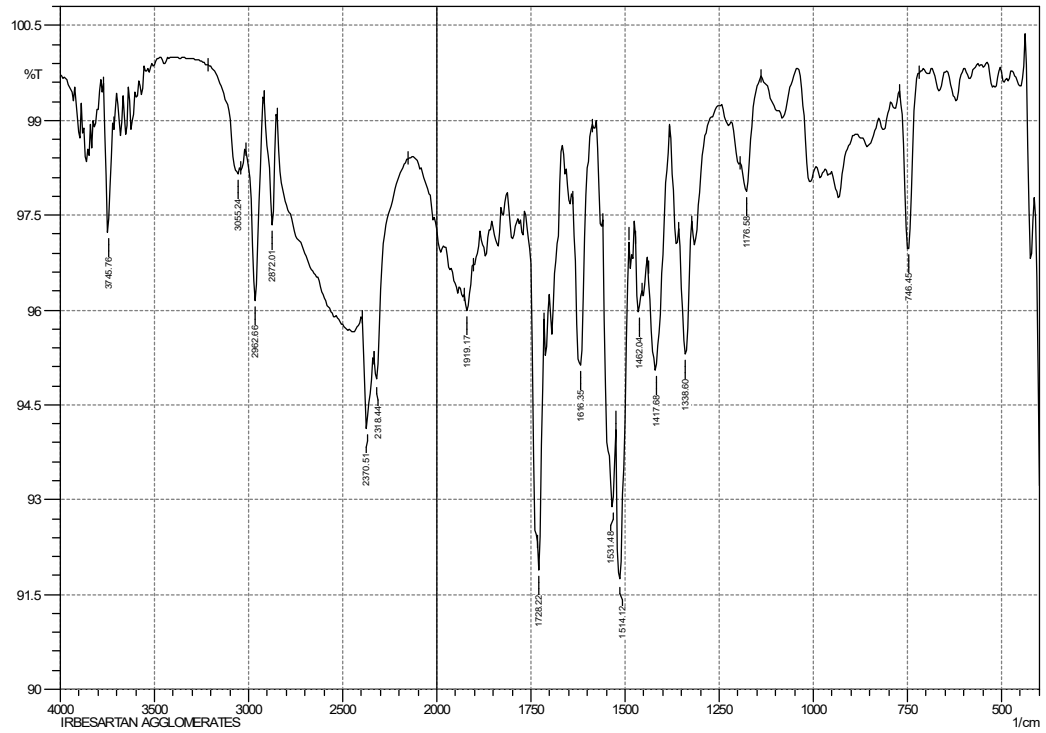

Figure 2: FTIR spectra of Irbesartan spherical agglomerates

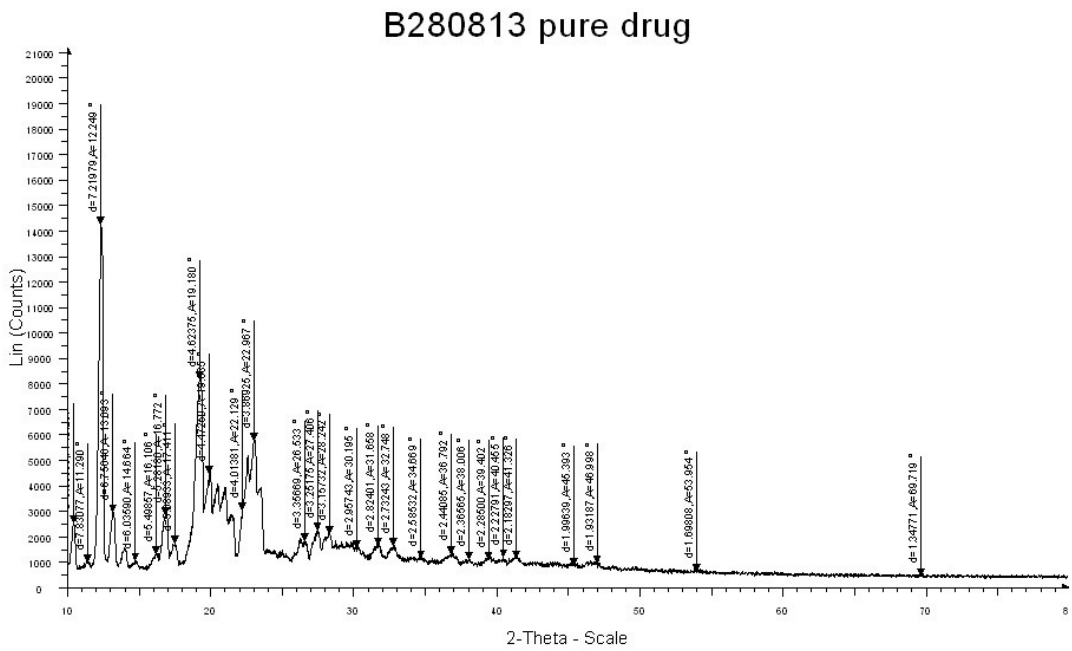

Figure 3: PXRD of Irbesartan spherical agglomerates

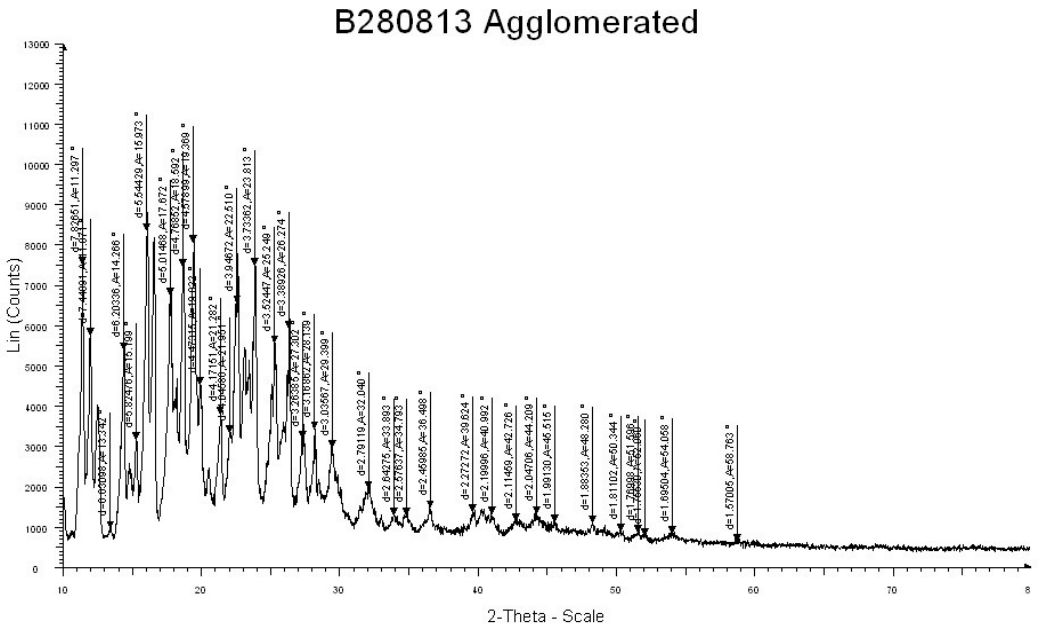

Figure 4: PXRD of Irbesartan spherical agglomerates

Figure 5: Prepared Irbesartan agglomerates

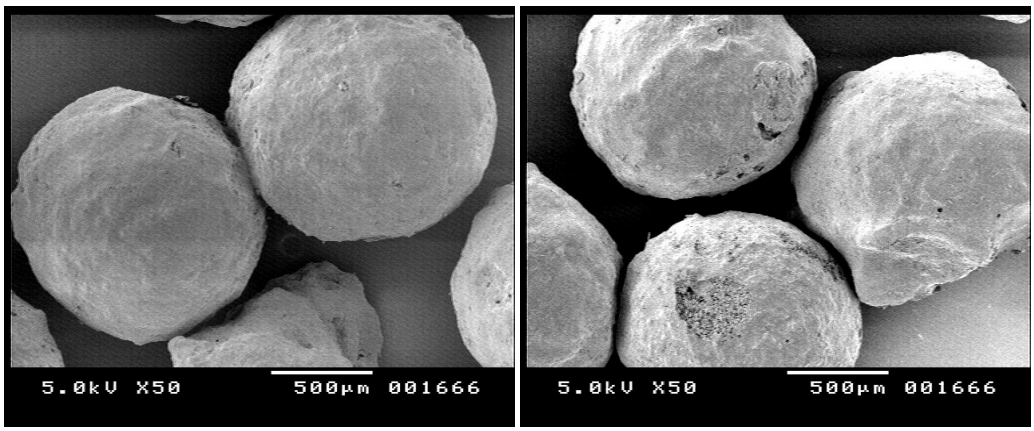

Figure 6: Scanning electron microscopy images of Irbesartan spherical agglomerates (50 X)

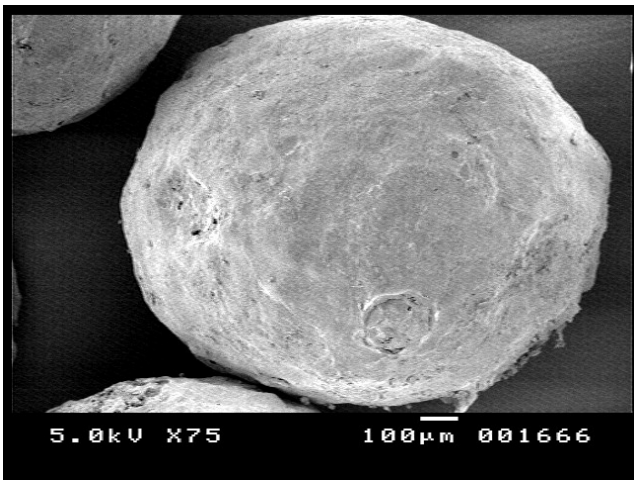

Figure 7: Scanning electron microscopy images of Irbesartan spherical agglomerates (75 X)

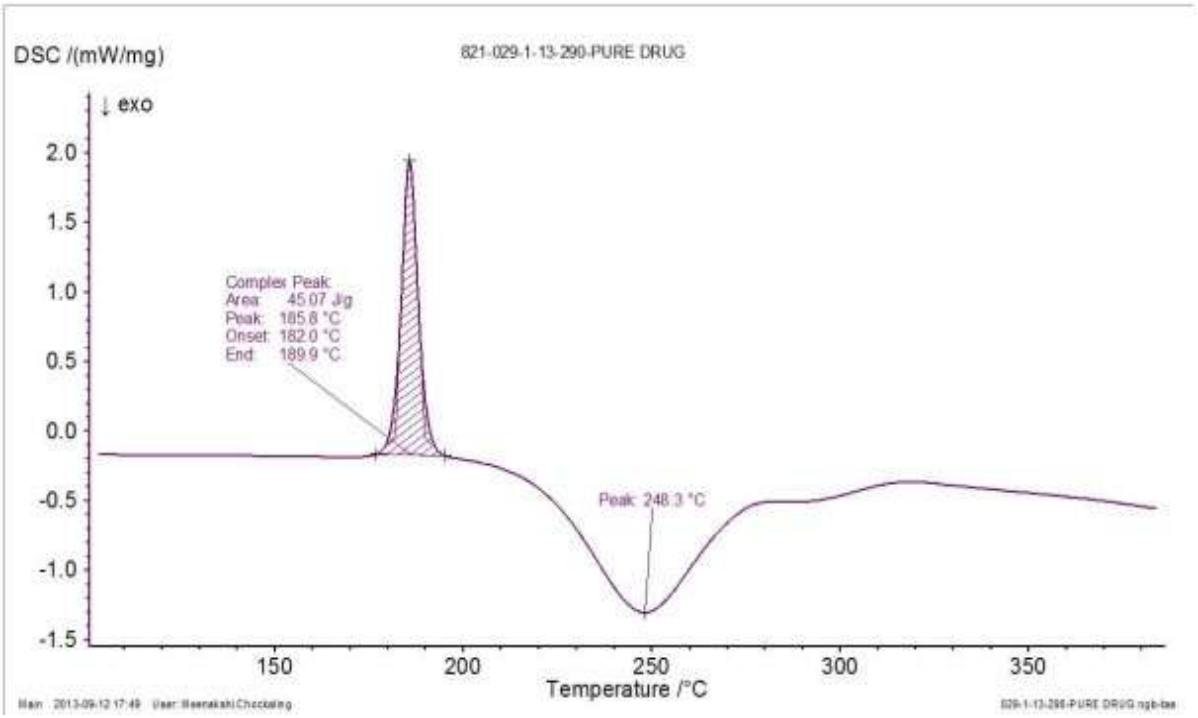

Figure 8: DSC Thermogram of Irbesartan pure drug

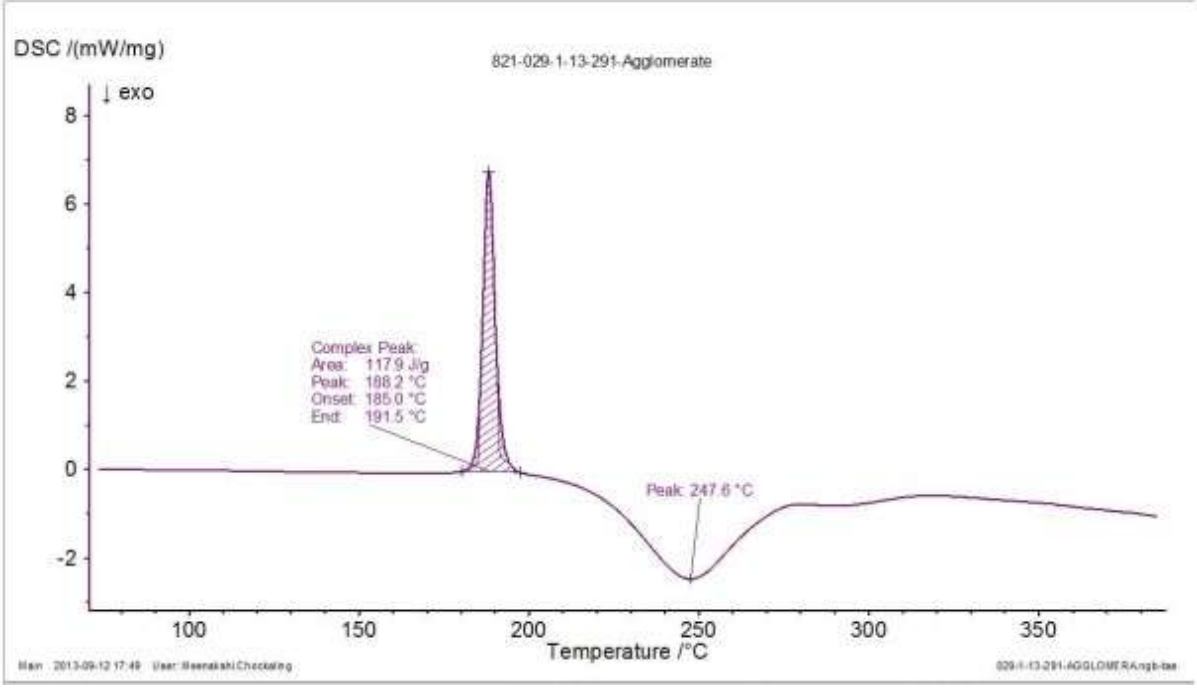

Figure 9: DSC Thermogram of Irbesartan agglomerates

Table 4: Flow properties of Irbesartan pure drug and spherical agglomerates.

Formulations	Bulk denisty (gm/cm³) *	Tapped denisty (gm/cm³) *	Compressibility index*	Hausners ratio*	Angle of repose (°) *
PURE	0.185±0.013	0.337±0.011	44.995±1.141	1.818±0.424	----------
F3	0.255±0.001	0.290±0.014	11.963±0.108	1.135±0.001	29.954±0.051
F4	0.262±0.008	0.304±0.012	13.330±0.385	1.153±0.005	30.058±0.720
F5	0.270±0.012	0.311±0.008	13.821±0.347	1.160±0.004	30.179±0.071
F6	0.257±0.009	0.302±0.013	14.732±0.150	1.172±0.002	31.226±0.045

Table 5: Post compression parameters of Irbesartan agglomerates tablets

Formulation code	Uniformityof weight(mg) (A.M±S.D) *	Thickness (mm) (A.M±S.D) *	Diameter (mm) (A.M±S.D) *	Hardness (kg/cm²) (A.M±S.D) *	Friability	Drugcontent (A.M±S.D) *
Pure	498.44± 1.007	5.31±0.007	10.99±0.015	5.28± 0.148	0.84	148.33± 1.379
F3	498.69± 1.289	5.32±0.01	10.99±0.010	5.22± 0.130	0.92	148.97± 1.171
F4	499.05± 0.998	5.21±0.01	10.99±0.015	5.08± 0.083	0.84	149.13± 0.288
F5	499.21± 0.584	5.23±0.008	11.00±0.010	5.22± 0.083	0.75	149.00± 0.721
F6	498.70± 0.799	5.33±0.01	11.00±0.010	5.22± 0.130	0.80	148.70± 0.519
Total weight (mg)	150	150	150	150	150	150

***Average of three determinations(n=3)**

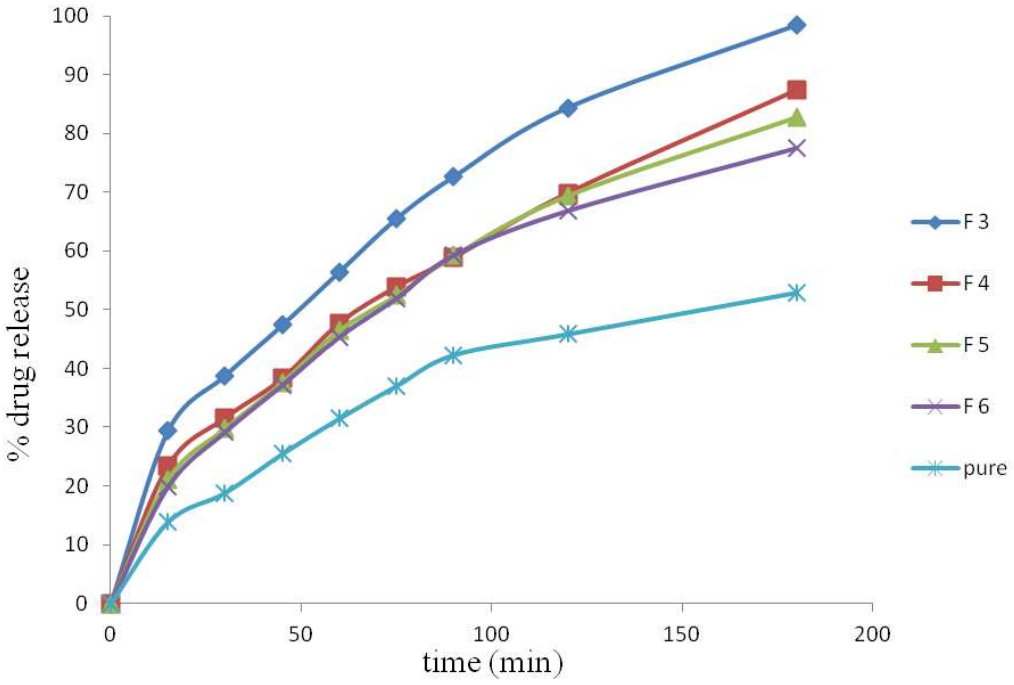

Figure 10: Dissolution – time profile of irbesartan pure drug and agglomerates

Formulation F3 showed highest drug release (98.43 ± 1.86), this is due to smallest sphere size and highest surface area among all the agglomerates **[10, 11]**.

CONCLUSIONS:

Spherical agglomerates of Irbesartan were prepared by solvent change method using DMF as (good solvent), water (poor solvent) and toluene (bridging liquid). SEM results concluded that the F3.F4, F5 and F6 formulations was spherical in appearance, and had a less smooth surface which leads to enhanced flow compared to irbesartan. The PXRD results showed that considerable decrease in crystallinity of spherical agglomerates. After the recrystallization no polymorphic phenomenon was detected, as all powder X-ray diffraction patterns of agglomerates were consistent with the pattern of original crystals. Spherical agglomerates of Irbesartan showed higher solubility than pure drug. *In vitro* studies of Irbesartan spherical agglomerates showed significant improvement in dissolution rate (98.43 %), than pure drug (77.4363%), this may be due to spherecity of crystal, which together increased the wettability of Irbesartan.

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